TABLE 249.8 First-Line Tuberculosis Medications[a]—cont'd

DRUG DOSE (MAXIMUM)	MAJOR ADVERSE REACTIONS	RECOMMENDED MONITORING	DOSAGE FORMS	COMMENTS
Rifapentine (RPT)				
Once weekly only C: Not approved for use in children A: 10 mg/kg (600 mg) *(Data indicate that 900 mg of RPT is well tolerated and CDC is recommending this higher dose for latent tuberculosis when given once weekly with INH.)*	Hepatitis, thrombocytopenia, neutropenia, leukopenia, hyperuricemia, flulike syndrome Reduces levels of many drugs, including methadone, warfarin (Coumadin), birth control pills, theophylline, dapsone, ketoconazole, PIs, and NNRTIs Orange discoloration of secretions (sputum, urine, sweat, tears) and may permanently stain soft contact lenses	Baseline hepatic enzymes, CBC, and platelets. Repeat if baseline values are abnormal, risk factors for hepatitis are present, or there are symptoms of adverse reactions	*Tablets (film-coated):* 150 mg *Indications:* Pulmonary TB patients who are HIV negative, noncavitary, not pregnant, with organisms pan-sensitive and culture negative at 2 months (two consecutive negative cultures) Administered once weekly with INH during the continuation phase of treatment.	See drug interactions with rifampin.

[a]Combination drugs are recommended in the rare instance in which a patient is placed on self-administered therapy: IsonaRif contains INH, 150 mg, RIF, 300 mg; Rifamate contains INH, 150 mg, RIF, 300 mg; Rifater contains INH, 50 mg, RIF, 120 mg, and PZA, 300 mg.
[b]In 2003, the CDC recommended dosing based on weight ranges for PZA and EMB. After reviewing available data, the Maryland TB Expert panel recommended that the previously recommended dosage ranges be used, advising use of the lowest possible dose in the dose range.
A, Adult; *C,* child; *CBC,* complete blood cell count; *CDC,* Centers for Disease Control and Prevention, *CNS,* central nervous system; *GI,* gastrointestinal; *HIV,* human immunodeficiency virus; *NNRTIs,* nonnucleoside reverse-transcriptase inhibitors; *PIs,* protease inhibitors.
Modified from the 2007 Maryland Guidelines for Prevention and Treatment of Tuberculosis. http://phpa.dhmh.maryland.gov/OIDPCS/CTBCP/CTBCPDocuments/tbguidelines.pdf.

cost-effective, especially when considering the cost of MDR-TB cases that are prevented.[292] Because all doses are observed, compliance is improved and the likelihood of emergence of resistance minimized. The ability of mandatory DOT to control drug resistance in a community is well established.[293,294] In some cases, recalcitrant patients must be detained for completion of therapy.

Regimens of Less Than 6 Months for Minimal Disease

Extent of disease can be quantified by the mycobacterial content of sputum, with smear- and culture-positive sputum representing most severe disease, smear-negative and culture-positive sputum representing intermediate disease, and smear- and culture-negative sputum representing the least amount of disease. The possibility that the early bactericidal activity of moxifloxacin or gatifloxacin in combinations might permit 4-month regimens in smear-positive, culture-positive cases has, to date, not been confirmed (see "Fluoroquinolones").[247,257,260] Good results have been obtained with as little as 4 months of therapy in patients with less extensive TB.[295] A 4-month course of treatment (2 months of INH, RIF, PZA, and EMB followed by 2 months of INH and RIF) is recommended for HIV-seronegative persons with smear-negative, culture-negative pulmonary TB.[239] In HIV-seropositive persons with culture-negative TB, a 6-month regimen is recommended.

Fixed-Dose Combination Tablets

Fixed-dose preparations are available; these contain 150 mg of INH and 300 mg of RIF (Rifamate); INH 50 mg, RIF 120 mg, and PZA 300 mg (Rifater); or INH 75 mg, RIF 150 mg, PZA 400 mg, and EMB 275 mg (Rifafour). These prevent the patient from omitting drugs and taking monotherapy and therefore decrease the risk for resistance. Fixed-dose combinations are particularly useful when DOT cannot be provided.

Treatment of Multidrug-Resistant Tuberculosis

Surprisingly, studies of four-drug, 6-month chemotherapy demonstrated that initial INH or STM resistance did not compromise outcome, but results were very poor (>50% lack of conversion or relapse) when initial RIF resistance was present.[291] In a meta-analysis, treatment failure and relapse were substantially higher in the presence of initial drug resistance.[296] A critical component in combatting the development of extensively resistant strains in patients with MDR-TB is access to effective second-line agents, with increased sputum culture, susceptibility testing, and genotypic data. In 832 patients with MDR disease followed by the Green Light Committee (GLC), the mandate of which is to facilitate increased access to these interventions in middle- and low-income countries, 8.9% without baseline resistance to second-line agents still acquired XDR disease, and as baseline drug resistance increased, the risk of new cases with acquired XDR TB increased also. There was less resistance acquired during treatment in GLC-approved sites.[297] Additional data from the United States support the need for increased monitoring for treatment failure associated with the acquisition of resistance to second-line drugs, with mortality significantly higher (26.5% vs. 10.0%) in patients with acquisition of resistance versus control patients.[298] Acquisition of resistance may impart greater risk than baseline resistance to the same drugs.[299] It is important to note retrospective results from the Russian Federation, where an "aggressive" regimen of at least five likely effective drugs was associated with a decreased risk of death and failure during MDR-TB treatment.[300]

For therapy for TB that is resistant to both INH and RIF, susceptibility testing for second-line drugs should be performed and treatment individualized according to the susceptibility test results. Support for this recommendation has been provided in a meta-analysis of studies including almost 9000 patients, in whom susceptibility testing for EMB, PZA, and second-line agents was associated with higher odds of treatment success.[301] In some settings, standardized second-line regimens are used. If a suboptimal regimen is prescribed, resistance to additional drugs may emerge and the opportunity for success may be lost. In a study from Denver, Colorado, only one-half of 171 HIV-negative patients with MDR-TB ever converted sputum cultures to negative despite prolonged administration of carefully selected regimens (not including fluoroquinolones).[302] In a follow-up study from the same institution, the long-term success rate was 75%.[303] In a study from Latvia, 66% of MDR-TB patients completed therapy or were cured.[304] In contrast, two smaller studies among HIV-seronegative patients from New York City and San Francisco noted remission in virtually all evaluable HIV-negative patients treated for MDR-TB.[305,306] A study from Bangladesh found that at least 9 months of gatifloxacin, clofazimine, EMB, and PZA, supplemented with prothionamide, kanamycin, and high-dose INH during an initial intensive phase of at least 4 months, resulted in an 88% relapse-free cure rate.[272] Recent preliminary results of the STREAM trial, in which the "Bangladesh" regimen was compared with standard therapy, demonstrated similar effectiveness of the 9-month regimen, although noninferiority was not demonstrated.[307] A randomized trial of the addition of clofazimine to "individual-based" drug regimens in China found a significant increase in treatment success in the clofazimine

group versus the control group (74% vs. 54%; $P = .035$).[308] In a CDC report, 38% of MDR isolates were resistant to PZA, so the role of PZA may be limited in MDR-TB.[309] For TB that is INH and RIF resistant but fluoroquinolone susceptible, a fluoroquinolone should always be administered along with other drugs to which the organism is susceptible. In this setting, 2-month sputum culture conversion rates are improved by adding bedaquiline.[262] The risk for treatment failure is increased if the *M. tuberculosis* isolate is also resistant to fluoroquinolones.[310,311] Levofloxacin may be preferred over ofloxacin, but moxifloxacin has the greatest in vitro activity against *M. tuberculosis*. Companion drugs may include aminoglycosides (STM, kanamycin, or amikacin) or capreomycin, ethionamide, and cycloserine.[305,312–315] The injectable agents are particularly important for good outcomes, although nephrotoxicity and ototoxicity are concerns. The uncertain efficacy of newer therapies is underlined by the report of the development of resistance to bedaquiline and delamanid during treatment of MDR-TB.[316] In a small observational study of imipenem/clavulanate added to an optimized background regimen, either indifferent or worse outcomes were noted, suggesting that adding imipenem-clavulanate in the setting of treatment failure was not likely to improve outcome.[317]

Therapy for Extensively Drug-Resistant Tuberculosis

Therapy for XDR-TB, which is defined as resistance to INH, RIF, any fluoroquinolone, and at least one of three injectable second-line drugs (amikacin, kanamycin, or capreomycin),[112] is difficult and usually associated with poor outcomes. The risk for treatment failure and death has been higher than in patients with MDR-TB in some series,[318,319] but not all.[320] Cure rate in a report from South Africa was 5%, and mortality was 78% at 60 months.[321] Treatment with at least five drugs to which the organism is susceptible is recommended. In a study of 41 patients with treatment-refractory XDR-TB, linezolid was associated with sputum culture conversion, but 82% of patients had clinically significant adverse events attributable to linezolid.[322] The cure rate 1 year after the end of treatment was 78%.[323] A similar trial in China also found a significantly higher cure rate (70% vs. 34% in the control group), but again with an adverse event rate in the linezolid group of 82%.[324] A retrospective report in a predominantly HIV-infected South African population noted improved culture conversion with clofazimine (40% vs. 29% in the comparator group), with only minor adverse effects.[325]

Course of Therapy and Duration of Observation

At least three sputum samples should be submitted for smear and culture before beginning treatment. If available, specimens for GeneXpert should also be obtained. In patients with presumed TB, treatment should be initiated immediately; a few days of antituberculous treatment will not interfere with bacteriologic diagnosis. If cultures are negative and there are no alternative diagnoses, clinical and radiographic response to therapy after 2 months of treatment is consistent with a diagnosis of TB. Beginning 1 month after initiation of therapy, three sputum cultures should be obtained monthly to monitor conversion to negative or, if sputum cultures remain positive, to detect treatment failure and the possible emergence of drug resistance. Sputum cultures should convert to negative within 2 months. In a minority of patients, sputum smears remain positive after cultures turn negative. Sporadic positive smears for long periods presumably represent inactive bacilli released from caseous foci. When cultures remain positive after 4 months of treatment, it is considered treatment failure. Causes of treatment failure include drug resistance, noncompliance with therapy, and malabsorption of antituberculosis drugs. Sensitivity testing should be performed and consideration given to adding at least two new drugs to which the organism was sensitive at the outset of treatment, at least until sensitivities are known. Addition of only one drug risks development of resistance to the added drug. Adherence to therapy should be ensured and serum drug levels considered to assess absorption.

Patients receiving INH, RIF, and PZA should be asked monthly about symptoms of hepatitis, and hepatic aminotransferase levels should be checked in symptomatic persons. In persons with abnormal hepatic aminotransferase levels at baseline, such laboratory findings should be monitored regularly, particularly early in the course of therapy. Patients receiving EMB should be regularly questioned regarding visual symptoms; their visual acuity should be measured (Snellen chart) and red-green color discrimination assessed monthly. Patients receiving STM should be examined for balance and high-frequency hearing loss, and their renal function should be monitored closely.

Relapse after adequate treatment of drug-sensitive infections is infrequent (2%–5%). Prolonged follow-up of appropriately treated patients is not necessary except in the case of unusually extensive disease, slow bacteriologic response to treatment, suspicion of poor compliance, drug-resistant disease, or high-risk patients with intercurrent diseases. In high-incidence settings, an additional 12 months of INH after completion of a 6-month RIF-containing regimen reduces the TB recurrence rate among HIV-infected adults.[326,327] However, such a practice is often not performed owing to logistical constraints.

Retreatment

Recurrent TB may be due to either relapse (same *M. tuberculosis* strain as the original episode) or reinfection (different *M. tuberculosis* strain). Genotyping (RFLP, MIRU, and spoligotyping) or WGS may be used to distinguish *M. tuberculosis* isolates. Clinical judgment based on experience is critical in re-treatment cases, and testing of susceptibility to first- and second-line drugs is required.[239] Some generalizations concerning re-treatment can be made:

1. In a patient with drug-susceptible TB who receives rifamycin-based DOT, relapse is likely due to a drug-susceptible organism. Such patients usually respond again to the initial regimen.
2. If compliance has been irregular, particularly if the patient has not received DOT, resistant organisms will probably be present.
3. When drug resistance is suspected, the treatment regimen should include INH, RIF, PZA, EMB, a fluoroquinolone, and an injectable agent (e.g., capreomycin), pending susceptibility results.
4. Capreomycin or amikacin can replace STM. Kanamycin is less effective and more toxic and is used as a last resort. There is usually no cross-resistance between capreomycin and STM, amikacin, or kanamycin, but amikacin and kanamycin are usually cross-resistant.
5. TB resistant to INH and RIF (i.e., MDR-TB) should be treated with a fluoroquinolone, ethionamide (or protionamide), PZA, and probably an injectable agent plus either cycloserine or PAS. The intensive phase of treatment is for 8 months, and the total treatment duration is 20 months.[314,315,328] For those who meet the criteria, the 9-month short-course regimen should be considered.[315]
6. TB resistant to INH, RIF, an injectable agent, and a fluoroquinolone (i.e., XDR-TB) should be treated with at least four second-line antituberculosis drugs likely to be effective, in addition to PZA during the intensive phase of treatment.[315,320] Surgical resection may be required. A prolonged course of treatment is necessary, but the optimal duration is unknown.

Other Forms of Treatment

Bed rest does not influence outcome when effective chemotherapy is given. Resection still has a role in the salvage of patients in whom treatment fails and who have localized, resectable disease, and extensive drug resistance.

Corticosteroids

Corticosteroids in conjunction with antituberculosis therapy improve neurologic outcome and mortality in persons with tuberculous meningitis. Use of corticosteroids is therefore recommended in this situation. For all other clinical manifestations of TB, however, there is no definite long-term benefit of adjunctive corticosteroids and therefore no therapeutic role.[329]

Treatment of Tuberculosis in HIV-Infected Patients

The treatment of HIV-related TB is complicated by major drug-drug interactions between antituberculosis drugs and ART. These interactions

affect the choice of therapy (and appropriate doses) for both diseases. Invaluable websites that provide extensive advice and information regarding treatment options for HIV-related TB, including managing and avoiding drug-drug interactions, are maintained by the Department of Health and Human Services[245] and the CDC.[330] These websites are updated regularly and should be consulted routinely because new antiretroviral agents and interactions are being discovered. Chapter 39 includes tables from the CDC website about use of antiretroviral agents together with RIF or rifabutin.

The rifamycins interact with many HIV-1 protease inhibitors, nonnucleoside reverse transcriptase inhibitors, and integrase strand transfer inhibitors.[245] Among the rifamycins, RIF has the most interactions; rifapentine appears to have a similar effect,[331] but rifabutin has less profound interactions. RIF is contraindicated for use with HIV-1 protease inhibitors (e.g., saquinavir, indinavir, nelfinavir, fosamprenavir, atazanavir, darunavir, tipranavir) and the nonnucleoside reverse-transcriptase inhibitors etravirine and rilpivirine. RIF also lowers nevirapine levels, so there are concerns that these two drugs should not be given in combination.[245] Maraviroc can be used with RIF if the maraviroc dose is increased to 600 mg twice daily. The RIF pharmacokinetic interaction with saquinavir-ritonavir and lopinavir-ritonavir may be overcome with increased protease inhibitor dosages.[332,333] However, several healthy volunteer studies were prematurely terminated when individuals receiving RIF promptly developed marked hepatotoxicity with addition of ritonavir-boosted lopinavir,[332] saquinavir,[333] or atazanavir.[334] Accordingly, these combinations are generally not used. Rifabutin may be used in combination with protease inhibitors, with appropriate dose modification.[245] Unfortunately, rifabutin is not presently available in most resource-limited countries.

RIF modestly lowers plasma levels of efavirenz and, to a greater extent, nevirapine. However, among patients receiving multidrug regimens for TB, RIF has been shown to paradoxically increase plasma levels of efavirenz, particularly among *CYP2B6* slow metabolizers[335]; NAT2 slow metabolizers of INH may also contribute to increased efavirenz levels.[336] RIF does not appear to affect the antiviral efficacy of efavirenz, and they can be administered concomitantly with the efavirenz dose maintained at 600 mg daily, particularly in persons <60 kg. There are greater concerns about concomitant administration of RIF and nevirapine. Several small studies have demonstrated favorable clinical and virologic responses, but toxicity is greater than when RIF is given with efavirenz.[337] In persons with concurrent TB at the start of ART, failure to achieve virologic suppression was more common in persons who received nevirapine than efavirenz (both given with RIF).[338] RIF lowers raltegravir levels by 40%; the raltegravir dose should be increased to 800 mg twice daily and virologic response followed closely. No dosage adjustments are needed when raltegravir is given with rifabutin. RIF lowers maraviroc levels by 64%. Although it is preferred to not coadminister these drugs, if it is done, the dose of maraviroc should be increased to 600 mg twice daily. Additional interactions and drug dose adjustments are given in Chapter 39.

Despite this extensive list of interactions, it is not recommended that treatment of TB be delayed or that highly active ART be avoided. Because antimycobacterial drugs other than the rifamycins do not have substantial interactions, an alternative regimen with INH, STM, PZA, and EMB can be considered. However, in HIV-infected persons, regimens that are not rifamycin based may be less effective than rifamycin-based regimens.

Acquired rifamycin resistance in the setting of TB relapse is seen almost exclusively in patients with advanced AIDS who receive highly intermittent antituberculosis therapy, such as once-weekly INH plus rifapentine or twice-weekly INH plus rifabutin.[248,339] Additional data suggest that the risk of acquired RIF resistance is also increased in HIV-infected persons treated with thrice-weekly therapy.[340] It is therefore now recommended that HIV-infected persons should receive daily antituberculosis therapy in both the intensive and continuation phase of TB treatment.[239]

Patients with HIV-related enteropathy may not respond to chemotherapy because of inadequate absorption of oral agents, and, in some cases, pharmacokinetic monitoring may be necessary.[341]

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) results from rapid restoration of immune responses to opportunistic pathogens, most importantly *M. tuberculosis*. This has most often been described in patients receiving ART. It has additionally been seen in other immunodeficiencies, as in a report of a severe inflammatory reaction that occurred during therapy of disseminated TB in a Thai woman who had anti–interferon-γ antibodies.[342] Characteristic features include initiation of virologically effective ART within the previous 3 weeks (the period of most rapid immune recovery), clinical deterioration with exaggerated inflammation, and absence of an alternative explanation such as drug resistance, drug hypersensitivity, other infections, or lymphoma. TB-associated IRIS comprises two main categories: (1) onset in patients who are already being treated for TB (termed *paradoxical IRIS*) and (2) onset in patients with previously unrecognized, untreated TB (termed *unmasking IRIS*). During paradoxical IRIS, patients have typically been responding to TB therapy but develop recurrent, new, or worsening manifestations, such as fever, cough, lymph node enlargement, or radiographic abnormalities after starting antiretroviral agents.[343,344] Such patients demonstrate robust peripheral blood T-cell responses to PPD and increased proinflammatory cytokines.[345] Paradoxical IRIS is most likely to occur in patients with more advanced AIDS, disseminated and extrapulmonary TB, and a good immunologic and virologic response to antiretroviral agents and in those who initiate antiretroviral agents soon after starting antituberculous drugs.[346,347] Reported frequencies range from 8% to 43%.[346] Although symptoms of paradoxical IRIS are usually self-limited and last a median of 2 months,[348,349] morbidity can be substantial and mortality can occur but is rare. A 4-week course of prednisone improved symptoms and decreased the need for hospitalization in one clinical trial.[350] Paradoxical reactions such as lymph node enlargement or cerebral tuberculomas infrequently affect HIV-negative individuals or HIV-positive individuals not receiving antiretroviral agents. In one study, paradoxical reactions affected 36% of HIV-infected patients receiving therapy for both TB and HIV but only 2% of HIV-negative patients and 7% of HIV-infected patients not on ART.[343] Paradoxical reactions after the initiation of ART tend to be more severe and more likely to involve multiple organs. Paradoxical reactions in previously healthy patients can be confused with uncontrolled infection.

Less is understood about unmasking IRIS. In resource-limited settings, TB is frequently diagnosed during the initial months of ART, but underlying mechanisms vary.[351] Some represent new or progressive TB due to persistent immunodeficiency, some reflect active TB that was present but undiagnosed before ART was started, and others reflect subclinical TB that was truly unmasked by restoration of robust immune responses to *M. tuberculosis*. Consensus case definitions have been published to facilitate research into TB-associated IRIS in resource-limited settings.[346]

The optimal timing of ART initiation in HIV-infected persons with TB has been evaluated in three clinical trials.[352–354] Among persons with fewer than 50 $CD4^+$ T cells/mm^3, initiation of ART within 2 to 4 weeks of starting antituberculosis therapy was associated with improved AIDS-free survival compared with delayed initiation of ART. Among persons with more than 50 $CD4^+$ T cells/mm^3, initiation of ART 8 to 12 weeks after initiation of antituberculosis therapy was associated with a lower risk for IRIS and adverse events without increasing the risk for AIDS or death.[353,354] The most recent TB treatment guidelines recommend the timing of ART initiation in these patient groups according to these findings.[239,288]

Duration of Therapy

The duration of antituberculosis therapy is determined by relapse risk. Several observational studies noted comparable relapse rates in HIV-infected and HIV-uninfected persons after 6 months of rifamycin-based antituberculosis therapy. Based on these data, the current recommendation is to treat for the same duration regardless of HIV status, particularly if the HIV-positive patient is receiving ART.[239,286,288] However, some observational studies have noted higher recurrence rates in HIV-infected than HIV-uninfected persons who receive 6 months of treatment.[355,356] A recent meta-analysis found that ART decreased the risk for TB relapse;

rifamycin-based therapy for 8 months or more and daily administration in the intensive phase were also associated with improved treatment outcomes.[357] In the only clinical trial of 6 versus 9 months of antituberculosis treatment in HIV-infected persons, TB recurrence risk was lower in those who received treatment for 9 months, but mortality rate did not differ; all persons received antituberculosis treatment three times a week, and none received ART.[358] The most recent ATS/CDC/IDSA guidelines recommend extending the duration of antituberculosis treatment to 9 months in HIV-positive persons who do not receive concomitant ART.[239]

Other Special Treatment Circumstances

Childhood

Pulmonary TB in childhood should be treated with INH, RIF, and PZA for 2 months, followed by INH and RIF for 4 months. The inability to monitor visual acuity limits the use of EMB in very young children, although it can be given if the bacillary burden is high, drug resistance is suspected, or both.[239]

Pregnancy

Treatment should not be deferred during pregnancy. For drug-sensitive TB, INH, RIF, and EMB comprise the regimen of choice. STM should not be used during pregnancy because of potential eighth nerve toxicity in the fetus. Although PZA is routinely recommended by international organizations, use has not been uniformly recommended in the United States because of inadequate teratogenicity data; its use should be considered on a case-by-case basis.[239]

Uremia and End-Stage Renal Disease

Dosages of INH and RIF need not be adjusted for renal failure but should be administered after dialysis, and pyridoxine supplementation should be routine. In patients with creatinine clearance less than 30 mL/min and those on hemodialysis, EMB should be administered at 20 to 25 mg/kg, and PZA at 25 to 35 mg/kg, both given three times per week (after dialysis for those on hemodialysis). Biochemical monitoring of hepatotoxicity during renal failure may be complicated by abnormally low aminotransferase levels in uremia.

Liver Disease

The selection and dosage of antituberculous agents do not need to be modified in most patients with underlying liver disease, but hepatic aminotransferase and bilirubin levels must be followed closely. In persons intolerant of INH owing to hepatotoxicity, a 6-month regimen of RIF, PZA, and EMB can be used. If PZA cannot be tolerated, a regimen of INH, RIF, and EMB for 2 months, followed by 7 months of INH and RIF, should be given.[239] For persons with extensive TB and severe hepatitis who should not have a prolonged treatment interruption, "bridging" regimens that include EMB, fluoroquinolone, and STM could be considered until a more standard regimen can be instituted.[239] Preexisting liver disease (e.g., hepatitis C virus infection) may complicate the detection of drug-related hepatotoxicity; accordingly, clinical and biochemical supervision should be assiduous.

Patients Receiving Immunosuppressive Drugs

TB that develops during immunosuppressive treatment of another disease should be treated with the same regimens used to treat immunocompetent hosts. Immunosuppressive therapy need not be discontinued. Given the increased predisposition to TB among persons receiving a TNF-α inhibitor (e.g., etanercept, infliximab, adalimumab), discussion between all of the patient's medical providers (e.g., rheumatologist, gastroenterologist, pulmonologist, and infectious disease specialist) may be helpful to determine a rational treatment strategy.

Treatment of Latent Tuberculous Infection

Soon after INH became available, it became widely used in the United States to treat not only persons with active disease (as part of combination therapy) but also *M. tuberculosis* infection, to prevent progression to active TB. In contrast, many other countries have used a TB-prevention strategy based primarily on BCG vaccination at birth rather than treatment of LTBI. The current strategy in the United States is to test for *M. tuberculosis* infection using the TST or an interferon-γ release assay in persons who are at high risk for progressing to active TB, and then to treat all persons with a positive test result regardless of age. Criteria for TST positivity and groups for whom treatment of LTBI is indicated are listed in Table 249.9.[172,359]

TABLE 249.9 Criteria for Tuberculin Positivity by Risk Group

REACTION ≥5 MM OF INDURATION	REACTION ≥10 MM OF INDURATION	REACTION ≥15 MM OF INDURATION
HIV-positive persons	Recent immigrants (within 5 yr) from high-prevalence countries	Persons with no risk factors for tuberculosis
Recent contacts of tuberculosis case patients	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior tuberculosis	Residents and employees of high-risk congregate settings (prisons and jails, nursing homes, hospitals and other health care facilities, residential facilities for patients with AIDS, and homeless shelters)	
Patients with organ transplants and other immunosuppressed patients (receiving equivalent of ≥15 mg/day of prednisone for at least 1 mo)	Children <4 yr of age, or infants, children, and adolescents exposed to adults at high risk	

AIDS, Acquired immunodeficiency syndrome; *HIV,* human immunodeficiency virus.
Modified from centers for disease control and prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. American thoracic society. MMWR Morb Mortal Wkly Rep. *2000;49(Rr-6):1–51.*

Drug Regimens

Nine months of INH, up to 300 mg daily, is a recommended regimen for treatment of LTBI in adults and children, regardless of HIV status.[172,360] Although 90% efficacious, its effectiveness is limited by low treatment completion rates. When necessary, supervised intermittent treatment of LTBI with INH, 15 mg/kg (up to 900 mg) twice weekly, can be used. Pyridoxine supplementation, 10 to 50 mg daily, is recommended to prevent peripheral neuropathy in persons older than 65 years; pregnant and breastfeeding women; persons with diabetes mellitus, chronic renal failure, or alcoholism; persons undergoing treatment with anticonvulsants; and persons who are malnourished. A 3-month regimen of once-weekly INH plus rifapentine given to adults and children under direct observation is as effective as 9 months of INH.[361,362] Implementation of this 3-month regimen led to a 31% increase in completion of preventive therapy in New York City health clinics.[363] The weekly dose of both drugs for adults weighing more than 50 kg is 900 mg. This regimen is an equal alternative to 9 months of INH for persons 12 years of age and older who are at increased risk for progressing from latent infection to active TB; this includes HIV-infected persons who are not receiving ART.[364–366] It is important to exclude active TB in HIV-infected patients on this regimen. Permanent drug discontinuation due to an adverse event was more common with the 3-month regimen than with 9 months of INH alone (4.9% vs. 3.7%, respectively). The most common side effect was a flulike syndrome that has been seen before with intermittent RIF therapy, and with INH.[367] Another option is 4 months of RIF (10 mg/kg; 600 mg maximum).[172] This regimen is effective and well tolerated.[242,243,368] A 3-month regimen of daily INH and RIF is also effective. Although there have been limited head-to-head comparisons, a recent network meta-analysis demonstrated similar safety and effectiveness of 3 months of weekly INH plus rifapentine, 3 months of daily INH plus RIF, and 4 months of daily RIF.[369]

A 2-month regimen of daily RIF-PZA is as effective as a 12-month daily regimen of INH in HIV-infected adults.[370] Unfortunately, initial enthusiasm for this 2-month regimen waned after numerous reports of severe liver injury and death, primarily in HIV-negative individuals.[251] This regimen is no longer recommended.[371]

Optimal treatment of LTBI when resistance to both INH and RIF (i.e., MDR-TB) is likely is not known. Regimens of PZA plus either EMB or a fluoroquinolone for 6 to 12 months have been recommended, but such regimens are poorly tolerated and their effectiveness has never been studied.[172]

Risk for Isoniazid Hepatotoxicity During Treatment of Latent Tuberculous Infection

Use of INH is associated with an increased risk for hepatotoxicity; the risk in a recent clinical trial of 9 months of INH was 2.7%.[361] A US Public Health Service survey found that the incidence of probable INH-associated hepatitis increased with age: Rates per 1000 persons were 0 for those younger than age 20, 3 for ages 20 to 34, 12 for ages 35 to 49, 23 for ages 50 to 64, and 8 for age older than 64.[240] The incidence in daily drinkers of alcohol was also high (26.5 per 1000). The number in the elderly was probably falsely low because of a small sample size. A much larger experience recorded hepatitis in 4.6% of patients older than 65.[372] A large European study reported a hepatitis incidence of 520 per 100,000 population; the figure was 280 per 100,000 for those younger than 35 years and 770 per 100,000 for those older than 54 years. Most hepatitis develops within the first 3 months, and the risk for death, once clinical hepatitis develops, is substantial.[240,373] Biochemical monitoring will likely prevent some deaths, because there is a subclinical phase of at least several weeks. Byrd and colleagues recorded increased serum aminotransferase levels in 18.3% of patients taking INH but no deaths in a biochemically monitored population. Many patients with severe biochemical hepatitis would not have been detected with monitoring of symptoms only.[374] In contrast, one public health clinic reported only 11 cases of clinical hepatotoxicity and no deaths among more than 11,000 persons receiving INH over a 7-year period.[375] Based on this and other considerations, emphasis is now placed on clinic monitoring for signs and symptoms of adverse effects, with prompt evaluation if these develop. Current recommendations advocate routine baseline and follow-up laboratory monitoring only for persons with HIV infection, pregnant and early postpartum women, and persons with chronic liver disease or who use alcohol regularly.[172]

Snider and Caras analyzed 177 cases of fatal hepatitis from various sources[376] and estimated a case rate of 14 per 100,000 of those starting and 23 per 100,000 of those completing therapy. Sixty-nine percent were female, with clustering around pregnancy.

Treatment of Contacts of Active Cases

The US Public Health Service contact study showed that treatment of LTBI decreased the incidence of subsequent TB among contacts of active cases from 1550 to 610 cases per 100,000, a 61% reduction over 10 years.[377] In those who were tuberculin negative when first surveyed, the figures (per 100,000) were 510 without and 150 with chemoprophylaxis, a 59% reduction. Estimates of the risk to contacts in some smaller studies are much higher. One year of INH therapy is about 70% effective in preventing disease, with failures most often caused by nonadherence.[378] INH prophylaxis may also fail in drug-resistant infections. It appears unlikely that prophylactic INH monotherapy taken reliably by contacts results in subsequent INH resistance.[360,379]

Treatment of LTBI is indicated for persons found to be interferon-γ release assay or TST positive (5 mm of induration for the latter) after contact with an active case. In children younger than 5 who are close contacts of an active case, the TST is preferred over the interferon-γ release assay[380]; if the TST result is negative, preventive therapy should be initiated and the test repeated after 3 months. If the result of the second test is positive, a preventive therapy course should be completed; if it is negative, treatment can be discontinued.

To address the risk to health care workers inadvertently exposed to TB, Stead reviewed 33 previously investigated hospital and nursing home outbreaks.[174] In this setting, on discovering that exposures have occurred, a list of all exposed personnel and their TST or interferon-γ release assay results before exposure should be assembled. Persons with a negative test result should be retested 8 weeks after the exposure to allow time for TST or interferon-γ release assay conversion. However, if exposure is particularly heavy, or in HIV-positive health care workers, preventive therapy should be started even before retesting. Treatment can later be discontinued in HIV-negative persons if they remain TST or interferon-γ release assay negative.[155]

Treatment of Quiescent, Previously Untreated Pulmonary Tuberculosis

Tuberculin-positive patients with fibrotic upper lobe lesions and patients who had active TB before drugs were available are at increased risk for developing TB.[378] Treatment is the same as for LTBI (see earlier discussion). The longer the lesion has been stable, the lower is the risk for relapse.

Treatment of Individuals With Recent Infection

The first 2 years after *M. tuberculosis* infection is the period of greatest risk for development of active disease. Most authorities recommend treatment of LTBI for any person known to have become infected within 2 years, regardless of age. This is documented by conversion of the TST or interferon-γ release assay result from negative to positive within 2 years.

Treating Latent Tuberculous Infection in Persons With HIV Infection

In the era before highly active ART, TST- and HIV-positive injection drug users had an annual risk for active TB of approximately 8% per year.[136] As indicated in Table 249.10, the CDC recommends that a TST showing greater than 5 mm induration or a positive interferon-γ release assay result is an indication for treating LTBI in persons with known or suspected HIV infection in whom active TB has been ruled out.[172] WHO recommends treating LTBI in HIV-positive persons with a positive or unknown TST; treatment options include 6 to 9 months of INH, 3 months of INH plus rifapentine, 3 to 4 months of INH plus RIF, or 3 to 4 months of RIF.[381] Due to concerns regarding reinfection, WHO recommends at least 36 months of INH in HIV-positive persons living in TB-endemic countries.[381] In Côte d'Ivoire, both immediate initiation of ART and completion of 6 months of INH preventive therapy demonstrated independent decreases in the risk of death or

TABLE 249.10 Miliary Tuberculosis

FACTOR OR FINDING	STUDY			
	BIEHL[400]	MUNT[401]	MAARTENS ET AL.[402]	KIM ET AL.[403]
No. of cases	69	68	109	38%[a]
Mean age	51	50	—	60%[a]
Nonwhite race	85%	87%	94%	79%[a]
Predisposing factors	15%	31%	42%	66%[a]
Weeks of symptoms	2-16	3-24	1-52	—
Meningitis	17%	19%	22%	—
Tuberculin positive	61%	84%	43%	28%
Miliary radiograph	93%	97%	—	91%[a]
Other foci of tuberculosis	32%	23%	—	—
Positive sputum smear	—	39%	33% (21/64)	36% (12/33)
Marrow diagnostic[b]	—	20%	41% (9/22)	9% (2/22)
Transbronchial biopsy diagnostic[c]	—	—	76% (39/51)	63% (5/8)

[a]This percentage includes interstitial and diffuse alveolar patterns.
[b]Marrow diagnostic if caseating granuloma or acid-fast bacilli are seen.
[c]Transbronchial biopsy diagnostic if any granuloma or acid-fast bacilli are seen.

severe HIV-related disease among HIV-positive persons with >500 $CD4^+$ lymphocytes/mm^3.[382]

Anergy testing in immunocompromised persons is unreliable, and treatment of latent TB in anergic HIV-infected persons with latent TB does not decrease the risk of reactivation. Therefore, since 1997 the CDC has recommended against routine anergy testing for HIV-positive persons at risk for TB (see "Tuberculin Skin Testing and HIV Infection").[383] The failure of predictive tests in high TB incidence areas is underlined by experience in Khayelitsha, South Africa, where there was no association between the benefit of INH preventive therapy and TST or interferon-γ release assay result, leading to the recommendation that all patients receiving ART in moderate- to high-incidence areas should receive INH preventive therapy.[384]

Mycobacterium tuberculosis Infection in Persons With Additional Risk Factors

Treatment of LTBI is advised for persons with *M. tuberculosis* infection who are from groups with a known high incidence of TB, including immigrants from developing countries, injection drug users, the homeless, prisoners, and residents of long-term care facilities.[172] An argument has been made for treating latent tuberculous infection in patients after gastrectomy and jejunoileal bypass surgery for obesity. There is a greatly increased incidence of TB in patients undergoing chronic renal dialysis[100] and in renal transplant patients. Treatment of LTBI is also recommended for infected persons with silicosis,and for those those with myeloproliferative disorders and hematologic malignancies, especially when corticosteroids are given. Prolonged treatment with high doses of corticosteroids undoubtedly predisposes to activation of latent TB. Latently infected individuals who are to receive anti–TNF-α monoclonal antibodies (e.g., infliximab, etanercept, or adalimumab) should receive treatment of latent tuberculous infection.[205] As much treatment as possible should be received before the patient starts immunosuppressive therapy; ideally a treatment course would be completed, and this may be facilitated by short-course regimens.

Hepatotoxicity of INH has made preventive therapy difficult in patients with severe liver disease or after liver transplant. Fluoroquinolones have been considered as an option, with recognition of issues such as tendon rupture, although data to support this use are sparse.[385,386]

Pregnant Women

Because INH treatment for latent tuberculous infection may be associated with a slightly increased risk for maternal hepatitis, added caution with respect to INH-induced hepatotoxicity is indicated. There are insufficient safety data for the other preventive therapy regimens in pregnancy.

The Nursing Home Problem

A major analysis by Stead and colleagues showed that 3.8% of men and 2.3% of women who were tuberculin positive at admission to nursing homes acquired active disease and that this could be decreased 10-fold with treatment of latent tuberculous infection.[372] Treatment of latent tuberculous infection was clearly beneficial in patients who tuberculin converted after admission, with 11.6% of men and 7.6% of women acquiring active disease without treatment of latent tuberculous infection, but only 0.2% with treatment.

Vaccination

BCG, a live-attenuated vaccine derived from a strain of *M. bovis,* is used in young children throughout much of the world. Vaccination of children results in a 60% to 80% decrease in the incidence of TB,[387] but efficacy has varied widely. Its use is reasonable in high-prevalence situations, greater than those that now exist in the United States and most industrialized nations. It should be administered only to tuberculin-negative persons. Although BCG vaccine does not prevent infection, it usually prevents progression to clinical disease and effectively prevents disseminated disease in young children. The risk for disseminated BCG infection after vaccination in infants born to HIV-positive mothers is small. BCG should not be given to persons known to be infected with HIV. Prior BCG vaccination does not alter guidelines for TST interpretation, particularly if at least 10 years have passed since vaccination.

The effect of BCG vaccination on tuberculin reactivity depends on the age at vaccination and interval before skin testing. In a study in Montreal, children vaccinated once with BCG before the age of 1 year had a 7.9% prevalence of positive TST results 10 to 25 years later, comparable to those who never received BCG.[388] Prevalence of positive TST results was 18% among those vaccinated between 1 and 5 years of age and 25.4% among those vaccinated after age 5. Although tuberculin reactivity wanes after infant BCG vaccination, later skin testing can cause a booster effect, a potential source of confusion. Interesting to note, there is no relationship between tuberculin reactivity after BCG vaccination and protection against development of active TB.[175]

Intravesicular BCG, used to treat bladder cancer, is a rare cause of miliary granuloma in the liver or lung, psoas abscess, or osteomyelitis.[389–391] This mycobacteriosis responds to treatment with INH and RIF.

The development of a better vaccine for TB is a high priority.[392] Some candidates are subunit vaccines wherein immunodominant antigens are expressed by viral vectors or formulated with adjuvant. Live-attenuated vaccines have the potential advantage of inducing responses to a broader array of antigens, and the current vaccine against TB—BCG—has been modified to produce greater amounts of immunodominant antigens.

The Aeras Foundation is a not-for-profit organization based in Rockville, Maryland, dedicated to the development and testing of new TB vaccine candidates. Candidate vaccines furthest along in the Aeras Foundation pipeline for testing in clinical trials include the following: M72/AS01E (a fusion protein derived from *M. tuberculosis* antigens MTB32A and MTB39A plus adjuvant AS01E); H4:IC31 (a fusion protein derived from antigens 85B and TB10.4 plus adjuvant IC31); H56:IC31 (a fusion protein derived from antigens 85B, ESAT-6, and Rv2660c plus adjuvant IC31); and MTBVAC (a live-attenuated vaccine based on a human *M. tuberculosis* isolate); MVA85A (Ag85A expressed by modified Vaccinia Ankara virus); Aeras-402 (adenovirus expressing Ag85B and TB10.4); M72F (a fusion of Rv1196 and Rv0125 delivered in AS01 adjuvant); H56 (a fusion of Ag85B, ESAT-6, and Rv2660 delivered in IC31 adjuvant); ID93 (a fusion of Rv1813, Rv2608, Rv3619, and Rv3620 delivered in GLA-SE adjuvant); and Hybrid-4 (a fusion of Ag85B and TB10.4 delivered in IC31 adjuvant).

In the first infant efficacy trial of any TB vaccine for nearly a half century, more than 2700 infants (given BCG as neonates) were enrolled, with 1399 infants given a boosting inoculation with MVA85A within 6 months after receiving BCG. Although MVA85A was well tolerated and induced modest cell-mediated immune responses, it unfortunately did not provide significant protection against the development of TB.[393] In contrast, a trial of M72/AS01E in HIV-negative adults with latent TB in Kenya provided 54% protection against reactivation.[394]

An improved understanding of host pathways for presenting antigens of intracellular pathogens and mechanisms by which *M. tuberculosis* suppresses antigen presentation may foster novel and effective live-attenuated vaccine candidates. The Stop TB Partnership regularly updates an online document describing new vaccine candidates.[395]

EXTRAPULMONARY TUBERCULOSIS

Extrapulmonary TB can be divided into three groups based on pathogenesis. The first comprises superficial mucosal foci resulting from the spread of infectious pulmonary secretions via the respiratory and gastrointestinal tracts. Such lesions were once almost inevitable complications of extensive cavitary pulmonary disease but are now rare. The second group comprises foci established by contiguous spread, such as from a subpleural focus into the pleural space. The third group comprises foci established by lymphohematogenous dissemination, either at the time of primary infection or, less commonly, from established chronic pulmonary or extrapulmonary foci.

AIDS and Extrapulmonary Tuberculosis

Before 1985, cases of pulmonary TB in the United States decreased each year, whereas the number of extrapulmonary cases remained stable at about 4000 per year. The percentage of cases caused by extrapulmonary disease subsequently increased, largely as a result of coinfection with HIV. Unlike in non-AIDS patients, concomitant pulmonary and extrapulmonary disease is very common in AIDS patients with TB.

Cases of HIV-associated pulmonary and extrapulmonary TB have declined in the United States since 1992.[396] There are certain distinguishing features of AIDS-associated extrapulmonary TB. The frequency of disseminated disease (more than one focus or progressive hematogenous disease) is high—38% in one series—and rapidly progressive forms with diffuse pulmonary infiltrates, acute respiratory failure, and disseminated intravascular coagulation have been observed. TB pleuritis, when it occurs, is often bilateral and part of a disseminated process. Visceral lymphadenopathy, both mediastinal and abdominal, is frequent, and a contrast-enhanced CT scan showing nodes with central low attenuation suggests the diagnosis. Abscesses of the liver, pancreas, prostate, spleen, chest, abdominal wall, and other soft tissues have also been described. Among 320 cases of extrapulmonary TB from 1995 to 2007 managed at Grady Memorial Hospital in Atlanta, HIV coinfection was associated with a decreased likelihood of the pleural space as a site of extrapulmonary disease; among HIV-infected patients with extrapulmonary TB, those with fewer than 100 $CD4^+$ T cells/mm^3 were more likely to have central nervous system (CNS), meningeal, and/or disseminated TB.[397] Extrapulmonary TB appears to be predictive of an increased risk for developing paradoxical IRIS when ART is initiated (see "Immune Reconstitution Inflammatory Syndrome").[346]

General Comments on Treatment of Extrapulmonary Tuberculosis

Extrapulmonary foci usually respond to treatment more rapidly than does cavitary pulmonary TB, owing to the lower burden of organisms in the former. Therapy with four-drug regimens (INH, RIF, PZA, and EMB) for 2 months, followed by INH and RIF for 4 months, is advised in most cases caused by drug-sensitive organisms. The exceptions include bone and joint disease (6–9 months) and tuberculous meningitis (9–12 months, although optimal duration is unknown).[239] Adjunctive corticosteroids are recommended for persons with pericardial or CNS TB.

Diagnostic difficulty and delay can have a devastating impact on survival in critically ill patients. In a study from Uganda, a highly endemic country, empirical therapy for TB, despite negative sputum smears, led to improved survival in patients presenting with "danger signs," including fever greater than 39°C, tachycardia greater than 120 beats/min, or tachypnea greater than 30 breaths/min.[398] However, among HIV-positive persons with <50 $CD4^+$ lymphocytes/mm^3 starting ART, empirical four-drug therapy did not improve survival compared with INH preventive therapy alone.[399]

Miliary Tuberculosis

The term *miliary tuberculosis,* first used to describe its pathologic resemblance to millet seeds, now describes any progressive disseminated hematogenous TB. Miliary TB can be roughly divided into three groups: (1) acute miliary TB associated with a brisk and histologically typical tissue reaction; (2) cryptic miliary TB, a more prolonged illness with subtle clinical findings and an attenuated histologic response; and (3) nonreactive TB characterized by huge numbers of organisms, little organized tissue response, and often a septic or typhoidal clinical picture.[164]

Usual (Acute) Miliary Tuberculosis

In the prechemotherapy era, miliary TB occurred either soon after primary infection in children or young adults or as a terminal event in untreated chronic organ TB. In children, the illness is acute or subacute, with high intermittent fevers, night sweats, and occasional rigors. Pleural effusion, peritonitis, or meningitis occurs in as many as two-thirds of affected persons. The illness in young adults is usually more chronic and initially less severe. However, miliary TB is now more frequently observed in older individuals, often with underlying illnesses or conditions that may confuse diagnosis.

Four large series in the chemotherapy era[400–403] have emphasized the frequency of miliary TB in minority racial groups and the importance of underlying conditions such as alcoholism, cirrhosis, neoplasm, pregnancy, rheumatologic disease, and treatment with immunosuppressive agents (see Table 249.10).[400–403] There is usually no prior history of TB, and the onset is often subtle. Generalized symptoms of fever, anorexia, weakness, and weight loss are nonspecific. Headache may indicate meningitis; abdominal pain may be due to peritonitis; and pleural pain may result from pleuritis. Physical findings are likewise usually nonspecific, but a careful search for cutaneous eruptions, sinus tracts, scrotal masses, and lymphadenopathy may yield a prompt biopsy diagnosis. A miliary infiltrate on a chest radiograph is the most helpful finding and the usual reason miliary TB is suspected (Fig. 249.7). Unfortunately, many patients, particularly the elderly, succumb to miliary TB before the chest radiograph becomes abnormal.[404] The white blood cell count is usually normal, and anemia is the rule. Hyponatremia with the laboratory features of inappropriate secretion of antidiuretic hormone is frequent, particularly with meningitis.[401] Addison disease should be considered as a cause of hyponatremia. Increased levels of alkaline phosphatase and aminotransferases are common, as are hypoxemia, hypocapnia, and impairment of pulmonary diffusion capacity. Cultures of sputum, gastric contents, urine, and CSF are positive in some combination in most cases, but smears of sputum and pulmonary secretions alone are positive in fewer than one-third. Immediate diagnosis often results from examination of tissue (lymph nodes, scrotal masses when present, liver biopsy, or bone marrow specimens). Mycobacterial blood cultures may also be positive. Transbronchial biopsy is an excellent way to obtain tissue and should be performed promptly when the diagnosis is suspected.[405] The finding of caseating granulomas or AFB is virtually diagnostic.

FIG. 249.7 **Detail of a chest radiograph (left midlung zone) showing countless 0.5- to 1.0-mm nodules typical of miliary tuberculosis.**

Rapid diagnosis is mandatory. However, treatment should be initiated immediately based on strong clinical suspicion, because mortality from miliary TB is most often due to delays in treatment. Response may be prompt or may take several weeks. Fulminant miliary TB may be associated with severe refractory hypoxemia and disseminated intravascular coagulation.

Cryptic Miliary Tuberculosis and Late Generalized (Chronic Hematogenous) Tuberculosis

Chronic organ TB is probably always associated with intermittent, nonprogressive seeding of the bloodstream. In some individuals, however, especially as age or other factors compromise immunity, this becomes continuous and produces progressive hematogenous TB long after the primary infection.[406] The term *cryptic miliary tuberculosis* usually describes older patients with miliary TB in whom the diagnosis is obscure because of normal chest radiographs, negative TST results, and often confounding underlying illnesses to which symptoms are

mistakenly attributed[407]; this term has also been applied to miliary TB diagnosed at autopsy.[404]

The foci responsible for late generalized TB are often clinically silent—for example, renal, genitourinary, osseous, or visceral lymph nodes.[406] Chronic pulmonary foci are at times involved but are rarely the only source. The clinical picture is frequently fever of unknown origin, often with a normal chest radiograph and a negative TST result. Fever may be absent, and in one series antemortem diagnosis was made in only 15% of cases.[406] Late generalized TB may be associated with major hematologic abnormalities.

Nonreactive Tuberculosis

The histologic appearance in this rare form of disseminated hematogenous TB shows nonspecific necrosis containing disintegrating neutrophils and enormous numbers of tubercle bacilli.[190] In the typical case, granulomas and epithelioid cells are lacking, although intermediate cases have areas more typical for TB. The gross pathologic findings are soft abscesses from minute to 1 cm, which always involve the liver and spleen, usually the marrow, commonly the lungs and kidneys, but never the meninges. The clinical picture may be overwhelming sepsis, with splenomegaly and often an inconspicuous diffuse mottling on the chest radiograph. Major hematologic abnormalities are common (see "Miliary Tuberculosis and Hematologic Abnormalities").

Miliary Tuberculosis and Hematologic Abnormalities

Some patients with late generalized TB and most with nonreactive TB have serious hematologic abnormalities, including leukopenia, thrombocytopenia, anemia, leukemoid reactions, myelofibrosis, and polycythemia.[408] Leukemoid reactions may suggest acute leukemia, although most patients in whom hematogenous TB coexists with the clinical picture of leukemia have both diseases. Disseminated TB should be considered when pancytopenia is associated with fever and weight loss or as a cause of other obscure hematologic disorders.

Primary Hepatic Tuberculosis

Rarely, miliary TB may mimic cholangitis, with fever, liver function test abnormalities suggestive of obstructive disease, and little evidence of hepatocellular disease. Diagnosis is made through liver biopsy.

Miliary Tuberculosis in AIDS

In AIDS patients, 10% with TB and 38% with extrapulmonary TB have miliary disease.[232,409] Major constitutional symptoms and hectic fevers are characteristic. The chest radiograph is abnormal in 80% and may include typical miliary mottling. Only 10% of patients are tuberculin positive.[232] The sputum smear is positive in only 25%,[409] but cultures of many materials will be positive, including blood in 50% to 60%. Biopsy specimens during life show typical tuberculous histologic appearance but with more stainable organisms than in non-HIV miliary TB. In fatal cases, in contrast, the histologic picture is often nonreactive TB.[232]

Abscesses of various soft tissue and visceral organs have been described in patients with AIDS and TB, usually with other evidence of disseminated disease. Locations include the liver, spleen, pancreas, psoas muscle with or without spinal involvement, mediastinum, neck, chest wall, abdominal wall, and prostate.[232,409,410] Diagnosis is usually made by means of CT or ultrasonography and confirmed with needle or catheter aspiration. Clinical response to chemotherapy and drainage is usually good. An abscess may appear or reappear during therapy and respond to repeated aspiration.

Central Nervous System Tuberculosis: Tuberculous Meningitis

This condition is usually caused by rupture of a subependymal tubercle into the subarachnoid space rather than direct hematogenous seeding. Meningitis complicating miliary disease usually develops several weeks into the illness. In childhood, meningitis is an early postprimary event, and three-fourths of these persons have a concurrently active primary complex, pleural effusion, or miliary TB. Subependymal foci may remain quiescent indefinitely before rupturing. This may follow head trauma or be associated with general depression of host immunity as a result of alcohol abuse or other factors.

Pathologic Features

Meningeal involvement is most pronounced at the base of the brain. In long-standing cases, a gelatinous mass may extend from the pons to the optic nerves, being most prominent adjacent to the optic chiasm. In more chronic cases, fibrous tissue may encase cranial nerves. Vasculitis of local arteries and veins may lead to aneurysm, thrombosis, and focal hemorrhagic infarction. Perforating vessels to the basal ganglia and pons are most often involved, producing movement disorders or lacunar infarcts; involvement of branches of the middle cerebral artery may cause hemiparesis.

Clinical Manifestations

The usual illness begins with a prodrome of malaise, intermittent headache, and low-grade fever, followed within 2 to 3 weeks by protracted headache, vomiting, confusion, meningismus, and focal neurologic signs. The clinical spectrum is broad, ranging from chronic headache or subtle mental status changes to sudden, severe meningitis progressing to coma. Fever may be absent, and the peripheral white blood cell count is usually normal. Mild anemia is usual, and hyponatremia resulting from inappropriate antidiuretic hormone secretion is common. Evidence of concomitant extrameningeal TB is present in roughly three-fourths of cases,[411] with miliary shadowing on the chest radiograph being most suggestive. In many cases, however, there are no clinical or historical clues to suggest TB.

The cornerstone of diagnosis is examination of the CSF. The cell count generally ranges from 0 to 1500/mm^3, the protein level is increased, and the CSF glucose is characteristically low. A lymphocytic predominance is usual, although one-fourth of cases have a polymorphonuclear pleocytosis, usually early in the course. Identifying bacilli often requires examination of large volumes of fluid from repeated lumbar punctures. In one study, stains of sediment revealed AFB in 37% of cases on initial examination but in 90% when fluids from four large-volume lumbar punctures were examined.[411] Initial atypical findings such as neutrophilic pleocytosis, a normal glucose concentration, or even entirely normal CSF indices evolve to more typical mononuclear cell predominance with hypoglycorrhachia over time. Commercial kits for detecting *M. tuberculosis* in respiratory specimens by means of amplification technology (see Table 249.1) can also be used on CSF. Overall, the sensitivity of PCR assay for examination of the CSF is low. The CSF is often culture negative for *M. tuberculosis,* but the CSF PCR assay has been reported to be positive in roughly 60% to 90% of CSF samples that eventually are culture positive.[412,413] Results of testing CSF with the Xpert MTB/RIF Ultra assay were positive in 16 of 23 cases of proven or probable tuberculous meningitis, making this the preferred rapid test for this infection.[414]

In patients with meningitis, CT or MRI may reveal rounded lesions presumed to be tuberculomas, basilar arachnoiditis, cerebral infarction, or hydrocephalus (Fig. 249.8). Contrast-enhanced MRI frequently reveals concomitant spinal cord and radicular involvement (transverse and longitudinal myelitis, spinal tuberculoma, or abscess and other manifestations), which may lead to disabling complications.[415]

Prognosis is influenced by age, duration of symptoms, and neurologic deficits. Mortality is greatest in patients younger than age 5 (20%), in those older than age 50 (60%), or in those in whom illness has been present for more than 2 months (80%).[411] Patients without neurocognitive impairment, focal neurologic signs, or hydrocephalus at the start of therapy are likely to recover, whereas approximately half of patients who are stuporous or have dense paraplegia or hemiplegia die or recover with severe residual neurologic defects.[411] A prognostic score derived from cases in 43 centers in 14 countries found that altered consciousness, diabetes mellitus, immunosuppression, neurologic deficits, hydrocephalus, and vasculitis predicted an unfavorable outcome in culture-proven tuberculous meningitis.[416] Concomitant HIV infection does not appear to alter the clinical and laboratory manifestations or the prognosis of tuberculous meningitis, except that CNS mass lesions are more likely.[417]

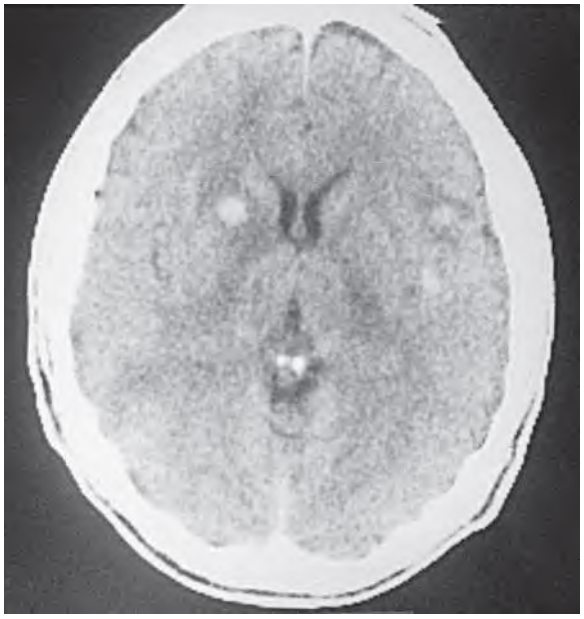

FIG. 249.8 Multiple cerebral cortical densities on computed tomography scan of a patient with tuberculous meningitis.

Therapy

In the presence of meningeal inflammation, both INH and PZA reach concentrations in the CSF equaling those in blood. RIF penetrates the blood-brain barrier less well but still adequately. In some cases, PZA is given beyond the first 2 months of treatment because of its excellent CNS penetration, although its activity after 2 months of treatment is unclear. The RIF dose is sometimes increased owing to its poor CNS penetration, particularly with concomitant administration of corticosteroids. Otherwise, the dosages are as for pulmonary TB. A recent study demonstrated that higher-dose RIF (13 mg/kg IV vs. the standard 10 mg/kg oral), together with INH, PZA, and corticosteroids, was associated with improved 6-month survival and neurologic recovery.[418] However, a trial of intensification with high-dose RIF (15 mg/kg/day) and levofloxacin for the first 8 weeks, added to a standard 9-month regimen, in Vietnam failed to improve survival.[419]

Most authorities recommend adjunctive corticosteroids in TB meningitis, particularly stage 2 (objective neurologic findings) and stage 3 (stupor-coma) patients, beginning prednisone at 60 to 80 mg daily. This may be gradually reduced after 1 to 2 weeks and discontinued by 6 to 8 weeks, as guided by symptoms. Symptoms and CSF abnormalities may rebound transiently as corticosteroids are tapered. Ventricular shunting may be beneficial if symptomatic hydrocephalus supervenes.

Tuberculomas

Intracranial tuberculomas are space-occupying lesions that may manifest as seizures. They are most frequently multiple, appearing on imaging studies as avascular masses with surrounding edema. Corticosteroids reduce edema and decrease symptoms, and chemotherapy prevents spread of infection in cases diagnosed at operation.

Tuberculous Spinal Meningitis

Infrequently, TB causes spinal meningitis with or without intracranial involvement. In advanced cases, the cord may be completely encased in a gelatinous exudate. An intramedullary tuberculoma or an extradural granulomatous mass can cause symptoms without meningeal involvement. Nerve root or cord compression causes pain, bladder or rectal sphincter weakness, hypesthesia, anesthesia, paresthesias in the distribution of a nerve root, or paralysis. Subarachnoid block may cause CSF protein concentrations to be extremely high, with or without cells.

Tuberculous Pleurisy (Serofibrinous Pleurisy With Effusion)

Types of Tuberculous Pleurisy

Early Postprimary Pleurisy With Effusion

When infection occurs early in life, tuberculous pleurisy with effusion follows the primary infection within weeks or months. The pathogenesis is rupture of a large subpleural component of the primary infection and delivery of infectious, antigenic material into the pleural space, with inflammation and seeding of foci over the visceral and parietal pleura. In the past, this affected mostly adolescents and young adults and, rarely, older adults. Immediate prognosis was excellent, with resolution of the effusion within several months in as many as 90% of cases. However, studies of soldiers during World War II (before chemotherapy) demonstrated that 65% relapsed with chronic organ TB within 5 years.[420] Early postprimary serofibrinous pleurisy with effusion identifies quantitatively large primary infections with a relatively poor long-term prognosis.

Pleurisy With Effusion Complicating Chronic Pulmonary Tuberculosis

In contrast to early studies,[420] an increased proportion of pleurisy with effusion since the early 1980s occurs in older individuals with chronic pulmonary TB, often with complicating illnesses such as cirrhosis or congestive heart failure to which the effusion is mistakenly attributed. In one study, one half of pleurisy cases occurred in the setting of established chronic pulmonary TB.[421]

Pleurisy With Effusion Complicating Miliary Tuberculosis

Pleural effusions occur in 10% to 30% of cases of miliary TB.[400,402] These may be associated with other progressive extrapulmonary foci and involvement of other serous membranes. Cases with coexistent pleural (at times bilateral), peritoneal, and pericardial TB have been referred to as *tuberculous polyserositis.*

Clinical Manifestations and Diagnosis

The clinical presentation may be low grade and subtle or abrupt and severe, easily confused with acute bacterial pneumonia. Cough and pleuritic chest pain are usual, and fever may be high. The effusion is usually less than massive and almost always unilateral except when associated with miliary TB. The pleural fluid typically contains 500 to 2500 white blood cells/mm^3, with more than 90% lymphocytes in two-thirds of cases. However, 38% of cases in one series had predominantly neutrophils and 15% had more than 90% neutrophils on the first tap.[422] Repeated taps demonstrate a shift to lymphocytic predominance. Mesothelial cells, characteristic of neoplastic effusions, are sparse or absent, eosinophils are rarely present, and less than 10% of effusions are serosanguineous. The pleural fluid protein level usually exceeds 2.5 g/dL, the glucose concentration is usually moderately low compared with serum values but rarely less than 20 mg/dL, and the pH is almost always 7.3 or lower and may be as low as 7.0. Increased pleural fluid adenosine deaminase levels have been suggested to be highly sensitive and specific for tuberculous pleuritis.[423,424] High pleural fluid adenosine deaminase levels with other conditions (e.g., neoplasia) limit its diagnostic utility in countries with a low prevalence of TB,[425] although levels with such conditions infrequently exceed the suggested cutoff for TB.[426,427] A significant negative association of age and pleural fluid adenosine deaminase suggests the need for a lower cutoff in patients older than 45 years, to decrease false-negative results.[428] Bloody pleural fluid suggests either TB or malignancy. In the usual case of early postprimary pleurisy with effusion, the acid-fast stain of the fluid sediment is seldom positive, the culture is positive in 25% to 30%, pleural needle biopsy yields granulomas in 75%, and culture of a needle biopsy specimen may be positive even in the 25% of cases with nonspecific pleuritis on histologic examination. Cases complicating chronic pulmonary TB more often have positive pleural acid-fast smears (50%) and positive cultures (60%) but are less likely (25%) to demonstrate granulomas on pleural biopsy. Repeat pleural biopsy may be necessary to establish the diagnosis, and a small open pleural biopsy or thoracoscopy is diagnostic in virtually all cases. Smears of sputum or gastric fluid are rarely positive in early

postprimary cases, and cultures are positive in 25% to 33%. In contrast, sputum smear is positive in 50% and the culture is positive in 60% of "reactivation" cases.[421] TB is often not considered as the cause of a pleural effusion in an older person with complicating illnesses such as cirrhosis or congestive heart failure.[422] When pleural effusion complicates miliary TB, findings associated with the latter condition usually dominate the clinical picture.

Therapy

Early postprimary pleural effusions spontaneously resolve in 2 to 4 months. Chemotherapy does not hasten resolution but prevents active disease elsewhere in the body, which will otherwise occur in 65% of cases.[420] Therapy is as described for pulmonary TB. Multiple thoracenteses are not necessary once the diagnosis is established and treatment initiated. A small minority heals with pleural fibrosis. Corticosteroid therapy hastens symptomatic improvement and fluid resorption, but no long-term benefit has been shown and therefore it is not recommended.

Tuberculous Empyema and Bronchopleural Fistula

Tuberculous empyema occurs when a major cavity ruptures into the pleural space. This often catastrophic illness is usually associated with bronchopleural fistula formation and frank pus. Before antituberculous drugs were available, tuberculous empyema was almost always rapidly fatal. It virtually never occurs in patients being treated with chemotherapy.

Tuberculous Pericarditis

Tuberculous pericarditis is most often caused by extension from a contiguous focus of infection, usually mediastinal or hilar nodes but also the lung, spine, or sternum. Less commonly, it occurs during miliary TB. It sometimes develops during the course of otherwise effective drug therapy. In the United States, tuberculous pericarditis is an uncommon complication of AIDS; but in two series from sub-Saharan Africa, the vast majority of effusive pericarditis cases were tuberculous and almost all patients were HIV positive.[429,430]

Clinical Manifestations and Diagnosis

The onset may be abrupt, resembling acute idiopathic pericarditis, or insidious, resembling congestive heart failure. Symptoms of infection or cardiovascular compromise may be present. Individual cases may manifest as chronic constrictive pericarditis and may be mistaken for cirrhosis with ascites. As many as 39% of patients also have a pleural effusion, providing a convenient source for diagnostic fluid and tissue.[431,432] Echocardiography demonstrates effusion when present and may reveal multiple loculations suggestive of TB.

Pericarditis with effusion is usually quickly diagnosed based on physical findings and radiologic examination, but establishing that it is tuberculous in nature is often difficult. The TST result may be negative, and evidence of extrapericardial TB lacking. In areas of high endemicity, a presumptive diagnosis is often correctly made.[431,432] In the United States, however, many cases are initially misdiagnosed as idiopathic, uremic, or rheumatoid pericarditis.[433]

Pericardiocentesis (ideally performed in a cardiac catheterization laboratory) is indicated for hemodynamic compromise. However, because pericardiocentesis carries risk, and because 90% of acute pericarditis in the United States is idiopathic (presumed viral) and subsides spontaneously in 2 to 3 weeks, some authorities advise against early pericardiocentesis. If improvement has not occurred by that time, a subxiphoid pericardial window can be performed. This provides both fluid and tissue for diagnosis, although in some cases the biopsy demonstrates only nonspecific inflammation.[431,432] Tuberculous pericardial fluid demonstrates many of the characteristics of tuberculous pleural fluid, with acid-fast smears being rarely positive and cultures being positive in approximately 50% of cases. Bloody fluid suggests either TB or malignancy. The usefulness of adenosine deaminase determinations on pericardial fluid is not certain, but PCR assay for *M. tuberculosis* may be diagnostic, although sensitivity is low.

Therapy

Antibiotic treatment is the same as for pulmonary TB. In a large study from South Africa from the 1980s, treatment with corticosteroids (60 mg/day for 4 weeks, 30 mg/day for 4 weeks, and 15 mg/day for 2 weeks) decreased mortality from 11% in controls to 4% in treated patients. Pericardiectomies were also less frequently necessary in patients given corticosteroids (30% in controls vs. 11% in corticosteroid-treated patients). However, a larger comparative trial of immunotherapy with either *Mycobacterium indicus pranii* (1250 patients) or prednisolone (1400 patients), for definite or probable tuberculous pericarditis, failed to demonstrate a significant effect on a composite score of death, cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis.[434] The incidence of constrictive pericarditis and hospitalization was decreased in prednisolone-treated patients, and rates of adverse events, especially cancer, were elevated in HIV-infected patients. Because the size of this study was much larger than that in previous reports, current recommendations for the use of adjunctive corticosteroids in the management of tuberculous pericarditis have been revised: They should not be routinely used.[239] However, selective use of corticosteroids in persons at the highest risk of inflammatory complications should be considered. Surgical drainage via a subxiphoid pericardial window at the outset did not decrease either mortality or the eventual need for pericardiectomy, although it provided diagnostic tissue and obviated the need for recurrent pericardiocenteses. However, 2% surgical mortality was associated with the procedure.[431,435]

When hemodynamic compromise persists for 6 to 8 weeks, pericardiectomy is usually indicated, and this should probably be performed earlier rather than later. Approximately two-thirds of patients, however, do well without surgery.

Skeletal Tuberculosis: Pott Disease (Tuberculous Spondylitis)

One-third of cases of skeletal TB involve the spine, as a result of past hematogenous foci, contiguous disease, or lymphatic spread from pleural disease. The earliest focus is the anterior superior or inferior angle of the vertebral body. This usually spreads to the intervertebral disk and adjacent vertebra, producing the classic radiographic picture of anterior wedging of two adjacent vertebral bodies with destruction of the intervening disk and the physical finding of a tender spine prominence or gibbus. The lower thoracic spine is involved most frequently, followed by the lumbar spine (Fig. 249.9).

In endemic countries, Pott disease usually occurs in older children and young adults, but in developed countries it has become a disease of older persons.[436] In a country such as Denmark, with large immigrant populations from endemic areas, spinal TB accounted for more than half of bone and joint disease and was mainly seen in younger immigrants.[437] Evidence of other foci of TB and systemic symptoms are often absent, early complaints may be back pain or stiffness with an initially normal radiograph, and diagnosis may be delayed until signs of advanced disease such as paralysis, deformity, or sinus formation develop. Bacilli are sparse, and smear and culture of pus or tissue are positive in only one-half of cases. Histologic studies reveal granulomas with or without caseation in three-fourths of cases.

Clinical Manifestations

Abscess and Sinus Formation

Paraspinal cold abscesses develop in 50% or more, in some cases appearing after treatment has been initiated, and in some cases visible only with CT or MRI. The pus, confined by tight ligamentous investments, can dissect along tissue planes for long distances to present as a mass or a draining sinus in the supraclavicular space, above the posterior iliac crest in the Petit triangle, or in the groin, the buttock, or even the popliteal fossa. The abscess can spread infection to distant vertebral bodies, sometimes without affecting the intervening vertebrae. Epidural or psoas abscess can also complicate tuberculous spondylitis.

Spinal Tuberculosis Without Bony Involvement on Plain Films

In high TB/HIV prevalence settings, radiculomyelitis may be a common manifestation of spinal TB, and often manifests as a paradoxical reaction.

FIG. 249.9 **Magnetic resonance image showing extensive destruction of L1 and L2 vertebral bodies and the intervening disk with posterior extension in a Pakistani man with Pott disease.**

Among 274 mostly HIV-positive South African patients who were referred to a center for patients with spinal disease but without bony involvement on plain films, MRI imaging revealed radiculomyelitis in 76%, spondylitis in 39%, subdural abscess in 15%, and intramedullary tuberculoma in 12%.[438]

Pott Paraplegia

In approximately half of cases, weakness or paralysis of the lower extremities is present or develops after treatment has begun, perhaps owing to arachnoiditis and vasculitis.[436] Less frequently, it will be due to compression of the cord by an inflammatory mass or rarely pressure in the abscess producing ischemic changes in the subjacent cord. Inflammatory thrombosis of the anterior spinal artery can occur, and sudden cord compression may result from marked spinal instability.

Therapy

A 6- to 9-month course of therapy that contains INH and RIF is at least as effective as 18-month regimens that include INH plus PAS and EMB.[439,440] Adjunctive surgical débridement or resection of the involved bone plus bone grafting did not improve outcome compared with antituberculosis therapy alone. Thus, current recommendations are to treat spinal TB with a 6- to 9-month regimen that includes INH and RIF, with PZA and EMB for the first 2 months.[239] Surgical intervention may be necessary in patients who do not respond to therapy or those with cord compression with neurologic deficits or spine instability.

Peripheral Osteoarticular Tuberculosis

Older reports described peripheral tuberculous arthritis as a chronic, slowly progressive monoarthritis in 90% of cases,[441] often without systemic symptoms or extraskeletal TB, and most frequently in the hip or knee. A history of trauma was common, followed weeks or months later by indolent progressive inflammation. More recent reports suggest a shift to an older population with a different clinical picture, including more systemic symptoms, multiple joint involvement, and periarticular abscess formation.[442] Tenosynovitis of the hand, arthritis of the wrist, and carpal tunnel syndrome can be caused by TB. Clinical confusion occurs when TB superinfects joints previously involved with other arthritides.

The earliest manifestation of tuberculous arthritis is pain, which may precede signs of inflammation and radiographic changes by weeks or months. Radiographs initially may show soft tissue swelling but later demonstrate osteopenia, periarticular bony destruction, periosteal thickening, and eventually destruction of cartilage and bone. Cold abscesses and draining sinuses often develop in chronic cases.

In the absence of coexistent extraarticular TB, diagnosis almost always requires biopsy. Histologic features compatible with TB warrant chemotherapy, although other chronic infections (fungi, nontuberculous mycobacteria) can cause identical clinical and histologic pictures. For early cases, prolonged chemotherapy results in complete resolution. Surgery is necessary only when serious joint instability requires fusion, and then only after chemotherapy has failed.

Tuberculous osteomyelitis can affect any bone, including the ribs, skull, phalanx, pelvis, and long bones.[443] Other causes of osteomyelitis of the rib are rare, and TB is the most common infectious cause of single or multiple osteomyelitic rib lesions. Tuberculous osteomyelitis outside the vertebral body manifests as a cold abscess, with swelling and only modest erythema or pain.

TABLE 249.11 Clinical Manifestations of Renal Tuberculosis in Two Series of Patients

FACTOR OR FINDING	STUDY: SIMON ET AL.[445]	STUDY: CHRISTENSEN[446]
No. of patients	102	78
Primarily genitourinary symptoms	61%	71%
Back and flank pain	27%	10%
Dysuria, frequency	31%	34%
Constitutional symptoms	33%	14%
Abnormal urine, no symptoms	5%	20%
Abnormal urinalysis	66%	93%
Abnormal intravenous pyelogram	68%	93%
Tuberculin positive	88%	95%
Abnormal chest radiograph	75%	66%
Active pulmonary tuberculosis	38%	7%
Other old or active extrapulmonary disease	5%	20%
Urine culture positive		
For tuberculosis	80%	90%
For routine pathogens	45%	12%
Epididymitis, orchitis	19%	17%
Chronic prostatitis	6%	6%

Genitourinary Tuberculosis: Renal Tuberculosis

Asymptomatic renal cortical foci may occur during all forms of TB. An autopsy study of pulmonary TB revealed unsuspected renal foci in 73% of cases, usually bilateral; in 25% of miliary cases, patients have positive urine cultures.[444] Cortical foci tend to be stable unless they penetrate to the medulla, where local factors favor accelerated infection. Most patients have evidence of concomitant extragenitourinary disease, usually pulmonary and most frequently inactive. In normal hosts, the interval between infection and active renal disease is usually years and sometimes decades. Local symptoms predominate, and advanced tissue destruction may occur long before the diagnosis is made.

The clinical manifestations in two large series of cases are presented in Table 249.11.[445,446] Although sterile pyuria is typical of renal TB, positive cultures for routine bacterial pathogens may lead to misdiagnosis, sometimes for years. The contrast-enhanced abdominal CT is usually abnormal. Early findings are nonspecific, but later changes may be more suggestive, including papillary necrosis, ureteral strictures, "pipestem" changes, "corkscrewing," "beading," hydronephrosis, gross parenchymal cavitation, and autonephrectomy. Focal calcification is particularly suggestive. The clinical disease is usually unilateral, although microscopic

changes are probably always bilateral. Culture of three morning urine specimens for mycobacteria establishes the diagnosis in 80% to 90% of cases. When a renal abnormality is present but urine cultures are negative, cytologic studies and culture of material obtained by fine-needle biopsy may be diagnostic. Ureteral cicatrization and obstruction may occur after otherwise effective chemotherapy, but surgery is rarely required.

Hypertension is not a feature of renal TB, and renal function is usually preserved. However, a rare condition called *tuberculous interstitial nephritis* may cause renal failure.[447] It is characterized by interstitial granulomas and normal-sized kidneys, usually in the presence of active extrarenal TB. AFB have been seen but not cultured from renal biopsy specimens, and renal dysfunction responds to corticosteroid therapy but not antituberculous chemotherapy alone. It is unclear that tuberculous interstitial nephritis is actually caused by tuberculous infection.

Male Genital Tuberculosis

Eighty percent of male genital TB is associated with coexistent renal disease, and most advanced renal TB is associated with some male genital focus.[448] Spread of infection from renal foci involves the prostate, seminal vesicles, epididymis, and testis, in that order. The usual clinical finding is a scrotal mass that may be tender or associated with a draining sinus. Calcified foci may form within the prostate during treatment of prostatic TB. Genital foci not associated with renal disease can be established by lymphohematogenous spread and usually present as a painful testicular or scrotal mass. Diagnosis may be suggested by the presence of epididymal or prostatic calcification, although the latter also occurs with nontuberculous chronic prostatitis. The diagnosis is usually established by biopsy, and response to chemotherapy is excellent.

Genitourinary Tuberculosis in AIDS

In a study of 79 HIV-positive patients with TB, 77% had positive urine cultures, usually as an incidental finding. Only two had male genital involvement, none had symptoms of renal disease, and in only 4% was the genitourinary tract the only apparent site of TB.[409]

Female Genital Tuberculosis

Female genital TB begins with a hematogenous focus in the endosalpinx, from which it may spread to the endometrium (50%), ovaries (30%), cervix (10%), and vagina (1%).[449] In the cervix, a granulomatous ulcerating mass may resemble carcinoma. Common complaints are infertility or local symptoms consisting of menstrual disorders and abdominal pain. The clinical picture may suggest pelvic inflammatory disease that is unresponsive to therapy. Spread to the peritoneum may also occur. Systemic symptoms are uncommon, and evidence of old TB need not be present. Pregnancies that occur in the presence of pelvic TB are often ectopic. Although cultures of menstrual blood or endometrial scrapings may be positive, the diagnosis is usually made by examination of tissue removed at operation. Response to chemotherapy is excellent, and surgery is needed only for residual large tubo-ovarian abscesses.

Gastrointestinal Tuberculosis

Before effective chemotherapy was available, 70% of patients with advanced pulmonary disease acquired gastrointestinal TB from swallowing infectious secretions and usually developed diarrhea and abdominal pain. Although most cases at present are likely due to swallowed respiratory secretions, radiographic evidence of pulmonary TB is less frequent, the diagnosis being made unexpectedly with surgery or endoscopy.[450]

Any location from mouth to anus can be involved. Nonhealing ulcers of the tongue or oropharynx and nonhealing sockets after tooth extraction may be due to TB. Esophageal disease is most frequently caused by an adjacent caseous node, which leads to stricture with obstruction or tracheoesophageal fistula formation and rarely to fatal hematemesis from an aortoesophageal fistula. Stomach involvement may be ulcerative or hyperplastic and may cause gastric outlet obstruction. Isolated duodenal disease can produce symptoms of peptic ulcer or obstruction. Small bowel involvement may lead to perforation, obstruction, enteroenteric and enterocutaneous fistulas, massive hemorrhage, and severe malabsorption. Small bowel lesions are frequently multiple. The ileocecal area is the most typical site of enteric TB, producing pain, anorexia, diarrhea, obstruction, hemorrhage that may be severe, and often a palpable mass. Clinical, radiographic, endoscopic, and even operative findings may suggest carcinoma. A successful diagnosis is usually made by means of colonoscopy. In a study of 50 cases, ileocecal involvement with or without involvement of other areas was found in 35 cases, isolated segmental colonic disease was found in 13 cases, and pancolitis was initially misdiagnosed as ulcerative colitis in 2 cases. Evidence of pulmonary TB was present in only 18 cases.[451] The response of gastrointestinal TB to chemotherapy is excellent. Once the diagnosis is established, surgery should be deferred if possible until the results of chemotherapy have been assessed.

Pancreatic TB may manifest as an abscess or as a mass involving local nodes and resembling carcinoma. The biliary tract may be obstructed by tuberculous nodes, and tuberculous ascending cholangitis has been described. TB is a frequent cause of granulomatous hepatitis. This is usually asymptomatic but may be associated with an increased alkaline phosphatase level that is out of proportion to bilirubin levels with normal aminotransferase levels. Very rarely, tuberculous granulomatous hepatitis causes jaundice without evidence of extrahepatic TB. This is called *primary tuberculosis of the liver. Focal hepatic tuberculosis* describes single or multiple tuberculous abscesses. These appear to occur most frequently in racial groups with little natural immunity to TB and in children.[452]

Gastrointestinal Tuberculosis in AIDS

Bowel involvement is not a common feature of extrapulmonary TB in AIDS patients. One series reported bowel fistulas in less than 4% of such cases,[409] another reported CT evidence of gastrointestinal abnormalities in 4 of 23 cases,[453] and a third study noted positive stool cultures for *M. tuberculosis* in 4 of 10 cases.[454] Tuberculous visceral abscesses, including hepatic, splenic, and pancreatic, may occur in AIDS patients. Pain and fever are usually present. Diagnosis is often made by means of CT or ultrasonographically guided drainage procedures. Chemotherapy alone has not been effective in all cases.[410]

Tuberculous Peritonitis

Tuberculous peritonitis results either from spread of adjacent tuberculous disease such as an abdominal lymph node, intestinal focus, or fallopian tube, or during miliary TB. In a summary of 11 series, evidence of associated pleuropulmonary TB was present in 25% to 83% of cases and the TST result was positive in 30% to 100% of cases.[455] Pleural effusion is the most frequent associated finding, but evidence of TB in other sites is often present. AIDS patients do not have an increased frequency of peritonitis.[409]

The clinical picture has been divided into *plastic* and *serous* types. The less common plastic type is characterized by tender abdominal masses and a "doughy abdomen." Serous effusions present as ascites with or without signs of peritonitis. Symptoms of fever, abdominal pain, and weight loss are common.[455] The onset may be insidious, although acute presentations resembling bacterial peritonitis also occur. In the past, diagnosis was often made at surgery for a mass or an acute abdominal condition. Tuberculous peritonitis often goes undiagnosed in patients with concomitant cirrhosis with ascites.[456] Of 20 patients with both conditions, the diagnosis of tuberculous peritonitis was suspected before death in only 11. Tuberculous peritonitis has been reported in peritoneal dialysis patients with the clinical picture of bacterial peritonitis unresponsive to routine antibiotics.[457]

The peritoneal fluid is exudative, usually containing 500 to 2000 cells. Lymphocytes typically predominate, although in some cases neutrophils are more abundant early in the process. Acid-fast smear of peritoneal fluid is seldom positive, and culture is positive in only 25% of cases. An increased adenosine deaminase level in ascitic fluid has been reported to have high sensitivity and specificity,[458] although among 140 patients in India the positive predictive value was only 25%.[459]

Analysis of peritoneal fluid with PCR, such as the Xpert MTB/RIF or Xpert MTB/RIF Ultra assay, may provide rapid diagnosis. In the absence of other foci of TB, peritoneal tissue may need to be obtained in order to make the diagnosis. Histologic examination of peritoneal biopsy specimens obtained with a Cope needle were positive in 64%

of cases and those obtained by peritoneoscopy in 85% in one series.[460] Fatal hemorrhages after both Cope needle biopsy and peritoneoscopy have been recorded.[455]

Treatment is the same as for pulmonary TB. There is some evidence that adjunctive corticosteroids decrease the likelihood of late intestinal obstruction,[460] but pending definitive studies, the routine use of adjunctive corticosteroids cannot be recommended.[461]

Tuberculous Lymphadenitis (Scrofula): Peripheral Nodes

Lymphadenitis is the most frequent form of extrapulmonary TB. In HIV-negative persons, it is usually unilateral and cervical in location.[462] The most common site is along the upper border of the sternocleidomastoid muscle, where it presents as a painless, red, firm mass. It is seen most frequently in young adult females of non-European ancestry, although it can affect any age or race. Children often have an ongoing primary infection, but in other age groups evidence of extranodal TB and systemic symptoms are usually absent. Lymphadenopathy outside the cervical and supraclavicular area indicates more serious TB, usually with systemic symptoms. The TST result is almost always positive. Fine-needle aspiration demonstrates cytologic evidence of granuloma, but smears or cultures are usually negative.[463] Biopsy with culture is often required for diagnosis, because nodes with a nonspecific histologic appearance have been positive for *M. tuberculosis* on culture, and material with typical histologic features may be due to other mycobacteria or fungi. Complete excision of involved nodes with no drain left in place is recommended in order to diminish the possibility of postoperative fistula formation. Untoward events such as node enlargement with pain, suppuration, sinus formation, and appearance of new nodes occur in 25% to 30% of cases, both during and after chemotherapy, and do not indicate failure of drug treatment. These likely represent reactions to retained tuberculous antigens rather than uncontrolled infection; they usually subside spontaneously, and short courses of corticosteroids may be beneficial when the problem persists.[464]

Conversely, in individuals with AIDS, peripheral tuberculous lymphadenitis is almost always multifocal and associated with major systemic symptoms such as fever, weight loss, and evidence of TB in the lungs (parenchyma, nodes, or pleura) or elsewhere (Fig. 249.10).[463] In an early series from New York City, TB caused 57% of generalized lymphadenopathy in HIV-positive injection drug users.[465] In contrast to non–HIV-infected persons, material removed with fine-needle aspiration is positive on acid-fast stain in the great majority of cases—as frequently as it is with culture. However, both cytologic and histologic findings are less specific than in HIV-negative persons.[466]

Mediastinal Tuberculous Lymphadenopathy

Mediastinal adenopathy during primary infection is often visible radiographically, especially in children. In African Americans, mediastinal adenopathy resulting from TB may also be seen in young adults, and cases in very old persons have been reported.[467] Associated systemic symptoms may or may not be present, causing confusion with other mediastinal masses such as histoplasmosis, lymphoma, and carcinoma. The finding of low-density areas in the nodes on CT scan suggests TB, but diagnosis usually requires mediastinoscopy. In HIV-infected persons with TB, in contrast, mediastinal lymphadenopathy is frequent. Multiple nodes are usually involved, coalescing into large mediastinal masses with low-density centers, peripheral contrast enhancement, and no calcification.[468,469]

Fibrosing Mediastinitis

TB can cause fibrosing mediastinitis, although less commonly than histoplasmosis. Patients present with dyspnea on exertion resulting from compression of pulmonary veins and arteries or, less commonly, superior vena cava syndrome. Hilar adenopathy or active pulmonary disease is rarely found. A perfusion lung scan helps define the extent of pulmonary vascular compression, but thoracotomy is required for diagnosis. Mediastinoscopy is either contraindicated because of superior vena cava syndrome or unsuccessful because of fibrosis.

FIG. 249.10 Axillary lymphadenitis caused by *Mycobacterium tuberculosis* in a patient with acquired immunodeficiency syndrome.

Mesenteric Tuberculous Lymphadenitis

In HIV-negative persons, isolated symptomatic mesenteric lymphadenitis without bowel disease or peritonitis is rare. It may cause abdominal pain, fever, a palpable mass, or symptoms of partial small bowel obstruction. In AIDS patients with TB, abdominal lymphadenopathy is common and may be massive.[469,470] Involvement is more often intraabdominal than retroperitoneal, and occasionally obstruction of the biliary tract, ureters, or bowel is observed. As with thoracic disease, the nodes often are low density or have low-density centers and peripheral enhancement. Other abnormalities on CT may include abscesses in the liver, spleen, pancreas, or kidney; local ileal thickening; extraluminal bowel gas indicating fistula formation; and ascites.

Cutaneous Tuberculosis

In the past, a number of cutaneous conditions were associated with TB elsewhere in the body, although *M. tuberculosis* could not be identified in the lesions. These have been considered allergic reactions to the infection and termed *tuberculids*. They include erythema induratum of Bazin, papulonecrotic tuberculids, and others. This association has been questioned, and some have attributed tuberculids to other processes, such as sarcoidosis.[471] *M. tuberculosis* DNA has been detected in erythema induratum skin lesions with PCR.[472] Erythema nodosum has been attributed to primary TB, although organisms cannot be cultured from the lesions.

The pathogenesis of cutaneous involvement in TB is varied. Skin involvement may result from exogenous inoculation (which in the previously nonsensitized host is associated with regional lymphadenitis). TB verrucosa cutis, arising from direct inoculation, has also been called prosector's wart, referring to inoculation of a hand at time of autopsy of a patient with TB. Infection may also spread from an adjacent focus to the overlying skin (as from lymphadenitis, osteomyelitis, or epididymitis), and hematogenous spread from a distant focus or as a part of the generalized hematogenous dissemination. This last is seen in patients with AIDS and tuberculous bacteremia.[473] The clinical picture of all cutaneous mycobacterial infections, including TB, is highly variable, and any unexplained skin lesion, especially if it has nodular or ulcerative components, may be due to TB, particularly in AIDS patients.

Tuberculous Laryngitis

In the prechemotherapy era, laryngeal TB occurred in more than a third of patients dying of pulmonary TB, often associated with painful ulcers of the epiglottis, pharynx, tonsils, and mouth, and with middle

ear involvement. Laryngeal disease was highly infectious and often caused terminal widespread bronchogenic dissemination throughout the lungs. At present, however, more than one-half of laryngeal TB cases are due to hematogenous seeding. Such cases are still highly contagious. Lesions vary from erythema to ulceration and exophytic masses resembling carcinoma.[474] Symptoms include cough, wheezing, hemoptysis, dysphagia, odynophagia, and otalgia.

Tuberculous Otitis

Tuberculous otitis media is rare and frequently misdiagnosed. Half of the cases have no other evidence of present or past TB. The classic clinical picture is painless otorrhea with multiple tympanic perforations, exuberant granulation tissue, early severe hearing loss, and mastoid bone necrosis. The diagnosis has been missed for years by excellent otolaryngologists, even when tissue was available. Tuberculous otitis may be complicated by facial nerve paralysis. Response to drug therapy is excellent, and surgery is usually not required.[475]

Miscellaneous Conditions

TB of the aorta with or without aneurysm formation can be caused by spread from contiguous diseased nodes, pericarditis, spondylitis, paravertebral abscesses, or empyema. Extensive hematogenous dissemination or aortic rupture may occur. TB produces various ocular syndromes, including choroidal tubercles, uveitis, iritis, and episcleritis (see Chapter 115). An interesting observation has been made in patients with uveitis (most suggestive of sarcoidosis) who had positive interferon-γ release assays to TB. Fifteen of the 20 patients had lived in an area endemic for TB before moving to the Netherlands. Despite the absence of documented tuberculous infection elsewhere in the body, antituberculosis therapy was associated with remission in 91% of those treated.[476] During disseminated TB in areas of high TB prevalence, choroidal TB (usually without symptoms) may occur in 5% to 20% of patients.[477] TB may also involve the breast, producing abscesses, sclerosing lesions resembling carcinoma, and multiple nodules. Destructive nasal lesions resembling Wegener granulomatosis both clinically and histologically have been caused by TB.[478] TB of the adrenal glands may cause adrenal enlargement with or without calcification, as may histoplasmosis, but granulomatous adrenal TB may cause Addison disease without either calcification or adrenal enlargement.[479]

Mycobacterium bovis and Bacillus Calmette-Guérin

M. bovis is a member of the *M. tuberculosis* complex. Isolation requires that decontamination and culture procedures used for TB be optimized. Sodium pyruvate is often substituted for glycerol in the culture medium. *M. bovis* may be mistaken as *M. tuberculosis* clinically, but molecular methods including WGS can distinguish the two. The BCG strain of *M. bovis* is used to vaccinate against TB. BCG Tice and BCG Connaught are the most widely used strains in North America and Europe, but very many other strains have been used to treat bladder cancer.[480]

Unlike *M. tuberculosis, M. bovis* largely infects humans as a zoonosis. Cattle are the primary reservoir, but a large variety of warm-blooded animals may be infected. In developing countries, infection is acquired from close contact with infected cattle or ingestion of infected dairy products.[481,482] From 2006 to 2013, *M. bovis* caused approximately 1% of TB cases in the United States, with higher prevalence among infants and children, foreign-born patients, Hispanics, females, and persons living near the Mexican border.[480] *M. bovis* infection may also complicate intravesicular BCG administered to treat intraepithelial bladder cancer.[483,484]

Intravesicular BCG is given as a series of bladder injections through a catheter, with each instillation containing as many as 8×10^8 bacilli. Symptoms of cystitis are common during treatment. Infections within the genitourinary tract can appear during the following weeks and may manifest as ulcers, plaques, or nodules in the bladder or urethra. Epididymo-orchitis or prostatitis may also occur months later. Spread beyond the urinary tract affects 3% to 7% of recipients.[483] A sepsis-like syndrome after intravesicular BCG manifests as fever, hypotension, and dyspnea. This can occur in the first few days after injection or appear with insidious onset of malaise, low-grade fever, weight loss, and dyspnea many weeks later.[485] A miliary pattern may affect the lungs. Granulomas may be seen in bone marrow, but cultures of blood and bone marrow are usually negative. Focal lesions can appear weeks or even years after intravesicular therapy, including thoracolumbar spondylodiscitis, granulomatous hepatitis, arthritis, uveitis, and mycotic aneurysm.[484] In a series of 20 cases of mycotic aortic aneurysm, the peak incidence was at 6 weeks after treatment, with declining incidence over 7 years.[486] In another series of mycotic aneurysms after intravesicular BCG, average time to diagnosis was 19 months.[487] Vascular grafts and prosthetic joints may also become infected. Culture isolation of *M. bovis* has occurred in only 41% of reported cases, although PCR may be positive at culture-negative sites.[483] Disruption of mucosal integrity from a recent urologic procedure or during the bladder treatment is suspected but unproven as the predisposing factor.[483]

Treatment largely includes RIF, INH, and EMB for 2 to 3 months, followed by 6 months of INH and RIF.[483,484] Most strains of *M. bovis*, including BCG strains, are PZA resistant. Fluoroquinolones have successfully replaced INH or RIF in some cases. Results are generally favorable except with mycotic aneurysm, which has a poor outcome.[486,487]

Ingestion of *M. bovis* in unpasteurized dairy products can cause cervical lymphadenitis.[488] Pulmonary *M. bovis* infection resembles typical TB and is acquired from exposure to infected animals or, rarely, humans.[489] In North America, reactivation of *M. bovis* acquired in other countries may occur. *M. bovis* accounts for 0.3% of diagnosed pulmonary TB cases in the Americas.[481] Isolates acquired from animals or humans, and rarely from vaccine, may be resistant to INH or RIF.[490]

In countries where BCG vaccine is routinely given to children, unrecognized primary immune deficiencies such as severe combined immunodeficiency or mutations in the IL-12/interferon-γ axis may predispose to disseminated *M. bovis* infection. In this setting, infection occurs at the injection site, contiguous axillary lymph nodes, and distant sites including bones. Restoration of immune response by means of allogeneic hematopoietic stem cell transplantation may be required for cure.[491]

Key References

The complete reference list is available online at Expert Consult.

1. World Health Organization, Tuberculosis (TB). http://www.who.int/tb/en/.
2. Shea KM, Kammerer JS, Winston CA, et al. Estimated rate of reactivation of latent tuberculosis infection in the United States, overall and by population subgroup. *Am J Epidemiol*. 2014;179:216–225.
3. Schmit KM, Wansaula Z, Pratt R, et al. Tuberculosis—United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2017;66:289–294.
4. Ho J, Byrne AL, Linh NN, et al. Decentralized care for multidrug resistant tuberculosis: a systematic review and meta-analysis. *Bull World Health Organ*. 2017;95:584–593.
5. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet*. 2006;368:1575–1580.
9. Ernst JD, Trevejo-Nunez G, Banaiee N. Genomics and the evolution, pathogenesis, and diagnosis of tuberculosis. *J Clin Invest*. 2007;117:1738–1745.
12. Gagneux S, Small PM. Global phylogeography of *Mycobacterium tuberculosis* and implications for tuberculosis product development. *Lancet Infect Dis*. 2007;7:328–337.
15. Gutierrez MC, Brisse S, Brosch R, et al. Ancient origin and gene mosaicism of the progenitor of *Mycobacterium tuberculosis*. *PLoS Pathog*. 2005;1:e5.
17. Mase SR, Ramsay A, Ng V, et al. Yield of serial sputum specimen examinations in the diagnosis of pulmonary tuberculosis: a systematic review. *Int J Tuberc Lung Dis*. 2007;11:485–495.
21. World Health Organization. Fluorescent Light-Emitting Diode (LED) Microscopy for Diagnosis of Tuberculosis Policy: Policy Statement. http://whqlibdoc.who.int/publications/2011/9789241501613_eng.pdf. Accessed May 28, 2014.
24. Hanna BA, Ebrahimzadeh A, Elliott LB, et al. Multicenter evaluation of the BACTEC MGIT 960 system for recovery of mycobacteria. *J Clin Microbiol*. 1999;37:748–752.
26. Moore DA, Evans CA, Gilman RH, et al. Microscopic-observation drug-susceptibility assay for the diagnosis of TB. *N Engl J Med*. 2006;355:1539–1550.
27. Kirwan DE, Ugarte-Gil C, Gilman RH, et al. Microscopic observation drug susceptibility assay for rapid diagnosis of lymph node tuberculosis and detection of drug resistance. *J Clin Microbiol*. 2016;54:185–189.
28. Wang L, Mohammad SH, Chaiyasirinroje B, et al. Evaluating the Auto-MODS assay, a novel tool for tuberculosis diagnosis for use in resource-limited settings. *J Clin Microbiol*. 2015;53:172–178.
29. Martin L, Coronel J, Faulx D, et al. A field evaluation of the Hardy TB MODS Kit for the rapid phenotypic diagnosis of tuberculosis and multi-drug resistant tuberculosis. *PLoS ONE*. 2014;9:e107258.
32. Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med*. 2010;363:1005–1015.

33. Sohn H, Aero AD, Menzies D, et al. Xpert MTB/RIF testing in a low tuberculosis incidence, high-resource setting: limitations in accuracy and clinical impact. *Clin Infect Dis*. 2014;58:970–976.
34. Luetkemeyer AF, Firnhaber C, Kendall MA, et al. Evaluation of Xpert MTB/RIF to identify pulmonary tuberculosis in tuberculosis suspects from low and higher prevalence settings compared to acid fast smear and culture. *Clin Infect Dis*. 2016;62:1081–1088.
35. Rufai SB, Singh A, Kumar P, et al. Performance of Xpert MTB/RIF assay in diagnosis of pleural tuberculosis by use of pleural fluid samples. *J Clin Microbiol*. 2015;53:3636–3638.
36. Abdurrahman ST, Mbanaso O, Lawson L, et al. Testing pooled sputum with Xpert MTB/RIF for diagnosis of pulmonary tuberculosis to increase affordability in low-income countries. *J Clin Microbiol*. 2015;53:2502–2508.
37. Churchyard GJ, Stevens WS, Mametja LD, et al. Xpert MTB/RIF versus sputum microscopy as the initial diagnostic test for tuberculosis: a cluster-randomised trial embedded in South African roll-out of Xpert MTB/RIF. *Lancet Glob Health*. 2015;3:e450–e457.
38. Division of Microbiology Devices, Office of In Vitro Diagnostics and Radiological Health, Center for Devices and Radiological Health, Food and Drug Administration; Centers for Disease Control and Prevention. Revised device labeling for the Cepheid Xpert MTB/RIF assay for detecting *Mycobacterium tuberculosis*. *MMWR Morb Mortal Wkly Rep*. 2015;64:193.
39. Lippincott CK, Miller MB, Popowitch EB, et al. Xpert MTB/RIF assay shortens airborne isolation for hospitalized patients with presumptive tuberculosis in the United States. *Clin Infect Dis*. 2014;59:186–192.
40. Marcy O, Ung V, Goyet S, et al. Performance of Xpert MTB/RIF and alternative specimen collection methods for the diagnosis of tuberculosis in HIV-infected children. *Clin Infect Dis*. 2016;62:1161–1168.
41. Theron G, Venter R, Calligaro G, et al. Xpert MTB/RIF results in patients with previous tuberculosis: can we distinguish true from false positive results? *Clin Infect Dis*. 2016;62:995–1001.
50. Ling DI, Flores LL, Riley LW, et al. Commercial nucleic-acid amplification tests for diagnosis of pulmonary tuberculosis in respiratory specimens: meta-analysis and meta-regression. *PLoS ONE*. 2008;3:e1536.
52. Lawn SD. Point-of-care detection of lipoarabinomannan (LAM) in urine for diagnosis of HIV-associated tuberculosis: a state of the art review. *BMC Infect Dis*. 2012;12:103–114.
54. Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med*. 2000;161:1376–1395.
59. Bemer P, Palicova F, Rusch-Gerdes S, et al. Multicenter evaluation of fully automated BACTEC Mycobacteria Growth Indicator Tube 960 system for susceptibility testing of *Mycobacterium tuberculosis*. *J Clin Microbiol*. 2002;40:150–154.
65. Sanchez-Padilla E, Merker M, Beckert P, et al. Detection of drug-resistant tuberculosis by Xpert MTB/RIF in Swaziland. *N Engl J Med*. 2015;372:1181–1182.
67. Barnard M, Albert H, Coetzee G, et al. Rapid molecular screening for multidrug-resistant tuberculosis in a high-volume public health laboratory in South Africa. *Am J Respir Crit Care Med*. 2008;177:787–792.
70. World Health Organization. Molecular Line Probe Assays for Rapid Screening of Patients at Risk of Multidrug-Resistant Tuberculosis (MDR-TB). http://www.who.int/tb/features_archive/mdrtb_rapid_tests/en/index.html. Accessed May, 2014.
71. Kipiani M, Mirtskhulava V, Tukvadze N, et al. Significant clinical impact of a rapid molecular diagnostic test (Genotype MTBDRplus assay) to detect multidrug-resistant tuberculosis. *Clin Infect Dis*. 2014;59:1559–1566.
77. Styblo K. Recent advances in epidemiological research in tuberculosis. *Adv Tuberc Res*. 1980;20:1–63.
78. Ribeiro FK, Pan W, Bertolde A, et al. Genotypic and spatial analysis of *Mycobacterium tuberculosis* transmission in a high-incidence urban setting. *Clin Infect Dis*. 2015;61:758–766.
80. Mancuso JD, Diffenderfer JM, Ghassemieh BJ, et al. The prevalence of latent tuberculosis infection in the United States. *Am J Respir Crit Care Med*. 2016;194:501–509.
81. Liu Y, Painter JA, Posey DL, et al. Estimating the impact of newly arrived foreign-born persons on tuberculosis in the United States. *PLoS ONE*. 2012;7:e32158.
83. Liu Y, Posey DL, Cetron MS, et al. Effect of a culture-based screening algorithm on tuberculosis incidence in immigrants and refugees bound for the United States: a population-based cross-sectional study. *Ann Intern Med*. 2015;162:420–428.
84. Winston CA, Menzies HJ. Pediatric and adolescent tuberculosis in the United States, 2008-2010. *Pediatrics*. 2012;130:e1425–e1432.
92. Khan K, Wang J, Hu W, et al. Tuberculosis infection in the United States: national trends over three decades. *Am J Respir Crit Care Med*. 2008;177:455–460.
94. Cain KP, Benoit SR, Winston CA, et al. Tuberculosis among foreign-born persons in the United States. *JAMA*. 2008;300:405–412.
97. Stead WW, Lofgren JP, Warren E, et al. Tuberculosis as an endemic and nosocomial infection among the elderly in nursing homes. *N Engl J Med*. 1985;312:1483–1487.
107. Wang L, Zhang H, Ruan Y, et al. Tuberculosis prevalence in China, 1990-2010; a longitudinal analysis of national survey data. *Lancet*. 2014;383:2057–2064.
110. Yang C, Shen X, Peng Y, et al. Transmission of *Mycobacterium tuberculosis* in China: a population-based molecular epidemiologic study. *Clin Infect Dis*. 2015;61:219–227.
112. From the Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report. Notice to readers: revised definition of extensively drug-resistant tuberculosis. *JAMA*. 2006;296:2792.
118. Zignol M, van Gemert W, Falzon D, et al. Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007-2010. *Bull World Health Organ*. 2012;90:111D–119D.
122. Templeton GL, Illing LA, Young L, et al. The risk for transmission of *Mycobacterium tuberculosis* at the bedside and during autopsy. *Ann Intern Med*. 1995;122:922–925.
123. Aguado JM, Torre-Cisneros J, Fortún J, et al. Tuberculosis in solid-organ transplant recipients: consensus statement of the group for the study of infection in transplant recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology. *Clin Infect Dis*. 2009;48:1276–1284.
124. Mortensen E, Hellinger W, Keller C, et al. Three cases of donor-derived pulmonary tuberculosis in lung transplant recipients and review of 12 previously reported cases: opportunities for early diagnosis and prevention. *Transpl Infect Dis*. 2014;16:67–75.
125. Haddad MB, Mitruka K, Oeltmann JE, et al. Characteristics of tuberculosis cases that started outbreaks in the United States, 2002-2011. *Emerg Infect Dis*. 2015;21:508–510.
126. O'Shea MK, Koh GC, Munang M, et al. Time-to-detection in culture predicts risk of *Mycobacterium tuberculosis* transmission: a cohort study. *Clin Infect Dis*. 2014;59:177–185.
127. Stead WW. Tuberculosis among elderly persons: an outbreak in a nursing home. *Ann Intern Med*. 1981;94:606–610.
130. Cruciani M, Malena M, Bosco O, et al. The impact of human immunodeficiency virus type 1 on infectiousness of tuberculosis: a meta-analysis. *Clin Infect Dis*. 2001;33:1922–1930.
131. Huang CC, Tchetgen ET, Becerra MC, et al. The effect of HIV-related immunosuppression on the risk of tuberculosis transmission to household contacts. *Clin Infect Dis*. 2014;58:765–774.
134. Trauer JM, Moyo N, Tay EL, et al. Risk of active tuberculosis in the five years following infection … 15%? *Chest*. 2016;149:516–525.
136. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med*. 1989;320:545–555.
137. Daley CL, Small PM, Schecter GF. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. *N Engl J Med*. 1992;36:231–235.
139. Pearson ML, Jereb JA, Frieden TR. Nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis:* a risk to patients and healthcare workers. *Ann Intern Med*. 1992;117:191–196.
141. Edlin BR, Tokars JI, Grieco MH, et al. An outbreak of multi-drug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1992;326:1514–1521.
156. Mphaphlele M, Dharmadhikari AS, Jensen PA, et al. Institutional tuberculosis transmission. controlled trial of upper room ultraviolet air disinfection: a basis for new dosing guidelines. *Am J Respir Crit Care Med*. 2015;192:477–484.
158. O'Garra A, Redford PS, McNab FW, et al. The immune response in tuberculosis. *Annu Rev Immunol*. 2013;31:475–527.
159. Comas I, Chakravartti J, Small PM, et al. Human T cell epitopes of *Mycobacterium tuberculosis* are evolutionarily hyperconserved. *Nat Genet*. 2010;42:498–503.
163. Canetti G. Present aspects of bacterial resistance in tuberculosis. *Am Rev Respir Dis*. 1965;92:687–703.
172. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. *MMWR Recomm Rep*. 2000;49(RR–6):1–51.
176. Pérez-Barbosa L, Esquivel-Valerio JA, Arana Guajardo AC, et al. Increased detection of latent tuberculosis by tuberculin skin test and booster phenomenon in early rheumatoid arthritis patients. *Rheumatol Int*. 2015;35:1555–1559.
178. Slovis BS, Plitman JD, Haas DW. The case against anergy testing as a routine adjunct to tuberculin skin testing. *JAMA*. 2000;283:2003–2007.
183. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection—United States, 2010. *MMWR Recomm Rep*. 2010;59(RR–5):1–25.
184. Roth PJ, Grim SA, Gallitano S, et al. Serial testing for latent tuberculosis infection in transplant candidates: a retrospective review. *Transpl Infect Dis*. 2016;18:14–21.
185. Andrews JR, Hatherill M, Mahomed H, et al. The dynamics of QuantiFERON-TB gold in-tube conversion and reversion in a cohort of South African adolescents. *Am J Respir Crit Care Med*. 2015;191:584–591.
186. Sester M, van Leth F, Bruchfeld J, et al. Risk assessment of tuberculosis in immunocompromised patients. A TBNET study. *Am J Respir Crit Care Med*. 2014;190:1168–1176.
190. Ewer K, Deeks J, Alvarez L, et al. Comparison of T-cell–based assay with tuberculin skin test for diagnosis of *Mycobacterium tuberculosis* infection in a school tuberculosis outbreak. *Lancet*. 2003;361:1168–1173.
191. King TC, Upfal M, Gottlieb A, et al. T-SPOT.TB Interferon-γ release assay performance in healthcare worker screening at nineteen U.S. hospitals. *Am J Respir Crit Care Med*. 2015;192:367–373.
195. Romeyn JA. Exogenous reinfection in tuberculosis. *Am Rev Respir Dis*. 1970;101:923–927.
196. Marx FM, Dunbar R, Enarson DA, et al. The temporal dynamics of relapse and reinfection tuberculosis after successful treatment: a retrospective cohort study. *Clin Infect Dis*. 2014;58:1676–1683.
204. Ou SM, Fan WC, Chou KT, et al. Systemic sclerosis and the risk of tuberculosis. *J Rheumatol*. 2014;41:1662–1669.
205. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha–neutralizing agent. *N Engl J Med*. 2001;345:1098–1104.
207. Carpio D, Jauregui-Amezaga A, de Francisco R, et al. Tuberculosis in anti-tumor necrosis factor treated inflammatory bowel disease patients after the implementation of preventive measures: compliance with recommendations and safety of retreatment. *J Crohns Colitis*. 2016;10:1186–1193.
208. Kisacik B, Pamuk ON, Onat AM, et al. Characteristics predicting tuberculosis risk under tumor necrosis factor-α inhibitors: report from a large multicenter cohort with high background prevalence. *J Rheumatol*. 2016;43:524–529.
209. Kim ES, Song GA, Cho KB, et al. Significant risk and associated factors of active tuberculosis infection in Korean patients with inflammatory bowel disease using anti-TNF agents. *World J Gastroenterol*. 2015;21:3308–3316.
210. Marcy O, Laureillard D, Madec Y, et al. Causes and determinants of mortality in HIV-infected adults with tuberculosis: an analysis from the CAMELIA ANRS 1295-CIPRA KH001 randomized trial. *Clin Infect Dis*. 2014;59:435–445.
211. Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med*. 2010;363:257–265.
214. Pitchenik AE, Rubinson HA. The radiographic appearance of tuberculosis in patients with the acquired immune deficiency syndrome (AIDS) and pre-AIDS. *Am Rev Respir Dis*. 1985;131:393–396.
215. Chaisson RE, Schecter GF, Theuer CP, et al. Tuberculosis in patients with the acquired immunodeficiency syndrome: clinical features, response to therapy, and survival. *Am Rev Respir Dis*. 1987;136:570–574.
216. Mtei L, Matee M, Herfort O, et al. High rates of clinical and subclinical tuberculosis among HIV-infected ambulatory subjects in Tanzania. *Clin Infect Dis*. 2005;40:1500–1507.
218. Behr MA, Warren SA, Salamon H, et al. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. *Lancet*. 1999;353:444–449.
224. Jones BE, Oo MM, Taikwel EK, et al. CD4 cell counts in human immunodeficiency virus-negative patients with tuberculosis. *Clin Infect Dis*. 1997;24:988–991.
231. Fisk TL, Hon HM, Lennox JL, et al. Detection of latent tuberculosis among HIV-infected patients after initiation of highly active antiretroviral therapy. *AIDS*. 2003;17:1102–1104.

238. Thompson BC. Survival rates in pulmonary tuberculosis. *Br Med J*. 1943;2:721.
239. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63:e147–e195.
241. Hayashi PH, Fontana RJ, Chalasani NP, et al. Under-reporting and poor adherence to monitoring guidelines for severe cases of isoniazid hepatotoxicity. *Clin Gastroenterol Hepatol*. 2015;13:1676–1682.e1.
245. Panel on Antiretroviral Guidelines for Adults and Adolescents, U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Updated October 17, 2017. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0 Accessed February 20, 2018.
247. Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med*. 2014;371:1599–1608.
251. Ijaz K, Jereb JA, Lambert LA, et al. Severe or fatal liver injury in 50 patients in the United States taking rifampin and pyrazinamide for latent tuberculosis infection. *Clin Infect Dis*. 2006;42:346–355.
256. Conde MB, Efron A, Loredo C, et al. Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomised, controlled phase II trial. *Lancet*. 2009;373:1183–1189.
257. Lee H, Jeong BH, Park HY, et al. Treatment outcomes with fluoroquinolone-containing regimens for isoniazid-resistant pulmonary tuberculosis. *Antimicrob Agents Chemother*. 2015;60:471–477.
258. Selvakumar N, Kumar V, Balaji S, et al. High rates of ofloxacin resistance in *Mycobacterium tuberculosis* among both new and previously treated patients in Tamil Nadu, South India. *PLoS ONE*. 2015;10:e0117421.
259. Thee S, Garcia-Prats JA, Draper HR, et al. Pharmacokinetics and safety of moxifloxacin in children with multidrug-resistant tuberculosis. *Clin Infect Dis*. 2015;60:549–556.
260. Merle CS, Fielding K, Sow OB, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. *N Engl J Med*. 2014;371:1588–1598.
261. Gillespie SH, Crook AM, McHugh TD, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med*. 2014;371:1577–1587.
262. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N Engl J Med*. 2009;360:2397–2405.
264. Gugglielmetti L, Le Du D, Jachym M, et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. *Clin Infect Dis*. 2015;60:188–194.
265. Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med*. 2014;371:723–732.
266. Cox E, Laessig K. FDA approval of bedaquiline—the benefit-risk balance for drug-resistant tuberculosis. *N Engl J Med*. 2014;371:689–691.
268. Akkerman OW, Odish OF, Bolhuis MS, et al. Pharmacokinetics of bedaquiline in cerebrospinal fluid and serum in multidrug-resistant tuberculous meningitis. *Clin Infect Dis*. 2016;62:523–524.
269. Svensson EM, Murray S, Karlsson MO, et al. Rifampicin and rifapentine significantly reduce concentrations of bedaquiline, a new anti-TB drug. *J Antimicrob Chemother*. 2015;70:1106–1114.
270. Svensson EM, Dooley KE, Karlsson MO. Impact of lopinavir-ritonavir or nevirapine on bedaquiline exposures and potential implications for patients with tuberculosis-HIV coinfection. *Antimicrob Agents Chemother*. 2014;58:6406–6412.
271. Centers for Disease Control and Prevention. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. *MMWR Recomm Rep*. 2013;62(RR–09):1–12.
272. Van Deun A, Maug AK, Salim MA, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med*. 2010;182:684–692.
274. Low M The tuberculosis treatment pipeline. http://www.pipelinereport.org/2017/tbtx. Accessed February 20, 2018.
277. Olaru ID, von Groote-Bidlingmaier F, Heyckendorf J, et al. Novel drugs against tuberculosis: a clinician's perspective. *Eur Respir J*. 2014;45:1119–1131.
278. Szumowski JD, Lynch JB. Profile of delamanid for the treatment of multidrug-resistant tuberculosis. *Drug Des Devel Ther*. 2015;9:677–682.
279. Dawson R, Diacon AH, Everitt D, et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. *Lancet*. 2015;385:1738–1747.
283. British Thoracic Association. A controlled trial of six months chemotherapy in pulmonary tuberculosis. Second report: results during the 24 months after the end of chemotherapy. *Am Rev Respir Dis*. 1982;126:460–462.
286. Hopewell PC, Pai M, Maher D, et al. International standards for tuberculosis care. *Lancet Infect Dis*. 2006;6:710–725.
288. World Health Organization - Guidelines for treatment of drug-susceptible tuberculosis and patient care. 2017 update. WHO/HTM/2017.05 http://www.who.int/tb/publications/2017/dstb_guidance_2017/en/ Accessed February 20, 2018.
294. Weis SE, Slocum PC, Blais FX, et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *N Engl J Med*. 1994;330:1179–1184.
297. Cegielski JP, Dalton T, Yagui M, et al. Extensive drug resistance acquired during treatment of multidrug-resistant tuberculosis. *Clin Infect Dis*. 2014;59:1049–1063.
298. Ershova JV, Kurbatova EV, Moonan PK, et al. Mortality among tuberculosis patients with acquired resistance to second-line antituberculosis drugs—United States, 1993-2008. *Clin Infect Dis*. 2014;59:465–472.
299. Cegielski JP, Kurbatova E, van der Walt M, et al. Multidrug-resistant tuberculosis treatment outcomes in relation to treatment and initial versus acquired second-line drug resistance. *Clin Infect Dis*. 2016;62:418–430.
300. Velásquez GE, Becerra MC, Gelmanova IY, et al. Improving outcomes for multidrug-resistant tuberculosis: aggressive regimens prevent treatment failure and death. *Clin Infect Dis*. 2014;59:9–15.
301. Bastos ML, Hussain H, Weyer K, et al. Treatment outcomes of patients with multidrug-resistant and extensively drug-resistant tuberculosis according to drug susceptibility testing to first- and second-line drugs: an individual patient data meta-analysis. *Clin Infect Dis*. 2014;59:1364–1374.
302. Goble M, Iseman MD, Madsen LA. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med*. 1993;328:527–532.
308. Tang S, Yao L, Hao X, et al. Clofazimine for the treatment of multidrug-resistant tuberculosis: prospective, multicenter, randomized controlled study in China. *Clin Infect Dis*. 2015;60:1361–1367.
309. Kurbatova EV, Cavanaugh JS, Dalton T, et al. Epidemiology of pyrazinamide-resistant tuberculosis in the United States, 1999-2009. *Clin Infect Dis*. 2013;57:1081–1093.
310. Yew WW, Chan CK, Chau CH, et al. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. *Chest*. 2000;117:744–751.
316. Bloemberg GV, Keller PM, Stucki D, et al. Acquired resistance to bedaquiline and delamanid in therapy for tuberculosis. *N Engl J Med*. 2015;373:1986–1988.
317. Tiberi S, Sotgiu G, D'Ambrosio L, et al. Effectiveness and safety of imipenem/clavulanate added to an optimized background regimen (OBR) versus OBR controls regimens in the treatment of multidrug and extensively drug-resistant tuberculosis. *Clin Infect Dis*. 2016;62:1188–1190.
320. Mitnick CD, Shin SS, Seung KJ, et al. Comprehensive treatment of extensively drug-resistant tuberculosis. *N Engl J Med*. 2008;359:563–574.
321. Pietersen E, Ignatius E, Streicher EM, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. *Lancet*. 2014;383:1230–1239.
323. Lee M, Cho SN, Barry CE 3rd, et al. Linezolid for XDR-TB–final study outcomes. *N Engl J Med*. 2015;373:290–291.
324. Tang S, Yao L, Hao X, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. *Eur Respir J*. 2015;45:161–170.
325. Padayatchi N, Gopal M, Naidoo R, et al. Clofazimine in the treatment of extensively drug-resistant tuberculosis with HIV coinfection in South Africa: a retrospective cohort study. *J Antimicrob Chemother*. 2014;69:3103–3107.
326. Fitzgerald DW, Desvarieux M, Severe P, et al. Effect of post-treatment isoniazid on prevention of recurrent tuberculosis in HIV-1-infected individuals: a randomised trial. *Lancet*. 2000;356:1470–1474.
330. Centers for Disease Control and Prevention. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis. Updated June 2013. http://www.cdc.gov/tb/TB_HIV_Drugs/default.htmtbhiv.pdf. Accessed May 28, 2014.
338. Boulle A, Van CG, Cohen K, et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA*. 2008;300:530–539.
340. Narendran G, Menon PA, Venkatesan P, et al. Acquired rifampicin resistance in thrice-weekly antituberculosis therapy: impact of HIV and antiretroviral therapy. *Clin Infect Dis*. 2014;59:1798–1804.
342. Xie YL, Rosen LB, Sereti I, et al. Severe paradoxical reaction during treatment of disseminated tuberculosis in a patient with neutralizing anti-IFNγ autoantibodies. *Clin Infect Dis*. 2016;62:770–773.
343. Narita M, Ashkin D, Hollender ES, et al. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med*. 1998;158:157–161.
346. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*. 2008;8:516–523.
352. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. 2011;365:1471–1481.
353. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. 2011;365:1482–1491.
354. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med*. 2011;365:1492–1501.
357. Ahmad Khan F, Minion J, Al-Motairi A, et al. An updated systematic review and meta-analysis on the treatment of active tuberculosis in patients with HIV infection. *Clin Infect Dis*. 2012;55:1154–1163.
361. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365:2155–2166.
363. Stennis NL, Burzynski JN, Herbert C, et al. Treatment for tuberculosis infection with 3 months of isoniazid and rifapentine in New York City Health Department Clinics. *Clin Infect Dis*. 2016;62:53–59.
364. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent *Mycobacterium tuberculosis* infection. *MMWR Morb Mortal Wkly Rep*. 2011;60:1650–1653.
367. Sterling TR, Moro RN, Borisov AS, et al. Flu-like and other systemic drug reactions among persons receiving weekly rifapentine plus isoniazid or daily isoniazid for treatment of latent tuberculosis infection in the PREVENT Tuberculosis Study. *Clin Infect Dis*. 2015;61:527–535.
373. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med*. 2006;174:935–952.
378. International Union Against Tuberculosis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull World Health Organ*. 1982;60:555–564.
382. TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med*. 2015;373:808–822.
384. Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet*. 2014;384:682–690.
385. Torre-Cisneros J, San-Juan R, Rosso-Fernández CM, et al. Tuberculosis prophylaxis with levofloxacin in liver transplant patients is associated with a high incidence of tenosynovitis: safety analysis of a multicenter randomized trial. *Clin Infect Dis*. 2015;60:1642–1649.
386. Tien V, Robilotti E, Callister D, et al. Tolerability of fluoroquinolones in management of latent tuberculosis in liver transplant candidates. *Clin Infect Dis*. 2015;61:1631–1632.
398. Katagira W, Walter ND, den Boon S, et al. Empiric TB treatment of severely ill patients with HIV and presumed pulmonary TB improves survival. *J Acquir Immune Defic Syndr*. 2016;72:297–303.
415. Garg RK, Malhotra HS, Gupta R. Spinal cord involvement in tuberculous meningitis. *Spinal Cord*. 2015;53:649–657.
416. Erdem H, Ozturk-Engin D, Tireli H, et al. Hamsi scoring in the prediction of unfavorable outcomes from tuberculous meningitis: results of Haydarpasa-II study. *J Neurol*. 2015;262:890–898.
419. Heemskerk AD, Bang ND, Mai NT, et al. Intensified antituberculosis therapy in adults with tuberculous meningitis. *N Engl J Med*. 2016;374:124–134.

420. Roper WH, Waring JJ. Primary serofibrinous pleural effusion in military personnel. *Am Rev Tuberc*. 1955;71:616–634.
428. Abrao FC, de Abreu IR, Miyake DH, et al. Role of adenosine deaminase and the influence of age on the diagnosis of pleural tuberculosis. *Int J Tuberc Lung Dis*. 2014;18:1363–1369.
431. Strang JIG, Gibson DG, Mitchison DA, et al. Controlled clinical trial of complete open surgical drainage and of prednisolone in treatment of tuberculous pericardial effusion in Transkei. *Lancet*. 1988;2:759–763.
432. Strang JIG, Gibson DG, Nunn AJ, et al. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. *Lancet*. 1987;23:1418–1422.
434. Mayosi BM, Ntsekhe M, Bosch J, et al. Prednisolone and *Mycobacterium indicus pranii* in tuberculous pericarditis. *N Engl J Med*. 2014;371:1121–1130.
437. Johansen IS, Nielsen SL, Hove M, et al. Characteristics and clinical outcome of bone and joint tuberculosis from 1994 to 2011: a retrospective register-based study in Denmark. *Clin Infect Dis*. 2015;61:554–562.
476. La Distia Nora R, van Velthoven ME, Ten Dam-van Loon NH, et al. Clinical manifestations of patients with intraocular inflammation and positive QuantiFERON-TB gold in-tube test in a country nonendemic for tuberculosis. *Am J Ophthalmol*. 2014;157:754–761.

References

1. World Health Organization, Global tuberculosis report 2017 http://www.who.int/tb/publications/global_report/en/ Accessed March 1, 2018.
2. Shea KM, Kammerer JS, Winston CA, et al. Estimated rate of reactivation of latent tuberculosis infection in the United States, overall and by population subgroup. *Am J Epidemiol*. 2014;179:216–225.
3. Schmit KM, Wansaula Z, Pratt R, et al. Tuberculosis—United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2017;66:289–294.
4. Ho J, Byrne AL, Linh NN, et al. Decentralized care for multidrug resistant tuberculosis: a systematic review and meta-analysis. *Bull World Health Organ*. 2017;95:584–593.
5. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet*. 2006;368:1575–1580.
6. Pillay M, Sturm AW. Evolution of the extensively drug-resistant F15/LAM4/KZN strain of *Mycobacterium tuberculosis* in Kwa-Zulu-Natal, South Africa. *Clin Infect Dis*. 2007;45:1409–1414.
7. Abubakar I, Zignol M, Falzon D, et al. Drug-resistant tuberculosis: time for visionary political leadership. *Lancet Infect Dis*. 2013;13:529–539.
8. Greenall M, Kunii O, Thomson K, et al. Reaching vulnerable populations: lessons from the Global Fund to Fight AIDS, Tuberculosis and Malaria. *Bull World Health Organ*. 2017;95:159–161.
9. Ernst JD, Trevejo-Nunez G, Banaiee N. Genomics and the evolution, pathogenesis, and diagnosis of tuberculosis. *J Clin Invest*. 2007;117:1738–1745.
10. de Jong BC, Antonio M, Gagneux S. *Mycobacterium africanum*—review of an important cause of human tuberculosis in West Africa. *PLoS Negl Trop Dis*. 2010;4:e744.
11. Evans JT, Smith EG, Banerjee A, et al. Cluster of human tuberculosis caused by *Mycobacterium bovis*: evidence for person-to-person transmission in the UK. *Lancet*. 2007;369:1270–1276.
12. Gagneux S, Small PM. Global phylogeography of *Mycobacterium tuberculosis* and implications for tuberculosis product development. *Lancet Infect Dis*. 2007;7:328–337.
13. Gagneux S. Ecology and evolution of *Mycobacterium tuberculosis*. *Nat Rev Microbiol*. 2018;16:202–213.
14. Oh P, Granich R, Scott J, et al. Human exposure following *Mycobacterium tuberculosis* infection of multiple animal species in a metropolitan zoo. *Emerg Infect Dis*. 2002;8:1290–1293.
15. Gutierrez MC, Brisse S, Brosch R, et al. Ancient origin and gene mosaicism of the progenitor of *Mycobacterium tuberculosis*. *PLoS Pathog*. 2005;1:e5.
16. Apers L, Mutsvangwa J, Magwenzi J, et al. A comparison of direct microscopy, the concentration method and the Mycobacteria Growth Indicator Tube for the examination of sputum for acid-fast bacilli. *Int J Tuberc Lung Dis*. 2003;7:376–381.
17. Mase SR, Ramsay A, Ng V, et al. Yield of serial sputum specimen examinations in the diagnosis of pulmonary tuberculosis: a systematic review. *Int J Tuberc Lung Dis*. 2007;11:485–495.
18. Bonnet M, Ramsay A, Githui W, et al. Bleach sedimentation: an opportunity to optimize smear microscopy for tuberculosis diagnosis in settings of high prevalence of HIV. *Clin Infect Dis*. 2008;46:1710–1716.
19. Steingart KR, Henry M, Ng V, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis*. 2006;6:570–581.
20. Perkins MD, Cunningham J. Facing the crisis: improving the diagnosis of tuberculosis in the HIV era. *J Infect Dis*. 2007;196(suppl 1):S15–S27.
21. World Health Organization. Fluorescent Light-Emitting Diode (LED) Microscopy for Diagnosis of Tuberculosis Policy: Policy Statement. http://whqlibdoc.who.int/publications/2011/9789241501613_eng.pdf. Accessed May 28, 2014.
22. Melese M, Jerene D, Alem G, et al. Decentralization of acid fast bacilli (AFB) external quality assurance using blind rechecking for sputum smear microscopy in Ethiopia. *PLoS ONE*. 2016;11:e0151366.
23. Hale YM, Pfyffer GE, Salfinger M. Laboratory diagnosis of mycobacterial infections: new tools and lessons learned. *Clin Infect Dis*. 2001;33:834–846.
24. Hanna BA, Ebrahimzadeh A, Elliott LB, et al. Multicenter evaluation of the BACTEC MGIT 960 system for recovery of mycobacteria. *J Clin Microbiol*. 1999;37:748–752.
25. Leitritz L, Schubert S, Bucherl B, et al. Evaluation of BACTEC MGIT 960 and BACTEC 460TB systems for recovery of mycobacteria from clinical specimens of a university hospital with low incidence of tuberculosis. *J Clin Microbiol*. 2001;39:3764–3767.
26. Moore DA, Evans CA, Gilman RH, et al. Microscopic-observation drug-susceptibility assay for the diagnosis of TB. *N Engl J Med*. 2006;355:1539–1550.
27. Kirwan DE, Ugarte-Gil C, Gilman RH, et al. Microscopic observation drug susceptibility assay for rapid diagnosis of lymph node tuberculosis and detection of drug resistance. *J Clin Microbiol*. 2016;54:185–189.
28. Wang L, Mohammad SH, Chaiyasirinroje B, et al. Evaluating the Auto-MODS assay, a novel tool for tuberculosis diagnosis for use in resource-limited settings. *J Clin Microbiol*. 2015;53:172–178.
29. Martin L, Coronel J, Faulx D, et al. A field evaluation of the Hardy TB MODS Kit for the rapid phenotypic diagnosis of tuberculosis and multi-drug resistant tuberculosis. *PLoS ONE*. 2014;9:e107258.
30. Lawn SD, Nicol MP. Xpert® MTB/RIF assay: development, evaluation and implementation of a new rapid molecular diagnostic for tuberculosis and rifampicin resistance. *Future Microbiol*. 2011;6:1067–1082.
31. Steingart KR, Schiller I, Horne DJ, et al. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev*. 2014;(1):CD009593.
32. Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med*. 2010;363:1005–1015.
33. Sohn H, Aero AD, Menzies D, et al. Xpert MTB/RIF testing in a low tuberculosis incidence, high-resource setting: limitations in accuracy and clinical impact. *Clin Infect Dis*. 2014;58:970–976.
34. Luetkemeyer AF, Firnhaber C, Kendall MA, et al. Evaluation of Xpert MTB/RIF to identify pulmonary tuberculosis in tuberculosis suspects from low and higher prevalence settings compared to acid fast smear and culture. *Clin Infect Dis*. 2016;62:1081–1088.
35. Rufai SB, Singh A, Kumar P, et al. Performance of Xpert MTB/RIF assay in diagnosis of pleural tuberculosis by use of pleural fluid samples. *J Clin Microbiol*. 2015;53:3636–3638.
36. Abdurrahman ST, Mbanaso O, Lawson L, et al. Testing pooled sputum with Xpert MTB/RIF for diagnosis of pulmonary tuberculosis to increase affordability in low-income countries. *J Clin Microbiol*. 2015;53:2502–2508.
37. Churchyard GJ, Stevens WS, Mametja LD, et al. Xpert MTB/RIF versus sputum microscopy as the initial diagnostic test for tuberculosis: a cluster-randomised trial embedded in South African roll-out of Xpert MTB/RIF. *Lancet Glob Health*. 2015;3:e450–e457.
38. Division of Microbiology Devices, Office of In Vitro Diagnostics and Radiological Health, Center for Devices and Radiological Health, Food and Drug Administration; Centers for Disease Control and Prevention. Revised device labeling for the Cepheid Xpert MTB/RIF assay for detecting *Mycobacterium tuberculosis*. *MMWR Morb Mortal Wkly Rep*. 2015;64:193.
39. Lippincott CK, Miller MB, Popowitch EB, et al. Xpert MTB/RIF assay shortens airborne isolation for hospitalized patients with presumptive tuberculosis in the United States. *Clin Infect Dis*. 2014;59:186–192.
40. Marcy O, Ung V, Goyet S, et al. Performance of Xpert MTB/RIF and alternative specimen collection methods for the diagnosis of tuberculosis in HIV-infected children. *Clin Infect Dis*. 2016;62:1161–1168.
41. Theron G, Venter R, Calligaro G, et al. Xpert MTB/RIF results in patients with previous tuberculosis: can we distinguish true from false positive results? *Clin Infect Dis*. 2016;62:995–1001.
42. Chakravorty S, Simmons AM, Rowneki M, et al. The new Xpert MTB/RIF Ultra: improving detection of *Mycobacterium tuberculosis* and resistance to rifampin in an assay suitable for point-of-care testing. *MBio*. 2017;8:pii: e812–pii: e817.
43. Dorman SE, Schumacher SG, Alland D, et al. Xpert MTB/RIF Ultra for detection of *Mycobacterium tuberculosis* and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *Lancet Infect Dis*. 2018;18:76–84.
44. Bahr NC, Nuwagira E, Evans EE, et al. Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. *Lancet Infect Dis*. 2018;18:68–75.
45. Kendall EA, Shumacher SG, Denkinger CM, et al. Estimated clinical impact of the Xpert MTB/RIF Ultra cartridge for diagnosis of pulmonary tuberculosis: a modeling study. *PLoS Med*. 2017;14:e1002472.
46. Barnes PF. Rapid diagnostic tests for tuberculosis—progress but no gold standard. *Am J Respir Crit Care Med*. 1997;155:1497–1498.
47. Guerrera RL, Hooper NM, Baker JF, et al. Use of the amplified *Mycobacterium tuberculosis* Direct Test in a public health laboratory. *Chest*. 2007;132:946–951.
48. Chen X, Yang Q, Chen Y. Real time PCR and amplified MTD for rapid detection of *Mycobacterium tuberculosis* in pulmonary specimens. *Int J Tuberc Lung Dis*. 2012;16:235–239.
49. Eddabra R, Benhassou HA. Rapid molecular assays for the detection of tuberculosis. *Pneumonia*. 2018;10:4.
50. Ling DI, Flores LL, Riley LW, et al. Commercial nucleic-acid amplification tests for diagnosis of pulmonary tuberculosis in respiratory specimens: meta-analysis and meta-regression. *PLoS ONE*. 2008;3:e1536.
51. Catanzaro A, Perry S, Clarridge JE, et al. The role of clinical suspicion in evaluating a new diagnostic test for active tuberculosis: results of a multicenter prospective trial. *JAMA*. 2000;283:639–645.
52. Lawn SD. Point-of-care detection of lipoarabinomannan (LAM) in urine for diagnosis of HIV-associated tuberculosis: a state of the art review. *BMC Infect Dis*. 2012;12:103–114.
53. Shah M, Hanrahan C, Wang ZY, et al. Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in HIV-positive adults. *Cochrane Database Syst Rev*. 2016;(5):CD011420.
54. Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med*. 2000;161:1376–1395.
55. Parsons LM, Brosch R, Cole ST, et al. Rapid and simple approach for identification of *Mycobacterium tuberculosis* complex isolates by PCR-based genomic deletion analysis. *J Clin Microbiol*. 2002;40:2339–2345.
56. National TB, Controllers Association/CDC Advisory Group on Tuberculosis Genotyping. Guide to the Application of Genotyping to Tuberculosis Prevention and Control. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2004.
57. United States Centers for Disease Control and Prevention. TB Genotyping. https://www.cdc.gov/tb/programs/genotyping/default.htm Accessed July 5, 2018.
58. Tortoli E, Benedetti M, Fontanelli A, et al. Evaluation of automated BACTEC MGIT 960 system for testing susceptibility of *Mycobacterium tuberculosis* to four major antituberculous drugs: comparison with the radiometric BACTEC 460TB method and the agar plate method of proportion. *J Clin Microbiol*. 2002;40:607–610.
59. Bemer P, Palicova F, Rusch-Gerdes S, et al. Multicenter evaluation of fully automated BACTEC Mycobacteria Growth Indicator Tube 960 system for susceptibility testing of *Mycobacterium tuberculosis*. *J Clin Microbiol*. 2002;40:150–154.
60. Telenti A, Honore N, Bernasconi C, et al. Genotypic assessment of isoniazid and rifampin resistance in *Mycobacterium tuberculosis*: a blind study at reference laboratory level. *J Clin Microbiol*. 1997;35:719–723.
61. Williams DL, Spring L, Gillis TP, et al. Evaluation of a polymerase chain reaction–based universal heteroduplex generator assay for direct detection of rifampin susceptibility of *Mycobacterium tuberculosis* from sputum specimens. *Clin Infect Dis*. 1998;26:446–450.
62. Kim B-J, Kim S-Y, Park B-H, et al. Mutations in the rpoB gene of *Mycobacterium tuberculosis* that interfere with PCR-single-strand conformation polymorphism analysis for rifampin susceptibility testing. *J Clin Microbiol*. 1997;35:492–494.
63. Nachamkin I, Kang C, Weinstein MP. Detection of resistance to isoniazid, rifampin, and streptomycin in clinical isolates of *Mycobacterium tuberculosis* by molecular methods. *Clin Infect Dis*. 1997;24:894–900.
64. Mdluli K, Slayden RA, Zhu Y, et al. Inhibition of a *Mycobacterium tuberculosis* β-ketoacyl ACP synthetase by isoniazid. *Science*. 1998;280:1607–1616.
65. Sanchez-Padilla E, Merker M, Beckert P, et al. Detection of drug-resistant tuberculosis by Xpert MTB/RIF in Swaziland. *N Engl J Med*. 2015;372:1181–1182.
66. Morgan MS, Kalantri S, Flores L, et al. A commercial line probe assay for the rapid detection of rifampicin resistance in *Mycobacterium tuberculosis*: a systematic review and meta-analysis. *BMC Infect Dis*. 2005;5:62.
67. Barnard M, Albert H, Coetzee G, et al. Rapid molecular screening for multidrug-resistant tuberculosis in a high-volume public health laboratory in South Africa. *Am J Respir Crit Care Med*. 2008;177:787–792.
68. Gardee Y, Dreyer AW, Koornhof HJ, et al. Evaluation of the GenoType MTBDRsl version 2.0 assay for second-line drug resistance detection of *Mycobacterium tuberculosis* isolates in South Africa. *J Clin Microbiol*. 2017;55:791–800.
69. Yadav R, Saini A, Kaur P, et al. Diagnostic accuracy of GenoType MTBDRsl Ver 2.0 in detecting second line drug resistance to M. tuberculosis. *Int J Tuberc Lung Dis*. 2018;22:419–424.
70. World Health Organization. Molecular Line Probe Assays for Rapid Screening of Patients at Risk of Multidrug-Resistant Tuberculosis (MDR-TB). http://www.who.int/tb/features_archive/mdrtb_rapid_tests/en/index.html. Accessed May, 2014.

71. Kipiani M, Mirtskhulava V, Tukvadze N, et al. Significant clinical impact of a rapid molecular diagnostic test (Genotype MTBDRplus assay) to detect multidrug-resistant tuberculosis. *Clin Infect Dis*. 2014;59:1559–1566.
72. Papaventsis D, Casali N, Kontsevaya I, et al. Nikolayevskyy V. Whole genome sequencing of *Mycobacterium tuberculosis* for detection of drug resistance: a systematic review. *Clin Microbiol Infect*. 2017;23:61–68.
73. Cryptic Consortium, et al. Prediction of susceptibility to first-line tuberculosis drugs by DNA sequencing. *N Engl J Med*. 2018;379:1403–1415.
74. World Health Organization. Global Tuberculosis Report 2017. http://www.who.int/tb/publications/global_report/en/. Accessed July 5, 2018.
75. Houben RMG, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med*. 2016;13:e1002152.
76. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2095–2128.
77. Styblo K. Recent advances in epidemiological research in tuberculosis. *Adv Tuberc Res*. 1980;20:1–63.
78. Ribeiro FK, Pan W, Bertolde A, et al. Genotypic and spatial analysis of *Mycobacterium tuberculosis* transmission in a high-incidence urban setting. *Clin Infect Dis*. 2015;61:758–766.
79. Stewart RJ, Tsang CA, Pratt RH, et al. Tuberculosis-United States, 2017. *MMWR Morb Mortal Wkly Rep*. 2018;67:317–323.
80. Mancuso JD, Diffenderfer JM, Ghassemieh BJ, et al. The prevalence of latent tuberculosis infection in the United States. *Am J Respir Crit Care Med*. 2016;194:501–509.
81. Liu Y, Painter JA, Posey DL, et al. Estimating the impact of newly arrived foreign-born persons on tuberculosis in the United States. *PLoS ONE*. 2012;7:e32158.
82. Binkin NJ, Zuber PLF, Wells CD, et al. Overseas screening for tuberculosis in immigrants and refugees to the United States: current status. *Clin Infect Dis*. 1996;23:1226–1232.
83. Liu Y, Posey DL, Cetron MS, et al. Effect of a culture-based screening algorithm on tuberculosis incidence in immigrants and refugees bound for the United States: a population-based cross-sectional study. *Ann Intern Med*. 2015;162:420–428.
84. Winston CA, Menzies HJ. Pediatric and adolescent tuberculosis in the United States, 2008-2010. *Pediatrics*. 2012;130:e1425–e1432.
85. Pang J, Teeter LD, Katz DJ, et al. Epidemiology of tuberculosis in young children in the United States. *Pediatrics*. 2014;133:e494.
86. Jereb JA, Kelly GD, Dooley SW, et al. Tuberculosis morbidity in the United States: final data, 1990. *MMWR Morb Mortal Wkly Rep*. 1991;40:23–27.
87. Valway SE, Sanchez MPC, Shinnick TK, et al. An outbreak involving extensive transmission of a virulent strain of *Mycobacterium tuberculosis*. *N Engl J Med*. 1998;338:633–639.
88. Mishu Allos B, Gensheimer KF, Bloch AB, et al. Management of an outbreak of tuberculosis in a small community. *Ann Intern Med*. 1996;125:114–117.
89. Cross ER, Hyams KC. Tuberculin skin testing in US Navy and Marine Corps personnel and recruits, 1980-1986. *Am J Public Health*. 1990;80:435–438.
90. Trump DH, Hyams KC, Cross ER, et al. Tuberculosis infection among young adults entering the US Navy in 1990. *Arch Intern Med*. 1993;153:211–216.
91. Smith B, Ryan MA, Gray GC, et al. Tuberculosis infection among young adults enlisting in the United States Navy. *Int J Epidemiol*. 2002;31:934–939.
92. Khan K, Wang J, Hu W, et al. Tuberculosis infection in the United States: national trends over three decades. *Am J Respir Crit Care Med*. 2008;177:455–460.
93. Zuber PLF, McKenna MT, Binkin NJ, et al. Long-term risk of tuberculosis among foreign-born persons in the United States. *JAMA*. 1997;278:304–307.
94. Cain KP, Benoit SR, Winston CA, et al. Tuberculosis among foreign-born persons in the United States. *JAMA*. 2008;300:405–412.
95. Patel KR. Pulmonary tuberculosis in residents of lodging houses, night shelters and common hostels in Glasgow: a 5-year prospective study. *Br J Dis Chest*. 1985;79:60–66.
96. Nardell E, McInnis B, Thomas B, et al. Exogenous reinfection with tuberculosis in a shelter for the homeless. *N Engl J Med*. 1986;315:1570–1575.
97. Stead WW, Lofgren JP, Warren E, et al. Tuberculosis as an endemic and nosocomial infection among the elderly in nursing homes. *N Engl J Med*. 1985;312:1483–1487.
98. Kim SJ, Hong YP, Lew WJ, et al. Incidence of pulmonary tuberculosis among diabetics. *Tuber Lung Dis*. 1995;76:529–533.
99. Naidoo S, Jinabhai CC. TB in health care workers in KwaZulu-Natal, South Africa. *Int J Tuberc Lung Dis*. 2006;10:676–682.
100. Andrew OT, Schoenfeld PY, Hopewell PC, et al. Tuberculosis in patients with end-stage renal disease. *Am J Med*. 1980;68:59–65.
101. Cuss FM, Carmichael DJ, Linington A, et al. Tuberculosis in renal failure: a high incidence in patients born in the third world. *Clin Nephrol*. 1986;25:129–133.
102. Louie E, Rice LB, Holzm RS. Tuberculosis in non-Haitian patients with acquired immunodeficiency syndrome. *Chest*. 1986;90:542–545.
103. Pitchenik AE, Cole C, Russell BW, et al. Tuberculosis, atypical mycobacteriosis, and the acquired immunodeficiency syndrome among Haitian and non-Haitian patients in South Florida. *Ann Intern Med*. 1984;101:641–645.
104. World Health Organization. Global Tuberculosis Report 2012. http://www.who.int/tb/publications/global_report/gtbr12_main.pdf. Accessed May 28, 2014. http://www.who.int/tb/challenges/mdr/MDR-RR_TB_factsheet_2017.pdf?ua=1.
105. World Health Organization. A World Free of TB. http://www.who.int/tb/en/. Accessed May 28, 2014.
106. Wang L, Liu J, Chin DP. Progress in tuberculosis control and the evolving public-health system in China. *Lancet*. 2007;369:691–696.
107. Wang L, Zhang H, Ruan Y, et al. Tuberculosis prevalence in China, 1990-2010; a longitudinal analysis of national survey data. *Lancet*. 2014;383:2057–2064.
108. Sharma SK, Liu JJ. Progress of DOTS in global tuberculosis control. *Lancet*. 2006;367:951–952.
109. Khatri GR, Frieden TR. Controlling tuberculosis in India. *N Engl J Med*. 2002;347:1420–1425.
110. Yang C, Shen X, Peng Y, et al. Transmission of *Mycobacterium tuberculosis* in China: a population-based molecular epidemiologic study. *Clin Infect Dis*. 2015;61:219–227.
111. UNAIDS. 2008 Report on the Global AIDS Epidemic. United Nations Programme on HIV/AIDS. UNAIDS, Geneva, Switzerland. http://www.unaids.org/en/. Accessed May 28, 2014.
112. From the Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report. Notice to readers: revised definition of extensively drug-resistant tuberculosis. *JAMA*. 2006;296:2792.
113. Pablos-Mendez A, Raviglione MC, Laszlo A, et al. Global surveillance for antituberculosis-drug resistance, 1994-1997. World Health Organization—International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. *N Engl J Med*. 1998;338:1641–1649.
114. Espinal MA, Laszlo A, Simonsen L, et al. Global trends in resistance to antituberculosis drugs. World Health Organization—International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. *N Engl J Med*. 2001;344:1294–1303.
115. Aziz MA, Wright A, Laszlo A, et al. Epidemiology of antituberculosis drug resistance (the Global Project on Anti-tuberculosis Drug Resistance Surveillance): an updated analysis. *Lancet*. 2006;368:2142–2154.
116. Zignol M, Dean AS, Falzon D, et al. Twenty years of global surveillance of antituberculosis-drug resistance. *N Engl J Med*. 2016;375:1081–1089.
117. Wright A, Zignol M, Van Deun A, et al. Epidemiology of antituberculosis drug resistance 2002-07: an updated analysis of the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. *Lancet*. 2009;373:1861–1873.
118. Zignol M, van Gemert W, Falzon D, et al. Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007-2010. *Bull World Health Organ*. 2012;90:111D–119D.
119. Ben-Dov I, Mason G. Drug-resistant tuberculosis in a southern California hospital: trends from 1969 to 1984. *Am Rev Respir Dis*. 1987;135:1307–1310.
120. Mathema B, Andrews JA, Cohen T, et al. Drivers of tuberculosis transmission. *JID*. 2017;216(suppl 6):S644–S653.
121. Frampton MW. An outbreak of tuberculosis among hospital personnel caring for a patient with a skin ulcer. *Ann Intern Med*. 1992;117:312–313.
122. Templeton GL, Illing LA, Young L, et al. The risk for transmission of *Mycobacterium tuberculosis* at the bedside and during autopsy. *Ann Intern Med*. 1995;122:922–925.
123. Aguado JM, Torre-Cisneros J, Fortún J, et al. Tuberculosis in solid-organ transplant recipients: consensus statement of the group for the study of infection in transplant recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology. *Clin Infect Dis*. 2009;48:1276–1284.
124. Mortensen E, Hellinger W, Keller C, et al. Three cases of donor-derived pulmonary tuberculosis in lung transplant recipients and review of 12 previously reported cases: opportunities for early diagnosis and prevention. *Transpl Infect Dis*. 2014;16:67–75.
125. Haddad MB, Mitruka K, Oeltmann JE, et al. Characteristics of tuberculosis cases that started outbreaks in the United States, 2002-2011. *Emerg Infect Dis*. 2015;21:508–510.
126. O'Shea MK, Koh GC, Munang M, et al. Time-to-detection in culture predicts risk of *Mycobacterium tuberculosis* transmission: a cohort study. *Clin Infect Dis*. 2014;59:177–185.
127. Stead WW. Tuberculosis among elderly persons: an outbreak in a nursing home. *Ann Intern Med*. 1981;94:606–610.
128. Klausner JD, Ryder RW, Baende E, et al. *Mycobacterium tuberculosis* in household contacts of human immunodeficiency virus type 1-seropositive patients with active pulmonary tuberculosis in Kinshasa, Zaire. *J Infect Dis*. 1993;168:106–111.
129. Martinez L, Sekandi JN, Castellanos ME, et al. Infectiousness of HIV-seropositive patients with tuberculosis in a high-burden African setting. *Am J Respir Crit Care Med*. 2016;194:1152–1163.
130. Cruciani M, Malena M, Bosco O, et al. The impact of human immunodeficiency virus type 1 on infectiousness of tuberculosis: a meta-analysis. *Clin Infect Dis*. 2001;33:1922–1930.
131. Huang CC, Tchetgen ET, Becerra MC, et al. The effect of HIV-related immunosuppression on the risk of tuberculosis transmission to household contacts. *Clin Infect Dis*. 2014;58:765–774.
132. Cauthen GM, Dooley SW, Onorato IM, et al. Transmission of *Mycobacterium tuberculosis* from tuberculosis patients with HIV infection or AIDS. *Am J Epidemiol*. 1996;144:69–77.
133. Horsburgh CR Jr. Priorities for the treatment of latent tuberculosis infection in the United States. *N Engl J Med*. 2004;350:2060–2067.
134. Trauer JM, Moyo N, Tay EL, et al. Risk of active tuberculosis in the five years following infection … 15%? *Chest*. 2016;149:516–525.
135. Bates JH, Stead WW. The history of tuberculosis as a global epidemic. *Med Clin North Am*. 1993;77:1205–1217.
136. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med*. 1989;320:545–555.
137. Daley CL, Small PM, Schecter GF. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. *N Engl J Med*. 1992;36:231–235.
138. Di Perri G, Danzi MC, DeChecchi G. Nosocomial epidemic of active tuberculosis among HIV-infected patients. *Lancet*. 1989;2:1502–1504.
139. Pearson ML, Jereb JA, Frieden TR. Nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis*: a risk to patients and healthcare workers. *Ann Intern Med*. 1992;117:191–196.
140. Fischl MA, Uttamchandani RB, Daikos GL, et al. An outbreak of tuberculosis caused by multiple-drug resistant tubercle bacilli among patients with HIV infection. *Ann Intern Med*. 1992;11:177–183.
141. Edlin BR, Tokars JI, Grieco MH, et al. An outbreak of multi-drug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1992;326:1514–1521.
142. Kramer F, Modilevsky T, Waliany AR, et al. Delayed diagnosis of tuberculosis in patients with human immunodeficiency virus infection. *Am J Med*. 1990;89:451–456.
143. Gandhi NR, Weissman D, Moodley P, et al. Nosocomial transmission of extensively drug resistant tuberculosis in a rural hospital in South Africa. *JID*. 2013;2017:9–17.
144. Shah S, Auld SC, Brust JCM, et al. Transmission of extensively drug resistant tuberculosis in South Africa. *N Engl J Med*. 2017;376:243–253.
145. Centers for Disease Control and Prevention. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care facilities, 1994. *MMWR Morb Mortal Wkly Rep*. 1994;43:1–132.
146. Cowan JF, Chandler AS, Kracen E, et al. Clinical impact and cost-effectiveness of Xpert MTB/RIF testing in hospitalized patients with presumptive pulmonary tuberculosis in the United States. *Clin Infect Dis*. 2017;64:482–489.
147. National TB. Controllers Association. Consensus statement on the use of Cepheid Xpert MTB/RIF® assay in making decisions to discontinue airborne infection isolation in healthcare settings. http://www.tbcontrollers.org/docs/resources/NTCA_APHL_GeneXpert_Consensus_Statement_Final.pdf. Accessed July 7, 2018.
148. Haddad MB, Wilson TW, Ijaz K, et al. Tuberculosis and homelessness in the United States, 1994-2003. *JAMA*. 2005;293:2762–2766.

149. National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP). Workshop on tuberculosis and homelessness: infection control measures in homeless shelters and other overnight facilities that provide shelter: summary of the workshop held September 28–29, 2015. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, Office of Infectious Diseases, NCHHSTP; 2018.
150. Prevention and control of tuberculosis in correctional and detention facilities: recommendations from CDC. Endorsed by the Advisory Council for the Elimination of Tuberculosis, the National Commission on Correctional Health Care, and the American Correctional Association. *MMWR Recomm Rep*. 2006;55:1–44.
151. Braun MM, Truman BI, Maguire B. Increasing incidence of tuberculosis in a prison inmate population: association with HIV infection. *JAMA*. 1989;261:393–397.
152. Lambert LA, Armstrong LR, Lobato MN, et al. Tuberculosis in jails and prisons: United States 2002-2013. *Am J Public Health*. 2016;106:2231–2237.
153. Sacchi FP, Praça RM, Tatara MB, et al. Prisons as reservoir for community transmission of tuberculosis, Brazi. *Emerg Infect Dis*. 2015;21:452–455.
154. Rao VK, Iademarco EP, Fraser VJ, et al. Delays in the suspicion and treatment of tuberculosis among hospitalized patients. *Ann Intern Med*. 1999;130:404–411.
155. Jensen PA, Lambert LA, Iademarco MF, et al. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR Recomm Rep*. 2005;54:1–141.
156. Mphaphlele M, Dharmadhikari AS, Jensen PA, et al. Institutional tuberculosis transmission. controlled trial of upper room ultraviolet air disinfection: a basis for new dosing guidelines. *Am J Respir Crit Care Med*. 2015;192:477–484.
157. Verkuijl S, Middelkoop K. Protecting our front-liners: occupational tuberculosis prevention through infection control strategies. *Clin Infect Dis*. 2016;62(suppl 3):S231–S237.
158. O'Garra A, Redford PS, McNab FW, et al. The immune response in tuberculosis. *Annu Rev Immunol*. 2013;31:475–527.
159. Comas I, Chakravartti J, Small PM, et al. Human T cell epitopes of *Mycobacterium tuberculosis* are evolutionarily hyperconserved. *Nat Genet*. 2010;42:498–503.
160. Torrelles JB, Schlesinger LS. Integrating lung physiology, immunology, and tuberculosis. *Trends Microbil*. 2017;25:688–697.
161. Lerner TR, Borel S, Guiterrez MG. The innate immune response in human tuberculosis. *Cell Microbiol*. 2015;17:1277–1285.
162. Edwards KM, Cynamon MH, Voladri RK, et al. Iron-cofactored superoxide dismutase inhibits host responses to *Mycobacterium tuberculosis*. *Am J Respir Crit Care Med*. 2001;164:2213–2219.
163. Canetti G. Present aspects of bacterial resistance in tuberculosis. *Am Rev Respir Dis*. 1965;92:687–703.
164. O'Brien JR. Nonreactive tuberculosis. *J Clin Pathol*. 1954;7:216–225.
165. Esmail H, Riou C, Bruyn ED, et al. The immune response to *Mycobacterium tuberculosis* in HIV-1-coinfected persons. *Annu Rev Immunol*. 2018;36:603–618.
166. Simmons JD, Stein CM, Seshadri C, et al Immunologic mechanisms of human resistance to persistent *Mycobacterium tuberculosis* infection. Nat Rev Immunol. 2018.
167. Marx FM, Floyd S, Ayles H, et al. High burden of prevalent tuberculosis among previously treated people in Southern Africa suggests potential for targeted control interventions. *Eur Respir J*. 2016;48:1227–1230.
168. den Boon S, van Lill SW, Borgdorff MW, et al. High prevalence of tuberculosis in previously treated patients, Cape Town, South Africa. *Emerg Infect Dis*. 2007;13:1189–1194.
169. Glynn JR, Murray J, Bester A, et al. High rates of recurrence in HIV-infected and HIV-uninfected patients with tuberculosis. *J Infect Dis*. 2010;201:704–711.
170. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. *Clin Infect Dis*. 2017;64:111–115.
171. Snider DE Jr. The tuberculin skin test. *Am Rev Respir Dis*. 1982;125:108–118.
172. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. *MMWR Recomm Rep*. 2000;49(RR–6):1–51.
173. The use of preventive therapy for tuberculous infection in the United States: recommendations of the Advisory Committee for the Elimination of Tuberculosis. *MMWR Morb Mortal Wkly Rep*. 1990;39:9–12.
174. Stead WW. Management of health care workers after inadvertent exposure to tuberculosis: a guide for the use of preventive therapy. *Ann Intern Med*. 1995;122:906–912.
175. Menzies D. What does tuberculin reactivity after bacille Calmette-Guérin vaccination tell us? *Clin Infect Dis*. 2000;31:S71–S74.
176. Pérez-Barbosa L, Esquivel-Valerio JA, Arana Guajardo AC, et al. Increased detection of latent tuberculosis by tuberculin skin test and booster phenomenon in early rheumatoid arthritis patients. *Rheumatol Int*. 2015;35:1555–1559.
177. Nash DR, Douglass JE. Anergy in active pulmonary tuberculosis: a comparison between positive and negative reactors and an evaluation of 5 TU and 250 TU skin test doses. *Chest*. 1980;77:32–37.
178. Slovis BS, Plitman JD, Haas DW. The case against anergy testing as a routine adjunct to tuberculin skin testing. *JAMA*. 2000;283:2003–2007.
179. Pouchot J, Grasland A, Collet C, et al. Reliability of tuberculin skin test measurement. *Ann Intern Med*. 1997;126:210–214.
180. Grzybowski S, Allen EA. The challenge of tuberculosis in decline: a study based on the epidemiology of tuberculosis in Ontario, Canada. *Am Rev Respir Dis*. 1964;90:707–720.
181. Johnson MP, Coberly JS, Clermont HC, et al. Tuberculin skin test reactivity among adults infected with human immunodeficiency virus. *J Infect Dis*. 1992;166:194–198.
182. Purified protein derivative (PPD) tuberculin anergy and HIV infection: guidelines for anergy testing and management of anergic persons at risk of tuberculosis. *MMWR Morb Mortal Wkly Rep*. 1991;40:27–33.
183. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection—United States, 2010. *MMWR Recomm Rep*. 2010;59(RR–5):1–25.
184. Roth PJ, Grim SA, Gallitano S, et al. Serial testing for latent tuberculosis infection in transplant candidates: a retrospective review. *Transpl Infect Dis*. 2016;18:14–21.
185. Andrews JR, Hatherill M, Mahomed H, et al. The dynamics of QuantiFERON-TB gold in-tube conversion and reversion in a cohort of South African adolescents. *Am J Respir Crit Care Med*. 2015;191:584–591.
186. Sester M, van Leth F, Bruchfeld J, et al. Risk assessment of tuberculosis in immunocompromised patients. A TBNET study. *Am J Respir Crit Care Med*. 2014;190:1168–1176.
187. Theel ES, Hilgart H, Breen-Lyles M, et al. Comparison of the QuantiFERON-TB Gold Plus and QuantiFERON-TB Gold In-Tube interferon gamma release assays in patients at risk for tuberculosis and in health care workers. *J Clin Microbiol*. 2018;56(e006):14–18.
188. Chien JY, Chiang HT, Lu MC, et al. Quantiferon-TB Gold Plus is a more sensitive screening tool than Quantiferon-TB Gold In-Tube for latent tuberculosis infection among older adults in long-term care facility. J Clin Microbiol. 2018.
189. Barcellini L, Borroni E, Brown J. First evaluation of QuantiFERON-TB Gold Plus performance in contact screening. *Eur Respir J*. 2016;48:1411–1419.
190. Ewer K, Deeks J, Alvarez L, et al. Comparison of T-cell–based assay with tuberculin skin test for diagnosis of *Mycobacterium tuberculosis* infection in a school tuberculosis outbreak. *Lancet*. 2003;361:1168–1173.
191. King TC, Upfal M, Gottlieb A, et al. T-SPOT.TB Interferon-γ release assay performance in healthcare worker screening at nineteen U.S. hospitals. *Am J Respir Crit Care Med*. 2015;192:367–373.
192. American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, ed. *Red Book: 2018-2021. Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:829–853.
193. Murray JF. Cursed duet: HIV infection and tuberculosis. *Respiration*. 1990;57:210–220.
194. Stead WW. Pathogenesis of a first episode of chronic pulmonary tuberculosis in man: recrudescence of residuals of the primary infection or exogenous reinfection? *Am Rev Respir Dis*. 1967;95:729–745.
195. Romeyn JA. Exogenous reinfection in tuberculosis. *Am Rev Respir Dis*. 1970;101:923–927.
196. Marx FM, Dunbar R, Enarson DA, et al. The temporal dynamics of relapse and reinfection tuberculosis after successful treatment: a retrospective cohort study. *Clin Infect Dis*. 2014;58:1676–1683.
197. Guerra-Assuncao JA, Houben RM, Crampin AC, et al. Recurrence due to relapse or reinfection with *Mycobacterium tuberculosis*: a whole-genome sequencing approach in a large, population-based cohort with a high HIV infection prevalence and active follow-up. *J Infect Dis*. 2015;211:1154–1163.
198. Kumar RA, Saran M, Verma BL, et al. Pulmonary tuberculosis among contacts of patients with tuberculosis in an urban Indian population. *J Epidemiol Community Health*. 1984;38:253–258.
199. Dahl RH. First appearance of pulmonary cavity after primary infection with relation to time and age. *Acta Tuberc Scand*. 1952;27:140–149.
200. Zak DE, Penn-Nicholson A, Scriba TJ, et al. A blood RNA signature for tuberculosis disease risk: a prospective cohort study. *Lancet*. 2016;387:2312–2322.
201. Hunter RL. Tuberculosis as a three –act play: a new paradigm for the pathogenesis of pulmonary tuberculosis. *Tuberculosis*. 2016;97:8–17.
202. Stead WW, Kerby GR, Schlueter DP, et al. The clinical spectrum of primary tuberculosis in adults: confusion with reinfection in the pathogenesis of chronic tuberculosis. *Ann Intern Med*. 1968;68:731–745.
203. Gedde-Dahl T. Tuberculous infection in the light of tuberculin matriculation. *Am J Hyg*. 1952;56:139–214.
204. Ou SM, Fan WC, Chou KT, et al. Systemic sclerosis and the risk of tuberculosis. *J Rheumatol*. 2014;41:1662–1669.
205. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha–neutralizing agent. *N Engl J Med*. 2001;345:1098–1104.
206. Mohan AK, Cote TR, Block JA, et al. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. *Clin Infect Dis*. 2004;39:295–299.
207. Carpio D, Jauregui-Amezaga A, de Francisco R, et al. Tuberculosis in anti-tumor necrosis factor treated inflammatory bowel disease patients after the implementation of preventive measures: compliance with recommendations and safety of retreatment. *J Crohns Colitis*. 2016;10:1186–1193.
208. Kisacik B, Pamuk ON, Onat AM, et al. Characteristics predicting tuberculosis risk under tumor necrosis factor-α inhibitors: report from a large multicenter cohort with high background prevalence. *J Rheumatol*. 2016;43:524–529.
209. Kim ES, Song GA, Cho KB, et al. Significant risk and associated factors of active tuberculosis infection in Korean patients with inflammatory bowel disease using anti-TNF agents. *World J Gastroenterol*. 2015;21:3308–3316.
210. Marcy O, Laureillard D, Madec Y, et al. Causes and determinants of mortality in HIV-infected adults with tuberculosis: an analysis from the CAMELIA ANRS 1295-CIPRA KH001 randomized trial. *Clin Infect Dis*. 2014;59:435–445.
211. Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med*. 2010;363:257–265.
212. Lee JH, Park SS, Lee DH, et al. Endobronchial tuberculosis: clinical and bronchoscopic features in 121 cases. *Chest*. 1992;102:990–994.
213. Chang S, Lee P, Perug P. Lower lung field tuberculosis. *Chest*. 1987;91:230–232.
214. Pitchenik AE, Rubinson HA. The radiographic appearance of tuberculosis in patients with the acquired immune deficiency syndrome (AIDS) and pre-AIDS. *Am Rev Respir Dis*. 1985;131:393–396.
215. Chaisson RE, Schecter GF, Theuer CP, et al. Tuberculosis in patients with the acquired immunodeficiency syndrome: clinical features, response to therapy, and survival. *Am Rev Respir Dis*. 1987;136:570–574.
216. Mtei L, Matee M, Herfort O, et al. High rates of clinical and subclinical tuberculosis among HIV-infected ambulatory subjects in Tanzania. *Clin Infect Dis*. 2005;40:1500–1507.
217. Perlman DC, El-Sadr WM, Nelson ET, et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus–related immunosuppression. The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). *Clin Infect Dis*. 1997;25:242–246.
218. Behr MA, Warren SA, Salamon H, et al. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. *Lancet*. 1999;353:444–449.
219. Kline SE, Hedemark LL, Davies SF. Outbreak of tuberculosis among regular patrons of a neighborhood bar. *N Engl J Med*. 1995;333:222–227.
220. Kent DC. Tuberculosis epidemics, U.S. Navy. *Bull Int Union Tuberc*. 1968;41:79–82.
221. Greenberg SD, Frager D, Suster B, et al. Active pulmonary tuberculosis in patients with AIDS: spectrum of radiographic findings (including a normal appearance). *Radiology*. 1994;193:115–119.
222. Marciniuk DD, McNab BD, Martin WT, et al. Detection of pulmonary tuberculosis in patients with a normal chest radiograph. *Chest*. 1999;115:445–452.
223. Pepper T, Joseph P, Mwenya C, et al. Normal chest radiography in pulmonary tuberculosis: implications for obtaining respiratory specimen cultures. *Int J Tuberc Lung Dis*. 2008;12:397–403.
224. Jones BE, Oo MM, Taikwel EK, et al. CD4 cell counts in human immunodeficiency virus-negative patients with tuberculosis. *Clin Infect Dis*. 1997;24:988–991.
225. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases society of

America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. *Clin Infect Dis*. 2017;64:111–115.

226. Conde MB, Soares SL, Mello FC, et al. Comparison of sputum induction with fiberoptic bronchoscopy in the diagnosis of tuberculosis: experience at an acquired immune deficiency syndrome reference center in Rio de Janeiro, Brazil. *Am J Respir Crit Care Med*. 2000;162:2238–2240.
227. Getahun H, Harrington M, O'Brien R, et al. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. *Lancet*. 2007;369:2042–2049.
228. Yajko DM, Nassos PS, Sanders CA, et al. High predictive value of the acid-fast smear for *Mycobacterium tuberculosis* despite the high prevalence of *Mycobacterium avium* complex in respiratory specimens. *Clin Infect Dis*. 1994;19:334–336.
229. Menzies R, Vissandjee B, Rocher I, et al. The booster effect in two-step tuberculin testing among adults in Montreal. *Ann Intern Med*. 1994;120:190–198.
230. Elzi L, Steffen I, Furrer H, et al. Improved sensitivity of an interferon-gamma release assay (T-SPOT.TB) in combination with tuberculin skin test for the diagnosis of latent tuberculosis in the presence of HIV co-infection. *BMC Infect Dis*. 2011;11:319.
231. Fisk TL, Hon HM, Lennox JL, et al. Detection of latent tuberculosis among HIV-infected patients after initiation of highly active antiretroviral therapy. *AIDS*. 2003;17:1102–1104.
232. Salzman SH, Schindel ML, Aranda CP, et al. The role of bronchoscopy in the diagnosis of pulmonary tuberculosis in patients at risk for HIV infection. *Chest*. 1992;102:143–146.
233. Miro AM, Gibilara E, Powell S, et al. The role of fiberoptic bronchoscopy for diagnosis of pulmonary tuberculosis in patients at risk for AIDS. *Chest*. 1992;101:1211–1214.
234. Kennedy DJ, Lewis WP, Barnes PF. Yield of bronchoscopy for the diagnosis of tuberculosis in patients with human immunodeficiency virus infection. *Chest*. 1992;102:1040–1044.
235. Reider HL, Kelly GD, Bloch AB, et al. Tuberculosis diagnosed at death in the United States. *Chest*. 1991;100:678–681.
236. van der Heijden YF, Maruri F, Blackman A, et al. Fluoroquinolone exposure prior to tuberculosis diagnosis is associated with an increased risk of death. *Int J Tuberc Lung Dis*. 2012;16:1162–1167.
237. Mok CK, Nandi P, Ong GB. Coexistent bronchogenic carcinoma and active pulmonary tuberculosis. *J Thorac Cardiovasc Surg*. 1978;76:469–472.
238. Thompson BC. Survival rates in pulmonary tuberculosis. *Br Med J*. 1943;2:721.
239. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63:e147–e195.
240. Kopanoff DE, Snider DE Jr, Caras GJ. Isoniazid-related hepatitis: a U.S. Public Health Service cooperative surveillance study. *Am Rev Respir Dis*. 1978;117:991–1001.
241. Hayashi PH, Fontana RJ, Chalasani NP, et al. Under-reporting and poor adherence to monitoring guidelines for severe cases of isoniazid hepatotoxicity. *Clin Gastroenterol Hepatol*. 2015;13:1676–1682.e1.
242. Menzies D, Dion MJ, Rabinovitch B, et al. Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months. *Am J Respir Crit Care Med*. 2004;170:445–449.
243. Page KR, Sifakis F, de Montes OR, et al. Improved adherence and less toxicity with rifampin vs isoniazid for treatment of latent tuberculosis: a retrospective study. *Arch Intern Med*. 2006;166:1863–1870.
244. Steele MA, Burk RF, Des Prez RM. Toxic hepatitis with isoniazid and rifampin: a meta-analysis. *Chest*. 1991;99:465–471.
245. Panel on Antiretroviral Guidelines for Adults and Adolescents, U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Updated October 17, 2017. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0. Accessed February 20, 2018.
246. Jarvis B, Lamb HM. Rifapentine. *Drugs*. 1998;56:607–616.
247. Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med*. 2014;371:1599–1608.
248. Vernon A, Burman W, Benator D, et al. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Tuberculosis Trials Consortium. *Lancet*. 1999;353:1843–1847.
249. Yee D, Valiquette C, Pelletier M, et al. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am J Respir Crit Care Med*. 2003;167:1472–1477.
250. Chang KC, Leung CC, Yew WW, et al. Hepatotoxicity of pyrazinamide: cohort and case-control analyses. *Am J Respir Crit Care Med*. 2008;177:1391–1396.
251. Ijaz K, Jereb JA, Lambert LA, et al. Severe or fatal liver injury in 50 patients in the United States taking rifampin and pyrazinamide for latent tuberculosis infection. *Clin Infect Dis*. 2006;42:346–355.
252. Zhang Y, Mitchison D. The curious characteristics of pyrazinamide: a review. *Int J Tuberc Lung Dis*. 2003;7:6–21.
253. Dankner WM, Waecker NJ, Essey MA, et al. *Mycobacterium bovis* infections in San Diego: a clinicoepidemiologic study of 73 patients and a historical review of a forgotten pathogen. *Medicine (Baltimore)*. 1993;72:11–37.
254. Narayanan P. Shortening short-course chemotherapy: a randomized clinical trial for treatment of smear-positive pulmonary tuberculosis with regimens using ofloxacin in the intensive phase. *Indian J Tuberc*. 2002;49:12.
255. Rustomjee R, Lienhardt C, Kanyok T, et al. A phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2008;12:128–138.
256. Conde MB, Efron A, Loredo C, et al. Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomised, controlled phase II trial. *Lancet*. 2009;373:1183–1189.
257. Lee H, Jeong BH, Park HY, et al. Treatment outcomes with fluoroquinolone-containing regimens for isoniazid-resistant pulmonary tuberculosis. *Antimicrob Agents Chemother*. 2015;60:471–477.
258. Selvakumar N, Kumar V, Balaji S, et al. High rates of ofloxacin resistance in *Mycobacterium tuberculosis* among both new and previously treated patients in Tamil Nadu, South India. *PLoS ONE*. 2015;10:e0117421.
259. Thee S, Garcia-Prats JA, Draper HR, et al. Pharmacokinetics and safety of moxifloxacin in children with multidrug-resistant tuberculosis. *Clin Infect Dis*. 2015;60:549–556.
260. Merle CS, Fielding K, Sow OB, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. *N Engl J Med*. 2014;371:1588–1598.
261. Gillespie SH, Crook AM, McHugh TD, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med*. 2014;371:1577–1587.
262. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N Engl J Med*. 2009;360:2397–2405.
263. Diacon AH, Donald PR, Pym A, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. *Antimicrob Agents Chemother*. 2012;56:3271–3276.
264. Gugglielmetti L, Le Du D, Jachym M, et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. *Clin Infect Dis*. 2015;60:188–194.
265. Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med*. 2014;371:723–732.
266. Cox E, Laessig K. FDA approval of bedaquiline—the benefit-risk balance for drug-resistant tuberculosis. *N Engl J Med*. 2014;371:689–691.
267. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. *Eur Respir J*. 2017;49.
268. Akkerman OW, Odish OF, Bolhuis MS, et al. Pharmacokinetics of bedaquiline in cerebrospinal fluid and serum in multidrug-resistant tuberculous meningitis. *Clin Infect Dis*. 2016;62:523–524.
269. Svensson EM, Murray S, Karlsson MO, et al. Rifampicin and rifapentine significantly reduce concentrations of bedaquiline, a new anti-TB drug. *J Antimicrob Chemother*. 2015;70:1106–1114.
270. Svensson EM, Dooley KE, Karlsson MO. Impact of lopinavir-ritonavir or nevirapine on bedaquiline exposures and potential implications for patients with tuberculosis-HIV coinfection. *Antimicrob Agents Chemother*. 2014;58:6406–6412.
271. Centers for Disease Control and Prevention. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. *MMWR Recomm Rep*. 2013;62(RR–09):1–12.
272. Van Deun A, Maug AK, Salim MA, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med*. 2010;182:684–692.
273. Trébucq A, Schwoebel V, Kashongwe Z, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. *Int J Tuberc Lung Dis*. 2018;22:17–25.
274. Low M The tuberculosis treatment pipeline. http://www.pipelinereport.org/2017/tbtx. Accessed February 20, 2018.
275. Delamanid for multidrug-resistant pulmonary tuberculosis, Gler MT, Skripconoka V, et al. *N Engl J Med*. 2012;366:2151–2160.
276. World Health Organization. *WHO Consolidated Guidelines on Drug-resistant Tuberculosis Treatment*. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.
277. Olaru ID, von Groote-Bidlingmaier F, Heyckendorf J, et al. Novel drugs against tuberculosis: a clinician's perspective. *Eur Respir J*. 2014;45:1119–1131.
278. Szumowski JD, Lynch JB. Profile of delamanid for the treatment of multidrug-resistant tuberculosis. *Drug Des Devel Ther*. 2015;9:677–682.
279. Dawson R, Diacon AH, Everitt D, et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. *Lancet*. 2015;385:1738–1747.
280. Perez-Stable EJ, Hopewell PC. Current tuberculosis treatment regimens: choosing the right one for your patient. *Clin Chest Med*. 1989;10:323–339.
281. Davidson PT, Le HQ. Drug treatment of tuberculosis—1992. *Drugs*. 1992;43:651–673.
282. Snider DE Jr, Zierski M, Graczyk J, et al. Short-course tuberculosis chemotherapy studies conducted in Poland during the past decade. *Eur J Respir Dis*. 1986;68:12–18.
283. British Thoracic Association. A controlled trial of six months chemotherapy in pulmonary tuberculosis. Second report: results during the 24 months after the end of chemotherapy. *Am Rev Respir Dis*. 1982;126:460–462.
284. East and Central African/British Medical Research Council. Controlled clinical trial of 4 short-course regimens of chemotherapy (three 6-month and one 8-month) for pulmonary tuberculosis. *Tubercle*. 1983;64:153–166.
285. Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. *Lancet*. 2004;364:1244–1251.
286. Hopewell PC, Pai M, Maher D, et al. International standards for tuberculosis care. *Lancet Infect Dis*. 2006;6:710–725.
287. Hopewell PC, Fair EL, Uplekar M. Updating the International Standards for Tuberculosis Care. Entering the era of molecular diagnostics. *Ann Am Thorac Soc*. 2014;11:277–285.
288. World Health Organization - Guidelines for treatment of drug-susceptible tuberculosis and patient care. 2017 update. WHO/HTM/2017.05 http://www.who.int/tb/publications/2017/dstb_guidance_2017/en/ Accessed February 20, 2018.
289. Dutt AK, Moers D, Stead WW. Short-course chemotherapy for tuberculosis with mainly twice-weekly isoniazid and rifampin: community physicians' seven-year experience with mainly outpatients. *Am J Med*. 1984;77:233–242.
290. Benator D, Bhattacharya M, Bozeman L, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet*. 2002;360:528–534.
291. Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *Am Rev Respir Dis*. 1986;133:423–430.
292. Moore RD, Chaulk CP, Griffiths R, et al. Cost-effectiveness of directly observed versus self-administered therapy for tuberculosis. *Am J Respir Crit Care Med*. 1996;154:1013–1019.
293. Fujiwara PI, Cook SV, Rutherford CM, et al. A continuing survey of drug-resistant tuberculosis, New York City, April 1994. *Arch Intern Med*. 1997;157:531–536.
294. Weis SE, Slocum PC, Blais FX, et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *N Engl J Med*. 1994;330:1179–1184.
295. Hong Kong Chest Service Tuberculosis Research Center, Madras, British Medical Research Council. A controlled trial of 3-month, 4-month, and 6-month regimens of chemotherapy for sputum smear-negative pulmonary tuberculosis: results at 5 years. *Am Rev Respir Dis*. 1989;139:871–876.

296. Lew W, Pai M, Oxlade O, et al. Initial drug resistance and tuberculosis treatment outcomes: systematic review and meta-analysis. *Ann Intern Med*. 2008;149:123–134.
297. Cegielski JP, Dalton T, Yagui M, et al. Extensive drug resistance acquired during treatment of multidrug-resistant tuberculosis. *Clin Infect Dis*. 2014;59:1049–1063.
298. Ershova JV, Kurbatova EV, Moonan PK, et al. Mortality among tuberculosis patients with acquired resistance to second-line antituberculosis drugs—United States, 1993-2008. *Clin Infect Dis*. 2014;59:465–472.
299. Cegielski JP, Kurbatova E, van der Walt M, et al. Multidrug-resistant tuberculosis treatment outcomes in relation to treatment and initial versus acquired second-line drug resistance. *Clin Infect Dis*. 2016;62:418–430.
300. Velásquez GE, Becerra MC, Gelmanova IY, et al. Improving outcomes for multidrug-resistant tuberculosis: aggressive regimens prevent treatment failure and death. *Clin Infect Dis*. 2014;59:9–15.
301. Bastos ML, Hussain H, Weyer K, et al. Treatment outcomes of patients with multidrug-resistant and extensively drug-resistant tuberculosis according to drug susceptibility testing to first- and second-line drugs: an individual patient data meta-analysis. *Clin Infect Dis*. 2014;59:1364–1374.
302. Goble M, Iseman MD, Madsen LA. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med*. 1993;328:527–532.
303. Chan ED, Laurel V, Strand MJ, et al. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. *Am J Respir Crit Care Med*. 2004;169:1103–1109.
304. Leimane V, Riekstina V, Holtz TH, et al. Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. *Lancet*. 2005;365:318–326.
305. Telzak EE, Sepkowitz K, Alpert P, et al. Multidrug-resistant tuberculosis in patients without HIV infection. *N Engl J Med*. 1995;333:907–911.
306. Burgos M, Gonzalez LC, Paz EA, et al. Treatment of multidrug-resistant tuberculosis in San Francisco: an outpatient-based approach. *Clin Infect Dis*. 2005;40:968–975.
307. STREAM Stage 1. 48th Union World Conference on Lung Health. 11-14 October, 2017. Guadalajara, Mexico. http://guadalajara.worldlunghealth.org/media/conference-news/updates/stream-clinical-trial-results-provide-vital-insight-into-nine-month-treatment-regimen-for-multidrug-resistant-tuberculosis Accessed February 20, 2018.
308. Tang S, Yao L, Hao X, et al. Clofazimine for the treatment of multidrug-resistant tuberculosis: prospective, multicenter, randomized controlled study in China. *Clin Infect Dis*. 2015;60:1361–1367.
309. Kurbatova EV, Cavanaugh JS, Dalton T, et al. Epidemiology of pyrazinamide-resistant tuberculosis in the United States, 1999-2009. *Clin Infect Dis*. 2013;57:1081–1093.
310. Yew WW, Chan CK, Chau CH, et al. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. *Chest*. 2000;117:744–751.
311. Yew WW, Chan CK, Leung CC, et al. Comparative roles of levofloxacin and ofloxacin in t he treatment of multidrug-resistant tuberculosis: preliminary results of a retrospective study from Hong Kong. *Chest*. 2003;124:1476–1481.
312. Treatment of tuberculosis and tuberculous infection in adults and children. *Am J Respir Crit Care Med*. 1994;149:1359–1374.
313. Centers for Disease Control and Prevention. Initial therapy for tuberculosis in the era of multidrug resistance: recommendations of the Advisory Council for the Elimination of Tuberculosis. *JAMA*. 1993;270:694–698.
314. Iseman MD. Treatment of multidrug-resistant tuberculosis. *N Engl J Med*. 1993;329:784–791.
315. World Health Organization - Treatment guidelines for drug-resistant tuberculosis. 2016 update. October 2016 revision. WHO/HTM/TB/2016.04 http://apps.who.int/iris/bitstream/10665/250125/5/9789241549639-webannexes-eng.pdf Accessed February 20, 2018.
316. Bloemberg GV, Keller PM, Stucki D, et al. Acquired resistance to bedaquiline and delamanid in therapy for tuberculosis. *N Engl J Med*. 2015;373:1986–1988.
317. Tiberi S, Sotgiu G, D'Ambrosio L, et al. Effectiveness and safety of imipenem/clavulanate added to an optimized background regimen (OBR) versus OBR controls regimens in the treatment of multidrug and extensively drug-resistant tuberculosis. *Clin Infect Dis*. 2016;62:1188–1190.
318. Kim HR, Hwang SS, Kim HJ, et al. Impact of extensive drug resistance on treatment outcomes in non–HIV-infected patients with multidrug-resistant tuberculosis. *Clin Infect Dis*. 2007;45:1290–1295.
319. Chan ED, Strand MJ, Iseman MD. Treatment outcomes in extensively resistant tuberculosis. *N Engl J Med*. 2008;359:657–659.
320. Mitnick CD, Shin SS, Seung KJ, et al. Comprehensive treatment of extensively drug-resistant tuberculosis. *N Engl J Med*. 2008;359:563–574.
321. Pietersen E, Ignatius E, Streicher EM, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. *Lancet*. 2014;383:1230–1239.
322. Lee M, Lee J, Carroll MW, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *N Engl J Med*. 2012;367:1508–1518.
323. Lee M, Cho SN, Barry CE 3rd, et al. Linezolid for XDR-TB–final study outcomes. *N Engl J Med*. 2015;373:290–291.
324. Tang S, Yao L, Hao X, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. *Eur Respir J*. 2015;45:161–170.
325. Padayatchi N, Gopal M, Naidoo R, et al. Clofazimine in the treatment of extensively drug-resistant tuberculosis with HIV coinfection in South Africa: a retrospective cohort study. *J Antimicrob Chemother*. 2014;69:3103–3107.
326. Fitzgerald DW, Desvarieux M, Severe P, et al. Effect of post-treatment isoniazid on prevention of recurrent tuberculosis in HIV-1-infected individuals: a randomised trial. *Lancet*. 2000;356:1470–1474.
327. Churchyard GJ, Fielding K, Charalambous S, et al. Efficacy of secondary isoniazid preventive therapy among HIV-infected Southern Africans: time to change policy? *AIDS*. 2003;17:2063–2070.
328. Mukherjee JS, Rich ML, Socci AR, et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. *Lancet*. 2004;363:474–481.
329. Dooley DP, Carpenter JL, Rademacher S. Adjunctive corticosteroid therapy for tuberculosis: a critical reappraisal of the literature. *Clin Infect Dis*. 1997;25:872–887.
330. Centers for Disease Control and Prevention. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis. Updated June 2013. http://www.cdc.gov/tb/TB_HIV_Drugs/default.htmtbhiv.pdf. Accessed May 28, 2014.
331. Dooley KE, Bliven-Sizemore EE, Weiner M, et al. Safety and pharmacokinetics of escalating daily doses of the antituberculosis drug rifapentine in healthy volunteers. *Clin Pharmacol Ther*. 2012;91:881–888.
332. Nijland HM, L'homme RF, Rongen GA, et al. High incidence of adverse events in healthy volunteers receiving rifampicin and adjusted doses of lopinavir/ritonavir tablets. *AIDS*. 2008;22:931–935.
333. Grange S, Schutz M, Schmitt C, et al Unexpected hepatotoxicity observed in a healthy volunteer study on the effects of multiple dose rifampicin on the steady-state pharmacokinetics of ritonavir-boosted saquinavir and vice versa [abstract 35]. In: Program and Abstracts of the 6th International Workshop on Clinical Pharmacology of HIV Therapy. Montreal, Quebec, Canada, April 28-30, 2005.
334. Haas DW, Koletar SL, Laughlin L, et al. Hepatotoxicity and gastrointestinal intolerance when healthy volunteers taking rifampin add twice-daily atazanavir and ritonavir. *J Acquir Immune Defic Syndr*. 2009;50:290–293.
335. Kwara A, Lartey M, Sagoe KW, et al. Pharmacokinetics of efavirenz when co-administered with rifampin in TB/HIV co-infected patients: pharmacogenetic effect of CYP2B6 variation. *J Clin Pharmacol*. 2008;48:1032–1040.
336. Luetkemeyer AF, Rosenkranz SL, Lu D, et al; Adult AIDS Clinical Trials Group A5221 and A5243 Study Teams. Combined effect of CYP2B6 and NAT2 genotype on plasma efavirenz exposure during rifampin-based antituberculosis therapy in the STRIDE study. *Clin Infect Dis*. 2015;60:1860–1863.
337. Manosuthi W, Mankatitham W, Lueangniyomkul A, et al. Standard-dose efavirenz vs. standard-dose nevirapine in antiretroviral regimens among HIV-1 and tuberculosis co-infected patients who received rifampicin. *HIV Med*. 2008;9:294–299.
338. Boulle A, Van CG, Cohen K, et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA*. 2008;300:530–539.
339. Burman W, Benator D, Vernon A, et al. Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. *Am J Respir Critic Care Med*. 2006;173:350–356.
340. Narendran G, Menon PA, Venkatesan P, et al. Acquired rifampicin resistance in thrice-weekly antituberculosis therapy: impact of HIV and antiretroviral therapy. *Clin Infect Dis*. 2014;59:1798–1804.
341. Berning SE, Huitt DA, Iseman MD, et al. Malabsorption of antituberculous medications by a patient with AIDS. *N Engl J Med*. 1992;327:1817–1818.
342. Xie YL, Rosen LB, Sereti I, et al. Severe paradoxical reaction during treatment of disseminated tuberculosis in a patient with neutralizing anti-IFNγ autoantibodies. *Clin Infect Dis*. 2016;62:770–773.
343. Narita M, Ashkin D, Hollender ES, et al. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med*. 1998;158:157–161.
344. Wendel KA, Alwood KS, Gachuhi R, et al. Paradoxical worsening of tuberculosis in HIV-infected persons. *Chest*. 2001;120:193–197.
345. Bourgarit A, Carcelain G, Martinez V, et al. Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients. *AIDS*. 2006;20:F1–F7.
346. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*. 2008;8:516–523.
347. Naidoo K, Yende-Zuma N, Padayatchi N, et al. The immune reconstitution inflammatory syndrome after antiretroviral therapy initiation in patients with tuberculosis: findings from the SAPiT trial. *Ann Intern Med*. 2012;157:313–324.
348. Burman W, Weis S, Vernon A, et al. Frequency, severity and duration of immune reconstitution events in HIV-related tuberculosis. *Int J Tuberc Lung Dis*. 2007;11:1282–1289.
349. Olalla J, Pulido F, Rubio R, et al. Paradoxical responses in a cohort of HIV-1–infected patients with mycobacterial disease. *Int J Tuberc Lung Dis*. 2002;6:71–75.
350. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis–associated immune reconstitution inflammatory syndrome. *AIDS*. 2010;24:2381–2390.
351. Lawn SD, Wilkinson RJ, Lipman MC, et al. Immune reconstitution and "unmasking" of tuberculosis during antiretroviral therapy. *Am J Respir Crit Care Med*. 2008;177:680–685.
352. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. 2011;365:1471–1481.
353. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. 2011;365:1482–1491.
354. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med*. 2011;365:1492–1501.
355. Nettles RE, Mazo D, Alwood K, et al. Risk factors for relapse and acquired rifamycin resistance after directly observed tuberculosis treatment: a comparison by HIV serostatus and rifamycin use. *Clin Infect Dis*. 2004;38:731–736.
356. Nahid P, Gonzalez LC, Rudoy I, et al. Treatment outcomes of patients with HIV and tuberculosis. *Am J Respir Crit Care Med*. 2007;175:1199–1206.
357. Ahmad Khan F, Minion J, Al-Motairi A, et al. An updated systematic review and meta-analysis on the treatment of active tuberculosis in patients with HIV infection. *Clin Infect Dis*. 2012;55:1154–1163.
358. Swaminathan S, Narendran G, Venkatesan P, et al. Efficacy of a 6-month versus 9-month intermittent treatment regimen in HIV-infected patients with tuberculosis: a randomized clinical trial. *Am J Respir Crit Care Med*. 2010;181:743–751.
359. Pediatric Tuberculosis Collaborative Group. Targeted tuberculin skin testing and treatment of latent tuberculosis infection in children and adolescents. *Pediatrics*. 2004;114:1175–1201.
360. Getahun H, Matteelli A, Abubakar I, et al. Management of latent *Mycobacterium tuberculosis* infection: WHO guidelines for low tuberculosis burden countries. *Eur Respir J*. 2015;46:1563–1576.
361. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365:2155–2166.
362. Villarino ME, Scott NA, Weis SE, et al; International Maternal Pediatric and Adolescents AIDS Clinical Trials Group; Tuberculosis Trials Consortium. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. *JAMA Pediatr*. 2015;169:247–255.
363. Stennis NL, Burzynski JN, Herbert C, et al. Treatment for tuberculosis infection with 3 months of isoniazid and rifapentine in New York City Health Department Clinics. *Clin Infect Dis*. 2016;62:53–59.
364. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent *Mycobacterium tuberculosis* infection. *MMWR Morb Mortal Wkly Rep*. 2011;60:1650–1653.
365. Sterling TR, Scott NA, Miro JM, et al. Tuberculosis Trials Consortium, the AIDS Clinical Trials Group for the

PREVENT TB Trial (TBTC Study 26ACTG 5259) Three months of weekly rifapentine and isoniazid for treatment of *Mycobacterium tuberculosis* infection in HIV-coinfected persons. *AIDS*. 2016;30:1607–1615.

366. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*. 2011;365:11–20.
367. Sterling TR, Moro RN, Borisov AS, et al. Flu-like and other systemic drug reactions among persons receiving weekly rifapentine plus isoniazid or daily isoniazid for treatment of latent tuberculosis infection in the PREVENT Tuberculosis Study. *Clin Infect Dis*. 2015;61:527–535.
368. Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin on nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med*. 2018;379:440–453.
369. Zenner D, Beer N, Harris RJ, et al. Treatment of latent tuberculosis infection: an updated network meta-analysis. *Ann Intern Med*. 2017;167:248–255.
370. Gordin F, Chaisson RE, Matts JP, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beirn CPCRA, the AACTG, the PAHO, and the CDC Study Group. *JAMA*. 2000;283:1445–1450.
371. Centers for Disease Control and Prevention. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection—United States, 2003. *MMWR Morb Mortal Wkly Rep*. 2003;52:735–739.
372. Stead WW, To T, Harrison RW, et al. Benefit-risk considerations in preventive treatment of tuberculosis in elderly persons. *Ann Intern Med*. 1987;107:843–845.
373. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med*. 2006;174:935–952.
374. Byrd RB, Horn BR, Griggs GA, et al. Isoniazid chemoprophylaxis: association with detection and incidence of liver toxicity. *Arch Intern Med*. 1970;137:1130–1133.
375. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA*. 1999;281:1014–1018.
376. Snider DE Jr, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. *Am Rev Respir Dis*. 1992;145:494–497.
377. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis: a general review. *Bibl Tuberc*. 1970;26:28–106.
378. International Union Against Tuberculosis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull World Health Organ*. 1982;60:555–564.
379. Balcells ME, Thomas SL, Godfrey-Faussett P, et al. Isoniazid preventive therapy and risk for resistant tuberculosis. *Emerg Infect Dis*. 2006;12:744–751.
380. Lewinsohn DM, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. *Clin Infect Dis*. 2017;64:111–115.
381. World Health Organization. Latent tuberculosis infection. Updated and consolidated guidelines for programmatic management. WHO/CDS/TB/2018.4 http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/ Accessed February 20, 2018.
382. TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med*. 2015;373:808–822.
383. Centers for Disease Control and Prevention. Anergy skin testing and preventive therapy for HIV-infected persons: revised guidelines. *MMWR Morb Mortal Wkly Rep*. 1997;46:1–10.
384. Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet*. 2014;384:682–690.
385. Torre-Cisneros J, San-Juan R, Rosso-Fernández CM, et al. Tuberculosis prophylaxis with levofloxacin in liver transplant patients is associated with a high incidence of tenosynovitis: safety analysis of a multicenter randomized trial. *Clin Infect Dis*. 2015;60:1642–1649.
386. Tien V, Robilotti E, Callister D, et al. Tolerability of fluoroquinolones in management of latent tuberculosis in liver transplant candidates. *Clin Infect Dis*. 2015;61:1631–1632.
387. Luelmo F. BCG vaccination. *Am Rev Respir Dis*. 1982;125:70–72.
388. Menzies R, Vissandjee B. Effect of bacille Calmette-Guérin vaccination on tuberculin reactivity. *Am Rev Respir Dis*. 1992;145:621–624.
389. Hakim S, Heaney JA, Heinz T, et al. Psoas abscess following intravesical bacillus Calmette-Guérin for bladder cancer: a case report. *J Urol*. 1993;150:188–189.
390. McParland C, Cotton DJ, Gowda KS, et al. Miliary *Mycobacterium bovis* induced by intravesical bacille Calmette-Guérin immunotherapy. *Am Rev Respir Dis*. 1992;146:1330–1333.
391. Lamm DL, Stogdill VD, Stogdill BJ, et al. Complications of bacillus Calmette-Guérin immunotherapy in 1278 patients with bladder cancer. *J Urol*. 1986;135:272–274.
392. Orme IM. Vaccine development for tuberculosis: current progress. *Drugs*. 2013;73:1015–1024.
393. Tameris MD, Hatherill M, Landry BS, et al. Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial. *Lancet*. 2013;381:1021–1028.
394. Der Meeren O, Hatherill M, Nduba V, et al. Phase 2b controlled trial of M72/AS01E vaccine to prevent tuberculosis. *N Engl J Med*. 2018;379:1621–1634.
395. Stop TB Partnership. http://www.tbvi.eu/home.html. Accessed May 28, 2014.
396. Centers for Disease Control and Prevention. Tuberculosis morbidity—United States, 1997. *MMWR Morb Mortal Wkly Rep*. 1998;47:253–257.
397. Leeds IL, Magee MJ, Kurbatova EV, et al. Site of extrapulmonary tuberculosis is associated with HIV infection. *Clin Infect Dis*. 2012;55:75–81.
398. Katagira W, Walter ND, den Boon S, et al. Empiric TB treatment of severely ill patients with HIV and presumed pulmonary TB improves survival. *J Acquir Immune Defic Syndr*. 2016;72:297–303.
399. Hosseinipour MC, Bisson GP, Miyahara S, et al; Adult AIDS Clinical Trials Group A5274 (REMEMBER) Study Team. Empirical tuberculosis therapy versus isoniazid in adult outpatients with advanced HIV initiating antiretroviral therapy (REMEMBER): a multicountry open-label randomised controlled trial. *Lancet*. 2016;387:1198–1209.
400. Biehl JP. Miliary tuberculosis: a review of sixty-eight adult patients admitted to a municipal general hospital. *Am Rev Tuberc*. 1958;77:605–622.
401. Munt PW. Miliary tuberculosis in the chemotherapy era: with a clinical review in 69 American adults. *Medicine (Baltimore)*. 1972;51:139–155.
402. Maartens G, Willcox PA, Benatar SR. Miliary tuberculosis: rapid diagnosis, hematologic abnormalities, and outcome in 109 treated adults. *Am J Med*. 1990;89:291–296.
403. Kim JH, Langston AA, Gallis HA. Miliary tuberculosis: epidemiology, clinical manifestations, diagnosis, and outcome. *Rev Infect Dis*. 1990;12:583–590.
404. Yu YL, Chow WH, Humphries MJ, et al. Cryptic miliary tuberculosis. *Q J Med*. 1986;59:421–428.
405. Willcox PA, Potgieter PD, Bateman ED, et al. Rapid diagnosis of sputum negative miliary tuberculosis using the flexible fiberoptic bronchoscope. *Thorax*. 1986;41:681–684.
406. Slavin RE, Walsh TJ, Pollock AD. Late generalized tuberculosis: a clinical pathologic analysis and comparison of 100 cases in the pre-antibiotic and antibiotic eras. *Medicine (Baltimore)*. 1980;59:351–366.
407. Proudfoot AT, Akhar AJ, Douglas AC, et al. Miliary tuberculosis in adults. *Br Med J*. 1969;2:273–276.
408. Cameron SJ. Tuberculosis and the blood: a special relationship. *Tubercle*. 1974;55:55–72.
409. Shafer RW, Kim DS, Weiss JP, et al. Extrapulmonary tuberculosis in patients with human immunodeficiency virus infection. *Medicine (Baltimore)*. 1991;70:384–397.
410. Lupatkin H, Brau N, Flomenberg P, et al. Tuberculous abscesses in patients with AIDS. *Clin Infect Dis*. 1992;14:1040–1044.
411. Kennedy DH, Fallon RJ. Tuberculous meningitis. *JAMA*. 1979;241:264–268.
412. Chedore P, Jamieson FB. Rapid molecular diagnosis of tuberculous meningitis using the Gen-Probe amplified *Mycobacterium tuberculosis* direct test in a large Canadian public health laboratory. *Int J Tuberc Lung Dis*. 2002;6:913–919.
413. Bonington A, Strang JI, Klapper PE, et al. Use of Roche AMPLI-COR *Mycobacterium* PCR in early diagnosis of tuberculous meningitis. *J Clin Microbiol*. 1998;36:1251–1254.
414. Bahr NC, Nuwagira E, Evans E, et al. Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. *Lancet Infect Dis*. 2018;18:68–75.
415. Garg RK, Malhotra HS, Gupta R. Spinal cord involvement in tuberculous meningitis. *Spinal Cord*. 2015;53:649–657.
416. Erdem H, Ozturk-Engin D, Tireli H, et al. Hamsi scoring in the prediction of unfavorable outcomes from tuberculous meningitis: results of Haydarpasa-II study. *J Neurol*. 2015;262:890–898.
417. Dube MP, Holtom PD, Larsen RA. Tuberculous meningitis in patients with and without human immunodeficiency virus infection. *Am J Med*. 1992;93:520–524.
418. Ruslami R, Ganiem AR, Dian S, et al. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. *Lancet Infect Dis*. 2013;13:27–35.
419. Heemskerk AD, Bang ND, Mai NT, et al. Intensified antituberculosis therapy in adults with tuberculous meningitis. *N Engl J Med*. 2016;374:124–134.
420. Roper WH, Waring JJ. Primary serofibrinous pleural effusion in military personnel. *Am Rev Tuberc*. 1955;71:616–634.
421. Antoniskis D, Amin K, Barnes PF. Pleuritis as a manifestation of reactivation tuberculosis. *Am J Med*. 1990;89:447–450.
422. Epstein DM, Kline LR, Albelda SM, et al. Tuberculous pleural effusions. *Chest*. 1987;91:106–109.
423. Roth BJ. Searching for tuberculosis in the pleural space. *Chest*. 1999;116:3–5.
424. Diacon AH, Van de Wal BW, Wyser C, et al. Diagnostic tools in tuberculous pleurisy: a direct comparative study. *Eur Respir J*. 2003;22:589–591.
425. Laniado-Laborin R. Adenosine deaminase in the diagnosis of tuberculous pleural effusion: is it really an ideal test? A word of caution. *Chest*. 2005;127:417–418.
426. Lee YC, Rogers JT, Rodriguez RM, et al. Adenosine deaminase levels in nontuberculous lymphocytic pleural effusions. *Chest*. 2001;120:356–361.
427. Jimenez CD, Diaz NG, Perez-Rodriguez E, et al. Diagnostic value of adenosine deaminase in nontuberculous lymphocytic pleural effusions. *Eur Respir J*. 2003;21:220–224.
428. Abrao FC, de Abreu IR, Miyake DH, et al. Role of adenosine deaminase and the influence of age on the diagnosis of pleural tuberculosis. *Int J Tuberc Lung Dis*. 2014;18:1363–1369.
429. Taelman H, Kagame A, Batungwanayo J, et al. Pericardial effusion and HIV infection. *Lancet*. 1990;335:924.
430. Maher D, Harries AD. Tuberculous pericardial effusion: a prospective clinical study in a low-resource setting—Blantyre, Malawi. *Int J Tuberc Lung Dis*. 1997;1:358–364.
431. Strang JIG, Gibson DG, Mitchison DA, et al. Controlled clinical trial of complete open surgical drainage and of prednisolone in treatment of tuberculous pericardial effusion in Transkei. *Lancet*. 1988;2:759–763.
432. Strang JIG, Gibson DG, Nunn AJ, et al. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. *Lancet*. 1987;23:1418–1422.
433. Agner RC, Gallis HA. Pericarditis differential diagnostic considerations. *Arch Intern Med*. 1979;139:407–412.
434. Mayosi BM, Ntsekhe M, Bosch J, et al. Prednisolone and *Mycobacterium indicus pranii* in tuberculous pericarditis. *N Engl J Med*. 2014;371:1121–1130.
435. Strang JI, Nunn AJ, Johnson DA, et al. Management of tuberculous constrictive pericarditis and tuberculous pericardial effusion in Transkei: results at 10 years follow-up. *QJM*. 2004;97:525–535.
436. Janssens JP, De Haller R. Spinal tuberculosis in a developed country: a review of 26 cases with special emphasis on abscesses and neurologic complications. *Clin Orthop Relat Res*. 1990;257:67–75.
437. Johansen IS, Nielsen SL, Hove M, et al. Characteristics and clinical outcome of bone and joint tuberculosis from 1994 to 2011: a retrospective register-based study in Denmark. *Clin Infect Dis*. 2015;61:554–562.
438. Marais S, Roos I, Mitha A, et al. Spinal tuberculosis: clinicoradiological findings in 274 patients. *Clin Infect Dis*. 2018;67:89–98.
439. Five-year assessment of controlled trials of short-course chemotherapy regimens of 6, 9 or 18 months' duration for spinal tuberculosis in patients ambulatory from the start or undergoing radical surgery. Fourteenth report of the Medical Research Council Working Party on Tuberculosis of the Spine. *Int Orthop*. 1999;23:73–81.
440. Controlled trial of short-course regimens of chemotherapy in the ambulatory treatment of spinal tuberculosis. Results at three years of a study in Korea. Twelfth report of the Medical Research Council Working Party on Tuberculosis of the Spine. *J Bone Joint Surg Br*. 1993;75:240–248.
441. Davidson PT, Horowitz I. Skeletal tuberculosis: a review with patient presentations and discussion. *Am J Med*. 1970;48:77–84.
442. LiZares LF, Valcarcel A, Del Castillo JM, et al. Tuberculous arthritis with multiple joint involvement. *J Rheumatol*. 1991;18:635–636.
443. Muradali D, Gold WL, Vellend H, et al. Multifocal osteoarticular tuberculosis: report of four cases and review of management. *Clin Infect Dis*. 1993;17:204–209.
444. Bentz RR, Dimcheff DG, Nemiroff MJ, et al. The incidence of urine cultures positive for *Mycobacterium*

tuberculosis in a general tuberculosis patient population. *Am Rev Respir Dis*. 1975;111:647–650.
445. Simon HB, Weinstein AJ, Pasternak MS, et al. Genitourinary tuberculosis: clinical features in a general hospital population. *Am J Med*. 1977;63:410–420.
446. Christensen WI. Genitourinary tuberculosis: review of 102 cases. *Medicine (Baltimore)*. 1974;53:377–390.
447. Morgan SH, Eastwood JB, Baker LR. Tuberculous interstitial nephritis: the tip of an iceberg? *Tubercle*. 1990;71:5–6.
448. Gorse GJ, Belshe RB. Male genital tuberculosis: a review of the literature with instructive case reports. *Rev Infect Dis*. 1985;7:511–524.
449. Carter JR. Unusual presentations of genital tract tuberculosis. *Int J Gynaecol Obstet*. 1990;33:171–176.
450. Jakubowski A, Elwood RK, Enarson DA. Clinical features of abdominal tuberculosis. *J Infect Dis*. 1988;158:687–692.
451. Shah S, Thomas V, Mathan M, et al. Colonoscopic study of 50 patients with colonic tuberculosis. *Gut*. 1992;33:347–351.
452. Kielhofner MA, Hamill RJ. Focal hepatic tuberculosis in a patient with acquired immunodeficiency syndrome. *South Med J*. 1991;84:401–404.
453. Hulnick DH, Megibow AJ, Naidich DP, et al. Abdominal tuberculosis: CT evaluation. *Radiology*. 1985;157:199–204.
454. Modilevsky T, Sattler FR, Barnes PF. Mycobacterial disease in patients with human immunodeficiency virus infection. *Arch Intern Med*. 1989;149:2201–2205.
455. Bastani B, Shariatzadeh MR, Dehdashti F. Tuberculous peritonitis: report of 30 cases and review of the literature. *Q J Med*. 1985;56:549–557.
456. Burack WR, Hollister RM. Tuberculous peritonitis. *Ann Intern Med*. 1960;28:510–523.
457. Cheng IK, Chan PC, Chan MK. Tuberculous peritonitis complicating long-term peritoneal dialysis. *Am J Nephrol*. 1989;9:155–161.
458. Fernandez-Rodriguez CM, Perez-Arguelles BS, Ledo L, et al. Ascites adenosine deaminase activity is decreased in tuberculous ascites with low protein content. *Am J Gastroenterol*. 1991;86:1500–1503.
459. Kaur A, Basha A, Ranjan M, et al. Poor diagnostic value of adenosine deaminase in pleural, peritoneal & cerebrospinal fluids in tuberculosis. *Indian J Med Res*. 1992;95:270–277.
460. Singh MM, Bhargava AN, Jain KP. Tuberculous peritonitis: an evaluation of pathogenetic mechanisms, diagnostic procedures and therapeutic measures. *N Engl J Med*. 1969;281:1091–1094.
461. Haas DW. Are adjunctive corticosteroids indicated during tuberculous peritonitis? *Clin Infect Dis*. 1998;27:57–58.
462. Summers GD, McNicol MW. Tuberculosis of superficial lymph nodes. *Br J Dis Chest*. 1980;74:369–373.
463. Dandapat MC, Mishra BM, Dash SP, et al. Peripheral lymph node tuberculosis: a review of 80 cases. *Br J Surg*. 1990;77:911–912.
464. Campbell IA. The treatment of superficial tuberculous lymphadenitis. *Tubercle*. 1990;71:1–3.
465. Hewlett D Jr, Duncanson FP, Jagadha V, et al. Lymphadenopathy in an inner city population consisting principally of intravenous drug abusers with suspected acquired immunodeficiency syndrome. *Am Rev Respir Dis*. 1988;137:1275–1279.
466. Shriner KA, Mathisen GE, Goetz MB. Comparison of mycobacterial lymphadenitis among persons infected with human immunodeficiency virus and seronegative controls. *Clin Infect Dis*. 1992;15:601–605.
467. Van den Brande P, Vijgen J, Demedts M. Isolated intrathoracic tuberculous lymphadenopathy. *Eur Respir J*. 1991;4:758–760.
468. Pastores SM, Naidich DP, Arnada CP, et al. Intrathoracic adenopathy associated with pulmonary tuberculosis in patients with human immunodeficiency virus infection. *Chest*. 1993;103:1433–1437.
469. Perich J, Ayuso MC, Vilana R, et al. Disseminated lymphatic tuberculosis in acquired immunodeficiency syndrome: computed tomography findings. *Can Assoc Radiol J*. 1990;41:353–357.
470. Radin DR. Intraabdominal *Mycobacterium tuberculosis* vs *Mycobacterium avium*-intracellulare infections in patients with AIDS: distinction based on CT findings. *AJR Am J Roentgenol*. 1991;156:487–491.
471. Beyt BE Jr, Ortbals DW, Santa Cruz DJ, et al. Cutaneous mycobacteriosis: analysis of 34 cases with a new classification of the disease. *Medicine (Baltimore)*. 1981;60:95–109.
472. Yen A, Rady PL, Cortes-Franco R, et al. Detection of *Mycobacterium tuberculosis* in erythema induratum of Bazin using polymerase chain reaction. *Arch Dermatol*. 1997;133:532–533.
473. Rohatgi PK, Palazzolo JV, Saini NB. Acute miliary tuberculosis of the skin in acquired immunodeficiency syndrome. *J Am Acad Dermatol*. 1992;26:356–359.
474. Lindell MM Jr, Jing BS, Wallace S. Laryngeal tuberculosis. *AJR Am J Roentgenol*. 1977;129:677–680.
475. Lee PY, Drysdale AJ. Tuberculous otitis media: a difficult diagnosis. *J Laryngol Otol*. 1993;107:339.
476. La Distia Nora R, van Velthoven ME, Ten Dam-van Loon NH, et al. Clinical manifestations of patients with intraocular inflammation and positive QuantiFERON-TB gold in-tube test in a country nonendemic for tuberculosis. *Am J Ophthalmol*. 2014;157:754–761.
477. Heiden D, Saranchuk P, Keenan JD, et al. Eye examination for early diagnosis of disseminated tuberculosis in patients with AIDS. *Lancet Infect Dis*. 2016;16:493–499.
478. Harrison NK, Knight RK. Tuberculosis of the nasopharynx misdiagnosed as Wegener's granulomatosis. *Thorax*. 1986;41:219–220.
479. Kelestimur F, Ozbakir O, Saglam A. Acute adrenocortical failure due to tuberculosis. *J Endocrinol Invest*. 1993;16:281–284.
480. Rentsch CA, Birkhauser FD, Biot C, et al. Bacillus Calmette-Guérin strain differences have an impact on clinical outcome in bladder cancer immunotherapy. *Eur Urol*. 2014;66:677–688.
481. Muller B, Durr S, Alonso S, et al. Zoonotic *Mycobacterium bovis*-induced tuberculosis in humans. *Emerg Infect Dis*. 2013;19:899–908.
482. Scott C, Cavanaugh JS, Pratt R, et al. Human tuberculosis caused by *Mycobacterium bovis* in the United States, 2006-2013. *Clin Infect Dis*. 2016;63:594–601.
483. Perez-Jacoiste Asin MA, Fernandez-Ruiz M, Lopez-Medrano F, et al. Bacillus Calmette-Guérin (BCG) infection following intravesical BCG administration as adjunctive therapy for bladder cancer: incidence, risk factors, and outcome in a single-institution series and review of the literature. *Medicine (Baltimore)*. 2014;93:236–254.
484. Pommier JD, Ben Lasfar N, Van Grunderbeeck N, et al. Complications following intravesical bacillus Calmette-Guérin treatment for bladder cancer: a case series of 22 patients. *Infect Dis (Lond)*. 2015;47:725–731.
485. Gonzalez OY, Musher DM, Brar I, et al. Spectrum of bacille Calmette-Guérin (BCG) infection after intravesical BCG immunotherapy. *Clin Infect Dis*. 2003;36:140–148.
486. Leo E, Molinari AL, Rossi G, et al. Mycotic abdominal aortic aneurysm after adjuvant therapy with bacillus Calmette-Guérin in patients with urothelial bladder cancer: a rare but misinterpreted complication. *Ann Vasc Surg*. 2015;29:1318.e1–e6.
487. Davis FM, Miller DJ, Newton D, et al. Successful treatment of a mycotic multifocal thoracoabdominal aortic aneurysm as a late sequelae of intravesical bacillus Calmette-Guérin therapy: case report and literature review. *Ann Vasc Surg*. 2015;29:840.e9–13.
488. Han PS, Orta P, Kwon DI, et al. *Mycobacterium bovis* cervical lymphadenitis: a representative case and review. *Int J Pediatr Otorhinolaryngol*. 2015;79:1798–1801.
489. Bourgoin A, Karabetsos A, Ouedraogo AS, et al. Intrafamilial transmission of pulmonary tuberculosis due to *Mycobacterium bovis*. *Med Mal Infect*. 2015;45:394–396.
490. Vazquez-Chacon CA, Martinez-Guarneros A, Couvin D, et al. Human multidrug-resistant *Mycobacterium bovis* infection in Mexico. *Tuberculosis (Edinb)*. 2015;95:802–809.
491. Smith LL, Wright BL, Buckley RH. Successful treatment of disseminated BCG in a patient with severe combined immunodeficiency. *J Allergy Clin Immunol Pract*. 2015;3:438–440.