Examples of this include ongoing inflammation at sites of lymphadenitis, worsened abnormalities on chest radiographs after several months of treatment, or the new appearance of pleural effusions during therapy for pulmonary tuberculosis. Such paradoxical worsening during treatment can occur in HIV-uninfected patients, as well as in HIV-infected patients (see "Immune Reconstitution Inflammatory Syndrome"). The diagnosis of a paradoxical reaction is made only after a thorough evaluation has excluded other etiologies, particularly tuberculosis treatment failure and drug resistance.

For patients who meet criteria for treatment failure, the possible reasons listed above should be addressed promptly. Recent mycobacterial isolates should be sent to a reference laboratory for susceptibility testing to both first-and second-line drugs. If clinicians are not familiar with the management of drug-resistant tuberculosis, immediate referral to, or consultation with a specialty center is indicated. If treatment failure is presumably due to drug resistance and the patient is seriously ill or has a positive sputum AFB smear, an empiric regimen is started immediately and continued until susceptibility tests are available to guide therapy; however, if the patient's clinical presentation is not severe, one may either initiate an empiric retreatment regimen or wait for drug susceptibility results from a recent isolate. Of note, patients who are not on the correct regimen remain infectious [102, 412].

A single new drug is never to be added to a failing regimen as it can lead to amplification of drug resistance, including acquired resistance to the newly added drug [413]. To lessen the likelihood of increasing resistance, it is generally prudent to add 2–3 new drugs to which susceptibility could logically be inferred (eg, using regional drug-resistance surveillance data and the patient's history of medication use). When drug susceptibility results are available, the regimen is adjusted accordingly.

Tuberculosis Caused by Drug-Resistant Organisms

Mycobacterium tuberculosis bacilli are continually undergoing spontaneous mutations that create resistance to individual antituberculosis drugs; however, the frequency of these mutations is sufficiently low that with appropriate combination chemotherapy that is reliably ingested, clinically significant resistance is very unlikely to develop [121, 414]. Acquired drug resistance can occur, however, when there is a large bacillary population (such as in pulmonary cavities), an inadequate drug regimen, a combined failure of both the patient and the provider to ensure that an adequate regimen is ingested, or malabsorption of one or more antituberculosis drugs [415, 416]. During extended or repeated treatment, amplification of resistance to multiple agents may occur. Patients with acquired drug resistance may transmit their strains to others who, if they develop tuberculosis, will have primary drug resistance. Notable clinical and demographic risk factors for drug-resistant tuberculosis include having a previous episode of tuberculosis treatment (in particular if the regimen was inadequate or adherence to the regimen was low), originating from or living for an extended period in a country with a high prevalence of drug-resistant tuberculosis, and having a history of exposure to an index case with drug-resistant tuberculosis.

Comprehensive guidance on the management of drug-resistant tuberculosis is beyond the scope of this document, though international guidelines exist [404]. An ATS/CDC/ERS/IDSA practice guideline for the management of drug-resistant tuberculosis is also currently under development using GRADE methodology.

RESEARCH AGENDA FOR TUBERCULOSIS TREATMENT

Much progress has been made over the last 10 years in the treatment of tuberculosis [109, 417]. The corpus of knowledge on new drug combinations, drug interaction with antiretrovirals, methods of dosing, and timing of dosing is increasing. Based on the writing of this guideline, however, several priority areas in need of additional research were identified.

New Antituberculosis Drugs and Regimens

Treatment of tuberculosis remains centered around the same 6-month, 4-drug regimen introduced >40 years ago. The identification of more potent drugs and drug regimens that permit shortening the duration of treatment remains a key priority. A number of new drugs and regimens for tuberculosis are currently being investigated in clinical trials. This includes repurposed drugs (eg, daily high-dose RPT and higher dosages of RIF, linezolid and carbapenems) and new drugs (eg, bedaquiline, delamanid, and pretomanid [formerly PA-824]). High-dose, daily RPT is being tested in a treatment-shortening phase 3 clinical trial, with dosage selected based on dose-ranging, drug-exposure optimization studies (ClinicalTrials.gov identifier: NCT02410772) [418]. Pretomanid is being tested as part of a combination regimen including moxifloxacin and PZA for the treatment of both drug-susceptible and drug-resistant tuberculosis (ClinicalTrials.gov identifier: NCT02193776). Bedaquiline, approved by the US FDA for treatment of multidrug-resistant tuberculosis in 2012, is also being investigated in drug-susceptible disease as part of a combination regimen including pretomanid and PZA and/or clofazimine in a phase 2 study (ClinicalTrials.gov identifier: NCT01691534). Broadly, the tuberculosis therapeutics development field would greatly benefit from dose-ranging and drug–drug interaction studies for new and existing drugs so as to identify the drug exposures and optimal combinations necessary to achieve maximal efficacy, while improving safety and tolerability.

Biomarkers of Treatment Effect and Individualization of Therapy

The success of therapy depends upon many diverse factors and only some are presently predictable, identifiable, or modifiable. Inclusion of biomarker substudies that assess both microbial and host biomarkers within phase 3 clinical trials will yield