

or drug interactions, reinfection or mixed infection with drug-resistant *M. tuberculosis*, and acquired drug resistance.

People with suspected treatment failure should be evaluated with a medical history, physical exam, and chest radiograph to determine whether a clinical response to therapy has occurred despite the absence of sputum culture conversion. The initial culture results and drug-resistance tests, treatment regimen, and adherence to the regimen also should be reviewed. Some experts would perform therapeutic drug monitoring to determine if serum concentrations of the TB drugs are within expected ranges and adjust dosage as necessary.^{151,249} In addition, samples from all available sites (e.g., sputum, blood, urine) should be collected for repeat culture and DST, and strong consideration should be given to performing rapid resistance testing on direct specimens or positive cultures to identify acquired drug resistance or mixed infection with a drug-resistant strain.

While awaiting results of repeat cultures and rapid resistance testing, broadening empiric TB treatment to include at least two additional second-line TB drugs should be considered in consultation with an expert in the field **(BIII)**.

Adverse Drug Reactions in TB Patients on Antiretroviral Therapy

Retrospective observational studies reported an increased risk of adverse drug reactions in patients treated with concomitant ART and anti-TB therapy. Many of these studies, however, included patients receiving older antiretrovirals which carried more frequent side effects.²⁵⁰ Three later randomized controlled trials reported similar rates of adverse events during anti-TB therapy with and without concomitant ART, suggesting no significant additive toxicity when ART is co-administered with anti-TB therapy.^{153,189,191} Nevertheless, managing suspected adverse drug reactions in this setting is complex because assigning causality to individual drugs in patients on anti-TB drugs, ART, and other agents is very difficult.

Because first-line anti-TB drugs are more effective and have fewer toxicities than alternative drugs, first-line drugs (especially isoniazid and rifampin or rifabutin) should not be stopped permanently, unless strong evidence exists that a severe drug reaction was caused by a specific anti-TB drug **(AIII)**. In such situations, decisions regarding rechallenge with first-line drugs and/or substitution of second-line drugs may be made in consultation with a specialist in treating TB disease in people with HIV.

Liver transaminases should be monitored at baseline and monthly for those with underlying risk factors for hepatotoxicity.¹⁵¹ Drug-induced liver injury (DILI) can be caused by isoniazid, rifamycins, pyrazinamide, some ARV drugs, and trimethoprim-sulfamethoxazole (TMP-SMX). Anti-TB DILI is defined as an ALT elevation ≥ 3 times the upper limit of normal (ULN) in the presence of symptoms (e.g., fever, rash, fatigue, nausea, anorexia, jaundice); ALT ≥ 3 times the ULN plus total bilirubin 2 times the ULN in the absence of symptoms; or ALT ≥ 5 times the ULN alone in the absence of symptoms. An increase in ALT concentration occurs in approximately 5% to 30% of people treated with the standard four-drug anti-TB regimen,^{97,251} but many of these have only transient, mild elevations of ALT.⁹⁷

If the criteria for anti-TB DILI are fulfilled, all potentially hepatotoxic drugs should be stopped, and the patient should be evaluated immediately **(AIII)**. Serologic testing for syphilis and hepatitis A, B, and C should be performed, and the patient should be questioned regarding symptoms suggestive of biliary tract disease and exposures to alcohol and other hepatotoxins. At least three anti-TB drugs not