Current Approaches to Tuberculosis in the United States

Fred M. Gordin, MD
Henry Masur, MD

Tuberculosis is a major threat to global health, infecting a third of the world's population. In the United States, however, control of tuberculosis has been increasingly successful. Only 3.2% of the US population is estimated to have latent tuberculosis and there are only 11 000 cases annually of active disease. More than half the cases in this country occur in individuals born outside the United States. Human immunodeficiency virus coinfection is not a major factor in the United States, since only approximately 10% of cases are coinfected. Drug resistance is also uncommon in this country. Because the United States has more resources for the diagnosis, therapy, and public health control of tuberculosis than many regions of the world, and because many hospitals have more cases of clinically significant nontuberculous mycobacteria than tuberculosis, the management approaches to tuberculosis need to be quite different in this country than in other regions. The resurgence in interest in developing new tools and the investment in public health infrastructure will hopefully be sustained in the United States so that the effect of tuberculosis on the US population will continue to diminish, and these new tools and approaches can be adapted to both high and low prevalence areas to meet the global challenge.

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CASE PRESENTATION

A 62-year-old black man with diabetes mellitus, heavy alcohol intake in the remote past, and hepatitis C presented to the emergency department complaining of foot pain and numbness. In the emergency department, the patient noted that he had a nonproductive cough for 3 weeks and weight loss of 11.25 kg over the last 3 to 4 months. A chest radiograph showed bilateral infiltrates in the right upper lobe and lingula of the left lung (FIGURE 1).

The patient was admitted to the hospital with a presumptive diagnosis of community-acquired or aspiration pneumonia. Initial examination was notable for temperature of 38.0°C. Complete blood cell count and blood chemistries were normal and a human immunodeficiency virus (HIV) test was negative. His purified protein derivative (PPD) skin test was positive (20 mm induration). On day 7, a sputum sample was reported to be smear positive for rare acid-fast bacilli. Ultimately 2 of 5 smears were smear positive for rare organisms and 4 of 5 (2 that were smear positive and 2 that were smear negative) grew *Mycobacterium tuberculosis*. Six weeks after admission, susceptibility testing for his isolate revealed the organism to be sensitive to all tested drugs. On further questioning, the patient stated that he had a positive skin test approximately 30 years earlier and remembered taking some unknown medication for tuberculosis (TB). No specific cause was identified for his foot pain and numbness.

On day 7, after the sputum smear was reported to be positive for presumed *M tuberculosis*, the patient entered a TB research trial and was treated with rifapentine (600 mg/d) in addition to isoniazid, pyrazinamide, and ethambutol. Approximately 3 weeks after initiating TB therapy, his bilirubin, which had been 0.7 mg/dL at baseline, increased to 4.4 mg/dL. Both the rifapentine and pyrazinamide were stopped and the patient was rechallenged with rifapentine and then pyrizinamine (the patient's bilirubin remained in the 2-4 mg/dL range throughout his course of therapy, returning to normal posttherapy). The patient completed a 6-month directly observed regimen without further difficulty. Follow-up 1 year later demonstrated a stable chest radiograph and no recurrence of disease.

This case demonstrates several characteristic aspects of TB. First, the patient had been diagnosed with a positive PPD test many years earlier but did not know what medicine he was given. He may well have received inadequate drugs or inad-

See also p 241.

CME available online at www.jamaarchivescme.com and questions on p 299.

Author Affiliations: Veterans Affairs Medical Center and George Washington University, Washington, DC (Dr Gordin); and Critical Care Medicine Department, National Institutes of Health Clinical Center, Bethesda, Maryland (Dr Masur).
Corresponding Author: Henry Masur, MD, National Institutes of Health Clinical Center, 10 Center Dr, Room 2C145, Bethesda, MD 20892 (hmasur@nih.gov).
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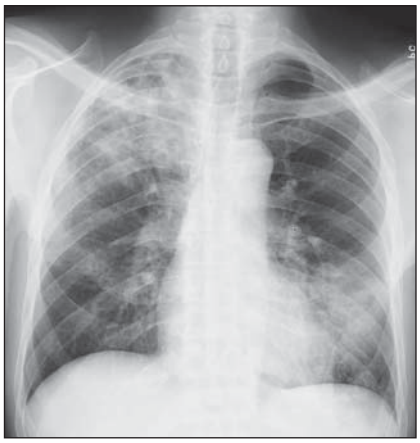
equate duration of therapy for whatever form of TB he had at that juncture. Whether the current infection was reactivation of his old latent infection or a recent infection could not be determined. Second, on initial evaluation he was thought to have community-acquired pneumonia, thus delaying initiation of appropriate therapy and respiratory isolation. In the United States, a substantial number of TB outbreaks are related to lack of clinician suspicion of TB when patients present with apparent community-acquired pneumonia.[1] Third, the patient had difficulty tolerating his medications as demonstrated by abnormal liver function tests, resulting in the need to stop and start various drugs. In addition, as for most patients, the time from when he first was diagnosed to completion of therapy required 6 months of directly observed therapy, thus using substantial resources from the health care system.

Figure 1. Case Patient's Chest Radiograph at Time of Admission



Admission chest radiograph showing bilateral lung infiltrates with prominence in the right upper lobe and lingula of the left lung.

BACKGROUND

Tuberculosis is a major problem worldwide: 2.2 billion persons, representing a third of the world's population, have latent TB; 9 million persons develop active TB annually; and 1.4 million persons die of TB each year.[2] Thus, in many parts of the world, TB is a major consideration diagnostically for a myriad of clinical syndromes, and laboratories and pharmacies need to be prepared to deal with large volumes of patients with TB.

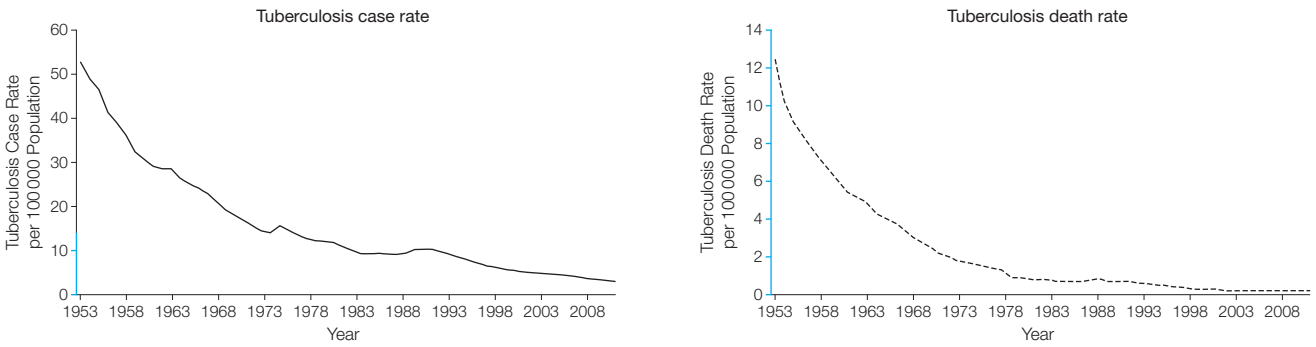
Fewer and fewer clinicians in the United States have experience managing active TB. The decline in cases of TB in the United States over this century has been impressive.[3,4] Even in 1953, when the Centers for Disease Control and Prevention (CDC) began publishing cumulative annual data on cases and deaths, there were more than 80 000 cases of TB annually in the United States, and more than 20 000 deaths (FIGURE 2 and eTable; available at http://www.jama.com). However, in 2010, there were only 11 182 cases of TB in the United States and only 547 deaths, a substantial decrease.[7,8] Moreover, only 11 million persons had latent TB in the United States (3.2% of the population) compared with 33% of the world population, as noted above.[9] Thus, the burden of TB in this country is a small fraction of the challenge that this disease presents in much of Asia, Africa, Eastern Europe, and Latin America.

After many years of disappointing progress in developing new diagnostic, therapeutic, and preventive approaches, the past decade has seen a resurgence in investment in TB research that has produced important new strategic approaches to management. This Grand Rounds will focus on the role that these advances are having in changing the approach to TB in a low endemic country, the United States.

Epidemiology

Tuberculosis is acquired by the inhalation of aerosol droplets, which can remain suspended in the air for 30 minutes after spread by a person with active pulmonary TB.[10-13] These aerosols can travel long distances in ventilation systems and drafts. The likelihood of spread depends on the intensity and duration of patient exposure to infected aerosols and the location of exposure since ultraviolet rays outside, for example, inactivate mycobacteria. If the index case is smear positive, approximately 50% of household contacts will convert their tuberculin skin tests from negative to positive, although if the index case is smear negative (and thus has a lower organism burden), approximately 5% of household contacts become infected.[14] In the United States, very few cases are transmitted in health care settings due to the paucity of hospitalized cases and hospital attention to infection control.

Figure 2. Tuberculosis Active Case and Death Rates per 100 000 Population in the United States, 1953-2011



Based on data from the US Centers for Disease Control and Prevention.[5,6] Y-axis shown in blue indicates range in rate from 0 to 14 per 100 000 population.

In the United States, TB prevention programs focus on (1) identifying latent TB in high-risk groups, (2) tracing contacts of patients with active TB, and (3) respiratory isolation of infectious patients in high-risk environments such as health care facilities. Such programs clearly depend on adequate funding for public health infrastructure and health care epidemiology programs. This funding is often imperiled when public health budgets are strained; reduction in this funding has been shown to be associated with resurgence of cases in numerous situations historically.

Table 1. Regimens for Treatment of Latent Tuberculosis Infection

Drug	Dose, mg	Frequency	Duration
Preferred regimen options			
Isoniazid	300	Daily	9 mo
Isoniazid	900	Twice weekly	9 mo by DOT
Isoniazid + rifapentine	900 + 900	Weekly	12 wk by DOT
Alternative regimen options[a]			
Isoniazid	300	Daily	6 mo
Isoniazid	900	Twice weekly	6 mo by DOT
Rifampin	600	Daily	4 mo

Abbreviation: DOT, directly observed therapy or treatment.
[a]These regimens are less effective than the preferred regimens.

Latent TB

In the United States, there are approximately 11 million cases of latent TB—these latent cases are responsible for 80% of the active disease in this country (ie, only 20% of active cases occur due to recent contact with an active case).[15,16] The patients most likely to have latent TB include immigrants from countries with endemic disease, elderly individuals who were alive when TB was more common in the United States, and those recently exposed to active disease. The patients most likely to progress from latent to active disease are those who have been most recently infected, persons with fibrotic changes on chest radiograph consistent with TB, and those who have impaired immunity. The CDC emphasizes the importance of focusing screening on those patients most likely to have been exposed and those patients most likely to progress if they have latent TB.

After exposure and infection, 5% to 10% of individuals who are immunologically normal develop TB during their lifetime, but 54% of the active cases develop in the first year after infection and 78% develop active disease within the first 2 years.[14] In contrast, for individuals infected with HIV, 8% to 10% develop active TB per year after acquiring infection, in comparison with 5% to 10% lifetime risk for immunologically normal individuals.[17] Thus, their cumulative lifetime risk is extraordinarily high unless their immunity is improved with antiretroviral therapy. Even with such reconstitution, however, their lifetime risk is still substantial compared with the HIV-negative, otherwise healthy population. In many regions of the world, HIV is a major cofactor in the pathogenesis of TB. Conversely, TB is the major cause of death for patients with HIV infection globally. Worldwide, including the United States, all patients with TB should be tested for HIV infection.

Latent TB has traditionally been diagnosed by the PPD skin test. There can be lot-to-lot variation in the potency of the PPD, health care professionals may be imprecise regarding the accuracy of test administration or evaluation, and patients may not return to the clinic to have their results documented. There has been great interest in developing a blood test to diagnose latent TB.[18,19] In 2010, the CDC issued updated guidelines for using a blood test, the interferon-γ–release assay (IGRA).[20] There are 2 commercially available IGRA assays. This test is being used by some health care facilities in preference to the PPD because test results can be obtained after only 1 patient visit. However, this test is more expensive than the PPD in terms of assay acquisition and laboratory processing cost, and it requires transport to the laboratory usually within less than a day. The IGRA has comparable sensitivity and specificity to the PPD in immunocompetent individuals. The IGRA has an additional advantage because it is more specific than skin testing for *M tuberculosis* as opposed to other nontuberculous mycobacterial species. Current assays target early secretory antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10), which are not present in bacille Calmette-Guérin or in most commonly encountered atypical mycobacteria. However, *Mycobacterium kansasii* and *Mycobacterium marinum* do cross-react with IGRA since they encode for ESAT-6 and CFP-10.

Performing both screening tests is not recommended, because there are no convincing data on how to interpret discordant results. Neither test performs well in heavily immunosuppressed populations. Thus, clinicians and health care organizations could choose either test with equal validity, depending on their specific needs and requirements.

Treatment of Latent TB

Isoniazid was first recommended for general use in 1965,[15] and has been the most commonly used agent for treatment of latent TB infection (Table 1). Although inexpensive and highly effective when properly used, isoniazid regimens have significant drawbacks in length of treatment and toxicities. Isoniazid needs to be taken for 9 months to be maximally effective. A 6-month regimen is considered acceptable but is 10% to 20% less effective than a 9-month regimen.[15] Some health departments use 6-month regimens due to financial constraints. Only 30% to 65% of patients complete their recommended regimen in many settings.[21,22] For the case presented in this Grand Rounds, one can only speculate as to whether, if this TB represented reactivated disease, the reactivation developed due to poor adher-

ence to his prophylactic regimen several decades earlier, or whether reactivated disease developed because the prescribed duration of the regimen was shorter than recommended.

The overall rate of hepatotoxicity from isoniazid is approximately 1%, but is 2% or higher in older populations and persons with preexisting liver disease.[23] Rash and peripheral neuropathies also occur. Isoniazid had to be discontinued in 3.7% of patients in a recent study[24] and discontinuation rates appear to be higher in clinical practice.

A 4-month regimen of rifampin used alone has also been endorsed as treatment for latent TB infection (Table 1).[15] Rifampin is predominately used in persons exposed to isoniazid-resistant TB or in persons unable to tolerate isoniazid. Rifampin has not been as well studied as isoniazid, and drug interactions are special problems with rifampin and drugs metabolized by common hepatic enzyme pathways.

Rifapentine is a long-acting rifamycin with excellent activity against TB in vitro, in animal models, and in human trials.[25-28] A large study of 1148 persons infected with HIV in South Africa demonstrated once-weekly rifapentine plus isoniazid to be similar in efficacy to daily regimens of isoniazid alone or twice-weekly isoniazid plus rifampin.[29]

This regimen of rifapentine plus isoniazid has also been assessed in another large study. The CDC TB Trials Consortium enrolled more than 8000 persons with skin-test positive PPD considered at high risk for development of active TB in the United States, Canada, Spain, and Brazil.[23] Patients were randomized either to 12 once-weekly doses of rifapentine plus isoniazid, given by directly observed therapy, or to 9 months of isoniazid, given daily and self-administered. The rates of development of active TB were quite low in both groups (0.16 per patient year in the isoniazid group vs 0.07 in the rifapentine plus isoniazid group), showing both regimens to be highly effective. Completion rates, however, were much higher in the 12-week combination regimen (82%) compared with the 9-month isoniazid-only regimen (69%). Rifapentine plus isoniazid was associated with a lower rate of drug-related hepatotoxicity (0.4%) compared with isoniazid alone (2.7%).

Based on these clinical studies, the CDC has recently endorsed the rifapentine-isoniazid regimen, which consists of only 12 once-weekly doses of isoniazid and rifapentine for the treatment of latent TB infection.[30] This regimen has only been proven effective when administered by direct observation and to patients who were predominantly not infected with HIV. None of the listed regimens in Table 1 should be used for persons exposed to multidrug resistant (isoniazid and rifampin-resistant) TB. For those patients with multidrug resistant TB, although microbiologically plausible regimens can be constructed, there are no regimens proven to be effective.

A 12-week regimen for latent TB infection, which includes only 12 doses of each drug, is a major advance in the armamentarium. Even shorter (4- to 6-week) regimens are needed to further enhance successful completion.

Active Disease

In the United States in 2009, there were fewer than 5000 cases of TB among US-born individuals.[7,8] Since 2001, the number of cases of TB among foreign-born individuals has exceeded the number of cases among US-born individuals. All major race and ethnic groups in the United States are included among those that acquired the disease domestically—42% were black, 32% were white, and 19% were Hispanic or Latino. The rates in the United States are decreasing in each of these groups. Rates are highest among those aged 65 years or older, although there are more absolute number of cases among those within the age ranges of 25 to 44 years and 45 to 64 years. Asian persons aged 65 years or older have the highest rate in this country. Geographically, 11 states (California, Nevada, Texas, Florida, Louisiana, Alabama, Georgia, New York, New Jersey, Alaska, Hawaii) plus the District of Columbia are above the national average rate. Most cases of TB among foreign-born persons involve persons originating from Mexico, Philippines, India, Vietnam, or China, and interestingly, more than half of these cases develop TB after being in the United States for more than 5 years, presumably due to reactivation in most cases. A variety of comorbid conditions predispose to active disease. The patient presented herein had diabetes mellitus, which is a known risk factor; other risk factors include advanced age, immunosuppression, end-stage renal disease, substance abuse, malnutrition, gastric surgery, and silicosis.

In many parts of the world, the incidence of TB has been augmented by the HIV epidemic, which enhances the likelihood that TB infection will result in active disease. Although the HIV epidemic appeared to be responsible for an upward spike in cases in the United States between 1985 and 1992, the trend in coinfected patients since then has been downward, and currently less than 10% of US cases of TB are coinfected with HIV.[8]

Tuberculosis should be considered as a potential cause for any case of pulmonary disease even in patients not infected with HIV. Patients can easily be assumed to have "community-acquired pneumonia," as in the case presented in this Grand Rounds, with no consideration given to TB, leading to unnecessary delays in appropriate therapy and unnecessary exposure of patients, staff, and those in routine day-to-day contact with the patient should TB in fact be the causative agent. Patients with HIV infection, in particular, have presentations that are atypical for TB—clinicians need to assiduously rule out TB when patients infected with HIV present with pulmonary manifestations.

There has been considerable focus in the media about drug-resistant TB. Although organisms resistant to both isoniazid and rifampin (multidrug-resistant TB) are a huge problem globally, with an estimated 440 000 cases (4.3% of all cases), there were only 88 cases of primary multidrug-resistant TB in the United States in 2009, and only 1 primary case of ex-

tensively resistant TB (resistant to isoniazid and rifampin plus a quinolone plus an injectable second-line drug such as amikacin).[8,31,32] Primary and secondary drug resistance (ie, resistance that is recognized at the time of initial presentation and resistance that occurs after a therapeutic trial is attempted) is not common in the United States, because patients have a high rate of completing therapy within the 12 months after diagnosis. In fact, 72 of 88 cases (82%) of primary multidrug-resistant TB in 2009 occurred in foreign-born persons.[31] Secondary resistance to drugs (ie, resistance developing after therapy is initiated, usually due to poor adherence) is more common than primary resistance in the United States. However, any decrease in support for public health and clinical infrastructure could quickly undermine these successes.

Table 2. Regimens for Treatment of Drug-Susceptible Pulmonary Tuberculosis[a]

Drug Regimen Options	Dosing Frequency
Initial Phase (First 2 mo)	
Isoniazid + rifampin + pyrazinamide + ethambutol	Daily or twice weekly or thrice weekly
Continuation Phase (Final 4 mo)[b]	
Isoniazid + rifampin	Twice weekly or thrice weekly
Isoniazid + rifapentine	Weekly

[a] All therapy should be given by direct observation. Persons infected with human immunodeficiency virus (HIV) with less than 100 CD4 cells need daily or thrice-weekly dosing. Individuals not infected with HIV may take twice-weekly dosing. Rifapentine should not be used in persons with HIV infection, persons who have a cavitary in chest radiograph at baseline, or persons who are smear positive after 2 months of treatment. Total duration of treatment may be decreased to 4 months for persons with culture-negative tuberculosis. Total duration of treatment should be extended to 9 months for persons with a cavitary on initial chest radiograph and remain culture positive after 2 months of treatment.
[b] The 2 continuation drug regimens are prescribed as either isoniazid + rifampin or isoniazid + rifapentineone and not both.

Diagnosis of Active Disease

In 1883, the Ziehl-Neelsen stain was developed to identify mycobacteria in respiratory specimens, and in 1932, the Lowenstein-Jensen culture medium was developed to grow TB in vitro. For much of the 20th century, laboratories throughout the United States relied on these laborious, suboptimally sensitive but highly specific techniques. The sensitivity and specificity of Ziehl-Neelsen staining was dependent on the expertise of the microscopist and the time the microscopist could devote to examining 1 or more specimens. Most laboratories reported that only approximately 10% to 30% of culture-positive specimens were detected by light microscopy, with somewhat higher yields (30%-60%) reported with fluorescent microscopy, which was more efficient for scanning specimens. Culture required 4 to 6 weeks to become positive. The development of automated liquid culture systems, such as a fluorescent TB testing system, allowed for more rapid results for both detection and susceptibility testing; culture test results were usually available within about 3 weeks and then subsequent drug susceptibility testing required another 3 weeks.

With the introduction of molecular techniques into microbiology, the detection of TB in respiratory specimens, and the determination of drug susceptibility have become much faster and more accessible.[33,34] Several commercial nucleic acid amplification tests have become available that can detect TB within hours of the time the laboratory initiates the molecular testing on a patient specimen such as sputum. These tests have high sensitivity—95% for smear-positive specimens and 50% to 80% for smear-negative specimens when 1 sample is tested—and they have almost 100% specificity.[35,36]

In 2009, the CDC issued a formal recommendation that nucleic acid amplification testing should be performed on at least 1 respiratory specimen when patients have a pulmonary syndrome suggestive of TB.[37] Most laboratories have constraints that make it impractical to perform testing at the time of specimen acquisition, rather than batching once per day or several times per week, or sending specimens to an outside laboratory for testing. However, tests are now commercially available that could be used at individual hospital laboratories, or at point of care at the time that each specimen is acquired, presuming that the resources were available for the equipment, space, safety devices, disposable reagents, and labor. Some of these systems (eg, GeneXpert, Cepheid) are self-contained and are currently being used outside the United States in highly endemic areas—safe processing requires that individual specimens be processed in a biosafety hood, after which they are introduced into a cassette, and then placed in the machine with results for organism detection and rifampin-susceptibility being reliably produced within 2 hours.[33,34] In such settings, these devices have high sensitivity (99% for smear-positive and 80% for smear-negative samples) and specificity (close to 100%). These systems need to be validated in low endemic areas such as the United States, where many laboratories identify far more nontuberculous mycobacteria (eg, *Mycobacterium avium* complex and *Mycobacterium fortuitum*) than TB.

In a region like the United States where atypical mycobacterial isolates are more common than *M tuberculosis* complex, rapid diagnostic tests would be useful that could confirm the presence of either atypical mycobacteria or *M tuberculosis* complex in a direct patient sample or in a culture. Molecular and mass spectroscopy techniques are becoming available that can provide such information that would inform early decisions about patient transmissibility and about empirical therapy.[38,39]

Treatment of Active TB

Since the 6-month "short-course" regimen was first introduced in 1990 (TABLE 2), the standard 4-drug therapy for active pulmonary TB has undergone only minor changes.[26] Most patients with drug-susceptible pulmonary TB can be successfully treated with a 6-month regimen of isoniazid, rifampin, ethambutol, and pyrazinamide for the initial 2 months, followed up by isoniazid and rifampin for the final 4-month "consolidation" phase. To

Table 3. Drugs in Development for Treatment of Tuberculosis

Drugs	Human Tuberculosis Studies
Available	
Moxifloxacin	Phase 3
Gatifloxacin	Phase 3
Higher doses of rifapentine	Phase 2
Linezolid	Phase 2
Not yet available	
Delamanid (OPC-67683)	Phase 3
Bedaquiline (TM-207)	Phase 2
PA-824	Phase 2
SQ-109	Phase 2
PNU-100480	Phase 2

maximize efficacy and minimize any development of drug resistance, all treatment should be given under direct observation.[26] For persons with cavitary pulmonary disease who remain smear positive at 2 months, total duration of treatment should be lengthened to 9 months. For patients with culture-negative pulmonary TB (often diagnosed empirically or epidemiologically), total duration of treatment may be shortened to 4 months. For patients with extrapulmonary TB, the duration of therapy must often be greater than 6 months (eg, spinal TB and meningeal TB).

In treating active TB in persons infected with HIV with less than 100 CD4 cells, it is important to provide treatment on a daily or thrice-weekly schedule to avoid the occurrence of rifampin-resistant TB.[26] Timing of the initiation of antiretroviral treatment is another important consideration. Recent data from controlled trials suggest that for persons infected with HIV with very advanced immunosuppression (<50 CD4 cells), antiretroviral treatment should be initiated within 2 to 4 weeks of beginning TB treatment.[40-42] For persons infected with HIV with more than 200 CD4 cells, and for patients with meningeal or perhaps pericardial disease, antiretroviral treatment is often delayed until week 8 of TB treatment or even later.[43]

Another modification to the 6-month regimen has been the substitution of rifapentine for rifampin, allowing for once-weekly dosing during the final 4 months of treatment.[25,26] Rifapentine has the advantage of a half-life longer than rifampin, allowing for less frequent administration. Patients who should not be treated with once-weekly rifapentine are those who are HIV positive, or who are smear positive at 2 months, or who had cavitary TB on initial chest radiograph.

The current 6-month multidrug regimen containing isoniazid to treat active TB is not ideal. First, it is too long for sufficient adherence—in the United States, only 85% of patients complete the 6-month regimen within 12 months.[8] Second, the 6-month regimen has a high rate of adverse effects. In 1 study,[44] more than 10% of patients experienced at least 1 serious adverse event related to their TB drugs. Third, the dependence on rifamycins results in many potential drug interactions, especially in persons coinfected with HIV. Moreover, the current regimen is not effective for persons with rifampin-resistant or multidrug-resistant disease.

Substantial resources are now engaged worldwide in the development of new regimens to treat active TB using currently approved drugs as well as investigational agents (**Table 3**).[45-47] Quinolone-containing regimens have been shown in murine models to reduce the duration of treatment needed for a successful microbiologic cure.[48] Clinical trials in humans, however, have had mixed results.[49-51] One phase 2 study in Brazil demonstrated more rapid 2-month conversion of sputum cultures to negative in patients receiving moxifloxacin compared with ethambutol.[50] These results were not confirmed in 2 multinational studies in which moxifloxacin was substituted for either ethambutol[49] or isoniazid.[51] There are currently 2 phase 3 clinical trials of quinolones ongoing that will help clarify the role of quinolones in shortening the duration of treatment for active TB.

Higher exposure to rifamycins is also being evaluated as a means to shorten the duration of treatment. Dose-ranging studies of rifapentine are currently in progress, aiming to select the optimum dose for trial in larger, phase 3 treatment-shortening studies.[25,52] Another agent is bedaquiline (TM-207), which has already demonstrated activity in persons with multidrug-resistant disease.[53]

CONCLUSIONS

The rates of active and latent TB are low and continue to decline in the United States despite the tremendous worldwide burden of TB. Cases domestically are largely driven by the reactivation of latent TB, and more than half of active TB occurs in persons born outside the United States. Although HIV is a major cofactor driving the TB epidemic globally, fewer than 10% of cases domestically are linked to HIV infection. The laboratory detection of latent and active TB has changed dramatically during the past decade. New therapies for latent TB infection and active disease are emerging. The recent investment in new diagnostics and therapeutics and aggressive investment in public health interventions have the potential to transform the tools for dealing with TB used by health care professionals in the United States and have the prospect for having profound impact globally on the success of TB control.

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Study concept and design, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content: Gordin, Masur.
Acquisition of data, administrative, technical, or material support, and study supervision: Masur.
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