pyrazinamide when a later-generation fluoroquinolone is included in the regimen in patients in whom there is toxicity anticipated or experienced because of pyrazinamide or when the patient has noncavitary, lower burden of disease. Finally, plasma peak concentration and exposure to moxifloxacin have been shown to decrease by approximately 30% when coadministered with rifampin (278, 279). The impact of these decreased exposures on outcomes has not been established. However, some experts opt to use levofloxacin when combined with rifampin.

Conclusions

We conclude that in patients with isoniazid-resistant TB, the addition of a later-generation fluoroquinolone to 6 months of daily rifampin, ethambutol, and pyrazinamide improves treatment success rates. In patients in whom toxicity from pyrazinamide is anticipated or experienced, or in patients with active TB with lower burden of disease (i.e., noncavitary), the committee viewed the balance of benefits and harms to favor shortening the duration of pyrazinamide when a later-generation fluoroquinolone is included in the regimen, acknowledging that the certainty in the evidence is very low and more research is needed.

Research Needs

All but 2 of the 23 studies included in the IPDMA were observational. Moreover, the analyzed population included only 37 children, 119 patients with diabetes, and 249 patients with HIV infection. Given the burden of isoniazid-resistant TB worldwide, clinical trials that include these special populations and evaluate new regimens, including the evaluation of the efficacy, safety, and tolerability of shorter versus longer durations of pyrazinamide, are urgently needed.

Treatment of MDR-TB in Special Situations

HIV Infection

Among patients with HIV and TB, rifampin resistance has been identified more often compared with those without HIV (280, 281). Patients with MDR-TB and HIV have up to a fourfold higher risk of mortality compared with patients with MDR-TB without HIV (282). Low CD4 cell counts (e.g., ⩽50 cells/μl) in patients with HIV and MDR-TB further correlate with higher mortality (283, 284). Numerous practice guidelines recommend HIV testing of people with suspected or confirmed TB (11, 20, 34, 285), regardless of drug resistance. Because of their high risk for mortality early in the course of TB disease, people with HIV in whom TB is suspected are recommended to receive rapid testing for TB using nucleic acid amplification tests coupled with molecular diagnostic DST for rifampin (with or without isoniazid) (13, 20).

For patients with HIV receiving therapy for drug-susceptible TB, studies found significantly lower mortality among patients receiving concurrent antiretroviral therapy (ART) compared with those not receiving ART (286–288). U.S. practice guidelines recommend starting ART within 2 weeks of initiating treatment for drug-susceptible non-CNS TB for patients with CD4 cell counts <50 cells/μl and by 8 to 12 weeks for patients with higher CD4 cell counts (11, 289). Although the optimal timing for starting ART to reduce patient mortality has not yet been adequately determined for patients with MDR-TB, lower mortality rates have been shown in multiple studies among patients with MDR-TB receiving concurrent ART compared with those not receiving ART (283, 290–297), especially among patients with TB with CD4 counts <50 cells/μl (283, 292). The decreased mortality seen in patients treated for MDR-TB who concurrently receive ART, especially among those with CD4 cell counts <50 cells/μl, supports a similar ART management approach as recommended for drug-susceptible TB.

MDR-TB of the CNS in patients with HIV presents additional challenges. TB meningitis with isoniazid-resistant TB, RR-TB, or MDR-TB can be associated with higher mortality compared with drug-susceptible disease (298–300). Starting ART early in patients with TB is associated with a higher incidence of immune reconstitution inflammatory syndrome (286, 288, 301), and this can be even more problematic in CNS disease. A recent study in Vietnam of patients with advanced AIDS found a higher incidence of potentially life-threatening (grade 4) adverse events among patients with TB meningitis starting ART early compared with those delaying ART until after 2 months of standardized first-line TB treatment and did not show a survival benefit of starting ART early (302). It has been recommended to delay starting ART by 8 weeks in patients with CNS TB and HIV (11); however, there is a paucity of data in patients with MDR-TB of the CNS. The optimal approach for initiation of ART in patients with this medical condition remains uncertain, and close clinical monitoring is warranted.

Drug interactions between antiretroviral and anti-TB agents are common in the management of patients with HIV and TB, particularly with rifamycins. Because the rifamycins (with the possible exception of rifabutin) are not used for treatment of MDR-TB, interactions of other TB medication classes with ART should be considered. Bedaquiline and/or delamanid might be considered for use in patients with HIV. Although efavirenz can produce a decrease in serum bedaquiline concentrations and this combination is avoided, other ART drugs, including the protease inhibitors and cobicistat, can result in increased serum bedaquiline levels. The current WHO recommendations for the use of delamanid apply to patients living with HIV (7). Drug–drug interaction studies in healthy volunteers of delamanid with tenofovir, efavirenz, and lopinavir/ritonavir show that no dose adjustments were needed (303). Nonetheless, when delamanid is included in the regimen for MDR-TB in HIV-infected patients, the design of their

PICO Question 21—Treatment of Contacts Exposed to MDR-TB: Should contacts exposed to an infectious patient with MDR-TB be offered LTBI treatment versus followed with observation alone?

Recommendation 21: For contacts with presumed MDR LTBI due to exposure to an infectious patient with MDR-TB, we suggest offering treatment for LTBI (conditional recommendation, very low certainty in the evidence). We suggest 6 to 12 months of treatment with a later-generation fluoroquinolone alone or with a second drug, on the basis of drug susceptibility of the source-case *M. tuberculosis* isolate. On the basis of evidence of increased toxicity, adverse events, and discontinuations, pyrazinamide should not be routinely used as the second drug.