sometimes producing toxicities. For example, administering ritonavir, a very potent CYP3A inhibitor, with the standard daily dose of RFB (300 mg) increases the serum concentrations of RFB (4-fold) and 25-O-desacetyl-rifabutin (35-fold) [194] and is associated with increased rates of leukopenia, arthralgias, skin discoloration, and anterior uveitis [195, 196]. Conversely, administering RFB with a CYP3A inducer such as efavirenz or phenytoin may decrease RFB concentrations [197], and this may lead to clinical failures and the selection of rifamycin-resistant *M. tuberculosis*. Recommendations for RFB dose adjustments are available at AIDSinfo, and at the CDC website (http://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/default.htm). Because interactions are complex and given the rapid emergence of new data on antiretroviral therapy (ART), the management of HIV-related tuberculosis cases should involve a physician with experience in this field.

- Absorption of the fluoroquinolones is markedly decreased by ingestion of medications containing divalent cations (calcium, iron, zinc) including antacids [198, 199]; supplements or vitamins containing calcium, iron, or zinc [200]; sucralfate [201]; and the chewable tablet formulation of didanosine [202]. These drug interactions can be avoided by ingesting medications containing divalent cations at least 2 hours apart from fluoroquinolones [203]. In addition, moxifloxacin serum concentrations are decreased by 25%–30% in the presence of RIF due to the induction of phase II metabolic enzymes (sulfation and glucuronidation) [204]. RPT and RFB also may decrease moxifloxacin serum concentrations, though the clinical significance of these drug–drug interactions in individual patients is uncertain.

Antituberculosis Drugs Affecting Other Drugs

Drug Interactions Due to Rifamycins

Most of the clinically relevant drug–drug interactions involving the antituberculosis drugs are due to the effect of the rifamycins (RIF, RFB, and RPT) on the metabolism of other drugs [205]. All of the rifamycins are inducers of a variety of metabolic pathways, particularly those involving the various isozymes of the cytochrome P450 (CYP) system [206]. By inducing the activity of metabolic enzymes, rifamycins decrease the serum concentrations of many drugs, sometimes to subtherapeutic levels [207]. RIF is the most potent enzyme inducer and RFB the least, while RPT's potency depends on its frequency of administration [208, 209]. Daily RPT is at least as potent as daily RIF, while once-weekly RPT (as used in combination with INH for latent tuberculosis infection [210]) has limited effects on other drugs.

The well-described, clinically relevant, drug–drug interactions involving the rifamycins are presented in Table 8 [206, 211]; however, many possible interactions involving the rifamycins have not been fully investigated and additional clinically relevant interactions undoubtedly will be described. Therefore, it is important to check all concomitant medications for possible, as well as confirmed, drug–drug interactions with rifamycins.

Rifamycin inductive effects typically take approximately 1–2 weeks to reach steady state after the rifamycin is started, and inductive effects typically resolve over approximately 2 weeks after the rifamycin is discontinued [209]. If the dose of a medication is increased to compensate for the effect of a rifamycin, it is critical to reduce the dose within 2 weeks after the rifamycin is discontinued and its inductive effect resolves.

RFB can be used in place of RIF if there is an unacceptable drug–drug interaction between RIF and another drug such as cyclosporine [212, 213] and most of the HIV-1 protease inhibitors [208, 214, 215]. All the rifamycins may cause unacceptable decreases in the serum concentrations of certain drugs such as itraconazole [216–218].

Drug Interactions Due to INH

INH is a relatively potent inhibitor of several CYP isozymes [219, 220] and increases concentrations of some drugs to the point of toxicity such as the anticonvulsants phenytoin [221, 222] and carbamazepine [223, 224]. INH also increases concentrations of benzodiazepines metabolized by oxidation, such as diazepam [225] and triazolam, but not those metabolized by conjugation, such as oxazepam [226]. Of note, the inductive effect of RIF on CYP isozymes outweighs the inhibitory effect of INH, so that the overall effect of combined therapy with RIF and INH is a decrease in the concentrations of drugs such as phenytoin [227] and diazepam [225].

INH may increase toxicity of other drugs—acetaminophen [228], valproate [229], serotonergic antidepressants [230], warfarin [231], and theophylline [232]—but these potential interactions have not been well studied. A possible interaction between INH and disulfiram was initially described [233]; however, a retrospective study found that disulfiram was safe when added to intermittent, directly observed INH-containing tuberculosis treatment [234].

Drug Interactions Due to the Fluoroquinolones

Ciprofloxacin [235] inhibits the metabolism of theophylline and can cause clinical theophylline toxicity [236]; however, levofloxacin [237], gatifloxacin [238], and moxifloxacin [239] do not affect theophylline metabolism.

Useful Websites Regarding Drug Interactions

Useful websites regarding drug interactions (tuberculosis/HIV and other) are available through the following hyperlinks: AIDSinfo, Centers for Disease Control and Prevention, University of California San Francisco, University of Liverpool, Indiana University, and University of Maryland.

Therapeutic Drug Monitoring

TDM generally consists of measurements of drug concentrations in serum specimens typically collected at 2 and 6 hours after a dose of the drug, or drugs, in question. Other sampling times may be used for selected situations. Blood samples are centrifuged; the serum is harvested and frozen, and then