New Approaches to the Treatment of Latent Tuberculosis

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ABSTRACT

It is estimated that one third of the global population is infected with *Mycobacterium tuberculosis*. Treatment of *M. tuberculosis* infection is an important strategy for tuberculosis elimination, but the effectiveness of this strategy is limited by poor adherence to therapy, which is due at least in part to the long duration of treatment. A 9-month course of isoniazid is the currently preferred treatment regimen for *M. tuberculosis* infection, due to the extensive data regarding the effectiveness and tolerability of isoniazid, and limited data on the effectiveness and tolerability of alternative shorter-course regimens. This review covers all currently available regimens, including less established alternative treatment regimens (e.g., rifampin for 4 months and isoniazid + rifampin for 3 months), as well as regimens that are currently under investigation (e.g., isoniazid + rifapentine for 3 months). Potential future regimens and experimental approaches are also discussed.

KEYWORDS: Treatment of *M. tuberculosis* infection, *M. tuberculosis,* tuberculosis, isoniazid, rifampin, rifapentine

The global burden of *Mycobacterium tuberculosis* infection is enormous, but most persons infected with *M. tuberculosis* do not subsequently develop tuberculosis disease. Treatment of persons at high risk of progressing from latent infection to active disease is very effective, however, and has been identified as a key component to achieving tuberculosis elimination. The most recent recommendations of the American Thoracic Society and Centers for Disease Control and Prevention, which were also endorsed by the Infectious Diseases Society of America and the American Academy of Pediatrics, were published in 2000[1]; additional guidelines for pediatrics were published in 2004,[2] and an update for adults was published in 2005.[3] These guidelines recommend a 9-month course of isoniazid as the preferred regimen for treatment of *M. tuberculosis* infection in both adults and children in the United States. However, treatment completion rates are low, necessitating evaluation of shorter-course regimens. After a discussion of the effectiveness and tolerability of isoniazid, this review will focus on the status of newer approaches to the treatment of latent *M. tuberculosis* infection, including novel regimens currently under investigation.

PREVALENCE OF LATENT *M. TUBERCULOSIS* INFECTION

It is estimated that one third of the global population, or 2 billion people, are infected with *M. tuberculosis*.[4] The prevalence of *M. tuberculosis* infection in the United States is lower and has been declining. Among persons aged 25 to 74, the prevalence decreased from 14.4% in 1971–72 to 5.6% in 1999–2000.[5] It has been estimated that 4.2% of the overall U.S. population (11,213,000

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Tuberculosis; Guest Editor, Neil W. Schluger, M.D.

Semin Respir Crit Care Med 2008;29:532–541.

DOI 10.1055/s-0028-1085704. ISSN 1069-3424.

persons) was infected with *M. tuberculosis* in 1999–2000, but the prevalence was higher among specific groups: the foreign born, non-Hispanic blacks, Mexican Americans, and persons living in poverty.[6]

RISK OF TUBERCULOSIS IF INFECTED WITH *M. TUBERCULOSIS*

Among infected persons, ~10% progress to active tuberculosis over their lifetime[7,8]; the risk is higher in persons with concomitant HIV infection (> 20%), evidence of old healed tuberculosis on chest radiograph (> 20%), or recent *M. tuberculosis* infection (10 to 20%).[9] In the majority of infected persons, the host immune response contains the replication of *M. tuberculosis* and prevents the development of disease.[10] Among infected persons who develop active disease, progression occurs either shortly after initial infection (progressive primary disease), or subsequent to the initial infection, when there is a breakdown in the host immune response. A person is at greatest risk of progressing to active disease during the first 2 years after infection with *M. tuberculosis*.[7] In addition to HIV infection and recent *M. tuberculosis* infection, other risk factors for progression to active tuberculosis include silicosis; diabetes mellitus; chronic renal failure; malnutrition; weight loss; leukemia; lymphoma; cancer of the head, neck, and lung; gastrectomy; and jejuno-ileal bypass surgery.[1,9]

DIAGNOSIS OF LATENT *M. TUBERCULOSIS* INFECTION

Diagnostic methods for latent *M. tuberculosis* infection are discussed in the article by Drs. Pai and O'Brien in this issue. Until recently, the diagnosis of *M. tuberculosis* infection has relied almost exclusively on the tuberculin skin test, an intradermal test that utilizes purified protein derivative (PPD). Because the mycobacterial proteins in PPD are not specific for *M. tuberculosis*, persons infected with other mycobacteria (e.g., environmental mycobacteria such as *M. avium intracellulare*, and *M. bovis*, the organism in the tuberculosis vaccine bacille Calmette-Guérin (BCG)) may have a false-positive test. In addition, the tuberculin skin test has low sensitivity, particularly in immunocompromised persons. Interferon-γ release assays (e.g., QuantiFERON-TB Gold, Cellestis Inc., Valencia, CA, and T-SPOT.TB, Oxford Immunotec Limited, Abingdon, Oxfordshire, UK) utilize antigens such as early secretory antigen 6 (ESAT-6) and culture filtrate protein 10 (CFP-10) that are present in *M. tuberculosis* but not *M. bovis* BCG or *M. avium intracellulare*. These tests are therefore more specific for *M. tuberculosis* infection than the tuberculin skin test; their sensitivity is comparable to that of the skin test when categorized according to clinical gradients of tuberculosis exposure.[11]

INDICATIONS FOR TREATMENT OF *M. TUBERCULOSIS* INFECTION

All persons with evidence of latent *M. tuberculosis* infection should be evaluated for the presence of active disease. The evaluation should include an assessment of the signs and symptoms of tuberculosis and a chest radiograph; in persons with symptoms or an abnormal chest radiograph, sputum for acid-fast smear and culture should also be obtained.[12] Once active disease has been excluded, all persons with evidence of latent *M. tuberculosis* infection who are at increased risk of progressing to active tuberculosis should receive treatment for latent infection.[1,2]

However, not all persons who are eligible for treatment of latent tuberculosis infection initiate therapy. In a study of close contacts of smear-positive pulmonary tuberculosis cases, 95 HIV-infected persons were eligible for treatment of latent infection, of whom only 30 (32%) were started on therapy.[13] In another study of close contacts of tuberculosis cases, of the 630 persons with newly documented positive tuberculin skin tests (all of whom were eligible for therapy), treatment was recommended in 447 (71%), and started in only 398 (63%).[14] Efforts must be made to improve the use of treatment of latent infection, particularly in those at highest risk of progression to active disease, such as HIV-infected persons and close contacts.

SCOPE OF TREATMENT OF *M. TUBERCULOSIS* INFECTION IN THE UNITED STATES AND CANADA

In a recent survey conducted at 19 sites throughout the United States and two sites in Canada, the 37,145 persons at U.S. study sites who initiated treatment for latent tuberculosis infection in 2002 were extrapolated to the entire U.S. population. Based on population and tuberculosis case rate data, it was estimated that 291,000 to 433,000 persons in the United States initiated treatment for latent tuberculosis infection in 2002. It was also estimated that this prevented 4000 to 11,000 tuberculosis cases.[15] Of the 37,857 total patients in the survey, 79% received treatment through a public health clinic, 6% at an immigrant/refugee clinic, and 6% at a jail or prison clinic.[15]

COMPLETION OF TREATMENT OF *M. TUBERCULOSIS* INFECTION

Completion rates of isoniazid in the clinic setting have been low, ranging from 30 to 64%.[1,9,16,17] In a follow-up cross-sectional survey conducted among a subset of patients at the study sites above in 2002, there were 1994 persons who initiated treatment for latent tuberculosis infection. Of these, 84% initiated 9 months of isoniazid, 9% initiated 6 months of isoniazid, and 5%

initiated 4 months of rifampin (2% initiated other regimens). Overall, only 47% of patients who initiated therapy completed it. A key risk factor for failing to complete therapy included initiating the 9-month regimen—compared with the other regimens, all of which were of shorter duration.[18] This study is important in that it demonstrates that most persons who receive treatment for latent tuberculosis infection in the United States and Canada initiate a regimen of 9 months of isoniazid, but most persons do not complete therapy. It also suggests that shorter treatment regimens are likely associated with higher treatment completion rates.

REGIMENS TO TREAT *M. TUBERCULOSIS* INFECTION

Infection with *M. tuberculosis* is often termed latent because of the absence of clinical manifestations, the slower replication rate of *M. tuberculosis,* and the lower burden of organisms compared with active disease.[19] Due to the relatively low burden of organisms, treatment of latent infection requires fewer drugs than active disease to facilitate cure and prevent the development of drug resistance. Use of a single antituberculosis agent is sufficient for latent infection but not for active disease. As detailed following here, treatment of latent *M. tuberculosis* infection can significantly decrease the risk of developing active tuberculosis.

Regimens to treat latent *M. tuberculosis* infection are reviewed in the following sections and summarized in Table 1 according to their effectiveness and tolerability. Because effectiveness and tolerability have often been assessed separately according to HIV-serostatus, the data are presented according to HIV-serostatus where available. Recommended doses of specific drugs are published elsewhere.[1]

Isoniazid for 9 Months

EFFECTIVENESS

HIV-Seronegative Persons Isoniazid is the best-studied regimen for the treatment of latent *M. tuberculosis* infection. More than 20 randomized, controlled trials have been conducted, which together enrolled $>100{,}000$ persons. Most of these studies were conducted in the 1950s and 1960s, and therefore enrolled only HIV-seronegative persons. Most of the studies assessed the effectiveness of 12 months of isoniazid versus placebo. The trial conducted by the International Union Against Tuberculosis (IUAT) assessed 3 versus 6 versus 12 months of therapy, and found that 6 months of isoniazid was less effective (65%) than 12 months (75%).[20] A post hoc analysis of previously conducted clinical trials found that 6 months of isoniazid provided insufficient protection, and that 9 to 10 months of isoniazid appeared to provide optimal protection.[21] Based on these findings, the American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), and Infectious Diseases Society of America (IDSA) guidelines recommend 9 months of isoniazid.[1] It should be noted, however, that the effectiveness and tolerability of 9 months of isoniazid have never been compared with a 6- or 12-month course in a clinical trial.

The efficacy of isoniazid in preventing tuberculosis exceeds 90% among persons who adhere to therapy,[20] but the effectiveness of isoniazid is lower due to low rates of adherence. Isoniazid may be more effective in children than in adults, with an effectiveness of 70 to 90%.[22,23]

HIV-Seropositive Persons Isoniazid effectiveness has been studied in HIV-seropositive persons, though not as extensively as in HIV-seronegative persons. Among tuberculin skin-test-positive persons, isoniazid is clearly more effective than placebo in preventing tuberculosis; this has been confirmed in a meta-analysis.[24] Isoniazid has been associated with improved survival in some studies[25–27] but not all.[24,28,29] Although there has not been a direct comparison of 6 versus 9 versus 12 months of isoniazid, 6 months appears to be less effective than 12 months. Based on the same rationale used for HIV-seronegative persons, and to ensure uniformity of recommendations, the ATS/CDC/IDSA guidelines recommend 9 months of isoniazid for HIV-seropositive persons.[1] Although HIV-infected persons are at increased risk of having a negative tuberculin skin test, particularly with advanced immunosuppression, isoniazid is not substantially more effective than placebo in preventing tuberculosis in such persons and therefore is not recommended.[24,30]

TOLERABILITY

HIV-Seronegative Persons In the initial studies of isoniazid, drug discontinuation rates were low and did not differ compared with rates among persons receiving placebo.[31] However, subsequent studies have noted higher rates of drug discontinuation due to toxicity, ranging from 2.2 to 31.3%.[32–37] Of note, only one of these studies was placebo controlled. Isoniazid can cause elevated hepatic transaminases,[32] but these liver function abnormalities are often transient and not representative of clinically significant hepatitis. In studies in which serum transaminases were monitored regularly regardless of symptoms, 10 to 22% of participants had at least one elevated transaminase level during the course of therapy.[33,36–41] Rates of clinically significant hepatitis are lower. In a surveillance study of

Table 1 Regimens for the Treatment of Latent Tuberculosis Infection

Regimen	Duration	Administration	Effectiveness	Toxicity Requiring Drug Discontinuation	Current Status	Comments
Isoniazid	9 months	Daily self-administered or twice-weekly via DOT	Not studied	Not studied	Recommended by ATS, CDC, IDSA, AAP for adults and children	Although the 9-month regimen has not been evaluated, post hoc analysis suggests optimal effectiveness at 9–10 months of treatment
			6 months: 65% 12 months: 75%	6–12 month regimens: HIV negative: 2.2–31.3% HIV positive: 0–9.2%		
Rifampin	4 months	Daily self-administered	Not studied		Recommended as alternative when patient unable to take isoniazid due to drug resistance or intolerance	Concern in HIV + persons, in whom TB can be difficult to diagnose; if patient has TB, could develop rifampin resistance
			3-month regimen: HIV negative: 46–50% HIV positive: not studied	HIV negative: 1.9–3.1% HIV positive: not studied		
Isoniazid + rifampin	3 months	Daily self-administered	HIV negative: 41%	HIV negative: 0–5.1%	Fair amount of data on tolerability and effectiveness; used in Great Britain but not in ATS/CDC recommendations	Probably a good alternative option
			HIV positive: 60%	HIV positive: 2.3%		
Isoniazid + rifapentine	3 months	Once-weekly via DOT	HIV negative: one small study; similar to rifampin + pyrazinamide	HIV negative: 0.5%	Under evaluation: TBTC Study 26, South Africa (JHU)	Shows promise, but more data needed before it can be used outside of clinical trials
			HIV positive: not studied	HIV positive: not studied		
Rifampin + pyrazinamide	2 months	Daily self-administered	HIV negative: not studied	HIV negative: 2.0–17.6%	Not recommended	High risk of severe hepatotoxicity
		Twice-weekly via DOT	HIV positive: similar to isoniazid	HIV positive: 0–9.5%		
				Hepatitis-associated mortality: 1 per 1000		

AAP, American Academy of Pediatrics; ATS, American Thoracic Society; CDC, Centers for Disease Control and Prevention; DOT, directly observed therapy; IDSA, Infectious Diseases Society of America; JHU, Johns Hopkins University; TBTC, Tuberculosis Trials Consortium.
See text for references regarding effectiveness and toxicity of the regimens.

the U.S. Public Health Service, 236/13,838 (1.7%) persons who received isoniazid developed hepatitis; when considering only those persons in whom the hepatitis was probably or possibly related to isoniazid, the rate was 174/13,838 (1.3%).[42] Hepatitis risk increased with age and concomitant alcohol consumption. In another study, a 7-year survey from one public health clinic, 11/11,141 (0.10%) patients who started isoniazid developed hepatotoxicity.[43]

Isoniazid-associated hepatotoxicity can be fatal, and the risk of death also increases with age. It is estimated that the hepatotoxicity-associated case-fatality rate per 10,000 persons initiating isoniazid is 0 for ages 20 through 34, 2 for ages 35 through 49, and 4 for ages 50 through 64.[36,42,44,45]

Although never tested in a trial, rates of hepatotoxicity may be lower when there is regular monitoring of signs and symptoms of hepatitis.[43,44] In the United States it is currently recommended that patients on isoniazid undergo monthly clinical assessments for adverse effects; they should also be evaluated whenever symptoms develop. Patients should be educated regarding the signs and symptoms of hepatotoxicity and instructed to discontinue the medicine and seek clinical evaluation if symptoms occur. Routine laboratory monitoring is recommended for persons with abnormal baseline liver function tests, persons at increased risk of hepatotoxicity (e.g., HIV infection, liver disease, alcoholism, pregnancy), and persons who develop symptoms while on therapy.[1]

Isoniazid can also cause peripheral neuropathy, but the risk is lower with concomitant use of vitamin B6 (pyridoxine).[46,47]

HIV-Seropositive Persons The rates of isoniazid-associated toxicity requiring drug discontinuation in HIV-seropositive persons range from 0 to 9.2%, and have generally been comparable to the rates among persons receiving placebo.[25,28,30,48,49] Although the data are not as extensive as in HIV-seronegative persons, isoniazid is generally well tolerated in this patient population.

Rifampin for 4 Months

EFFECTIVENESS

Among persons who are intolerant of isoniazid, or close contacts of tuberculosis cases in which the isolate of *M. tuberculosis* is resistant to isoniazid, rifampin can be used to treat latent *M. tuberculosis* infection.[1] There are limited data on the effectiveness of this regimen, but it does appear to be well tolerated. Given the importance of rifampin in the treatment of active tuberculosis, it is particularly important to exclude active disease before treating for latent *M. tuberculosis* infection because treatment of undiagnosed active tuberculosis with rifampin monotherapy will lead to rifampin resistance. This is of particular importance in HIV-infected persons, in whom the diagnosis of tuberculosis can be difficult to establish and in whom the risk of acquired rifamycin resistance among persons receiving treatment for tuberculosis is increased, particularly with advanced HIV.[50] HIV-infected persons with pulmonary tuberculosis have a higher likelihood of an atypical or even normal chest radiographic appearance than HIV-uninfected persons.[51] HIV-infected persons are less likely to have cavitary and smear-positive pulmonary disease and more likely to have extrapulmonary tuberculosis.[52] The latter is associated with a lower bacillary burden and is more likely to be culture negative.

HIV-Seronegative Persons The only randomized trial to evaluate the effectiveness of rifampin was conducted in Hong Kong among persons with latent *M. tuberculosis* infection and silicosis. Among all persons initiating therapy, 20/165 (12.1%) randomized to receive rifampin for 3 months developed tuberculosis, compared with 36/159 (22.6%) who received placebo, for an effectiveness of 46%.[53] Among persons who completed the 5-year study, rates were 17/103 (17%) and 34/99 (34%), respectively, for an effectiveness of 50%.[53] In an observational study among homeless persons with documented tuberculin skin-test conversion during an epidemic of tuberculosis resistant to isoniazid and streptomycin, 49 persons received rifampin; the average duration of therapy was 6.4 months. None of the 49 developed tuberculosis, compared with 6/71 (8.6%) persons who received no therapy.[54] In a study of 157 tuberculin skin-test positive adolescent close contacts of persons with isoniazid-resistant tuberculosis, all were treated with a 6-month course of rifampin; none developed tuberculosis during the 2-year evaluation period.[55] Although the effectiveness of 4 months of rifampin has never been studied, it is the currently recommended duration in the ATS/CDC/IDSA guidelines.[1]

HIV-Seropositive Persons There are no studies of the effectiveness of rifampin for the treatment of latent *M. tuberculosis* infection among HIV-seropositive persons. As noted earlier, active disease is more difficult to exclude in HIV-infected persons, and the risk of acquired rifamycin resistance among those with active disease is high. Therefore the use of rifampin in this patient population should probably be avoided.

TOLERABILITY

HIV-Seronegative Rifampin appears to be well tolerated. In the randomized trial conducted in Hong

Kong, 6/172 patients (3.5%) discontinued therapy due to adverse drug reaction while on study therapy; none of these patients developed hepatotoxicity.[53] In the study among homeless persons in Boston, 7/49 (14%) developed adverse effects requiring discontinuation of therapy, but there were no reports of hepatotoxicity.[54] Of the 157 adolescents who received rifampin, 18 (11.5%) interrupted therapy temporarily, and two (1.3%) permanently discontinued therapy.[55] In a recent study of persons randomized to receive either 4 months of rifampin or 9 months of isoniazid, 2/58 (3%) persons receiving rifampin developed adverse events requiring permanent drug discontinuation; none developed hepatitis.[56] In a retrospective observational study of 4 months of rifampin versus 9 months of isoniazid, permanent drug discontinuation rates were 1.9% versus 4.6%, respectively ($p < 0.001$); hepatotoxicity rates were 0.08% versus 1.8%, respectively ($p < 0.001$).[57] In another observational study of 4 months of rifampin versus 9 months of isoniazid, drug discontinuation due to adverse drug reactions was lower in the rifampin group, but not statistically significant (3.1% vs 6.1%; $p = 0.12$); there were no cases of drug-induced hepatotoxicity among the 261 patients who received rifampin.[58]

HIV-Seropositive Persons There are no published data on the safety of this regimen in HIV-seropositive persons.

Isoniazid + Rifampin for 3 Months

EFFECTIVENESS

HIV-Seronegative Persons There are few studies of isoniazid + rifampin for the treatment of latent *M. tuberculosis* infection in HIV-seronegative persons. In a small study among adults in Hong Kong, the efficacy (i.e., among adherent patients) of 3 months of isoniazid + rifampin was 41%.[53] In a study from Spain by Martinez-Alfaro et al among adults in which patients were either HIV-seronegative or HIV-untested, tuberculosis risk was similar in persons who received either 3 months of isoniazid + rifampin or 9 months of isoniazid.[59] In another relatively small study conducted among children over an 11-year period in Greece, 220 children with latent *M. tuberculosis* infection received 3 months of isoniazid + rifampin. Of the 209 children who were compliant, 11% subsequently had abnormal chest radiographs and were treated for active tuberculosis.[60]

HIV-Seropositive Persons Among HIV-seropositive tuberculin skin-test positive (≥ 5 mm induration) adults in Uganda, 3 months of daily isoniazid + rifampin was 60% effective in preventing tuberculosis compared with placebo.[28] In a meta-analysis that included five studies of both HIV-infected and -uninfected persons, the tuberculosis risk among persons receiving a 3-month course of daily isoniazid + rifampin was comparable to that seen among persons receiving 6 to 12 months of isoniazid, with a pooled risk difference of 0% (95% CI: -1 to 2%).[59]

TOLERABILITY

HIV-Seronegative Persons The regimen has been well-tolerated, though, as noted earlier, there have been relatively few studies conducted to date. In the study among HIV-seronegative adults, 8/167 (5%) persons discontinued therapy due to adverse drug reaction, compared with 8/173 (5%) persons who received 6 months of isoniazid.[53] Similar rates of drug discontinuation were reported in a study from Great Britain (5.1% vs 5.8%, respectively).[61] In a programmatic report among 213 children in Great Britain who received 3 months of isoniazid + rifampin, none had to discontinue therapy due to drug toxicity[62]; this was also true in the study from Greece.[60] And finally, in a pooled analysis of 6105 persons who received isoniazid + rifampin, 156 (2.5%) developed hepatitis.[63]

HIV-Seropositive Persons Among HIV-seropositive adults, the drug discontinuation rate due to adverse drug reaction was 13/556 (2.3%), slightly higher than the 0.6% rate among persons receiving 6 months of isoniazid.[28] In the meta-analysis mentioned earlier that included both HIV-infected and -uninfected persons, 3 months of isoniazid + rifampin was as safe as 6 to 12 months of isoniazid.[59]

Isoniazid + Rifapentine for 3 months

Rifapentine is a long-acting rifamycin that was approved by the U.S. Food and Drug Administration in 1998 for tuberculosis treatment. Its long half-life has allowed for once-weekly dosing when given in combination with isoniazid. A 3-month regimen of once-weekly isoniazid + rifapentine is being evaluated in clinical trials. Although currently there are insufficient tolerability and effectiveness data for it to be used outside of a clinical trial, preliminary results are promising.

EFFECTIVENESS

HIV-Seronegative Persons A recently published study conducted in Brazil compared the tolerability and effectiveness of once-weekly directly observed isoniazid 900 mg + rifapentine 900 mg for 3 months versus daily self-administered rifampin 450 to 600 mg + pyrazinamide 750 to 1500 mg for 2 months

among predominantly HIV-seronegative adult household tuberculosis contacts. There were 206 persons in the isoniazid + rifapentine arm and 193 in the rifampin + pyrazinamide arm. The study was discontinued early because of high toxicity rates in the rifampin + pyrazinamide arm. Although sample size was small and the event rate was low, tuberculosis risk was similar in both groups: three tuberculosis cases in 564 person-years (p-y) of follow-up in the isoniazid + rifapentine arm versus one tuberculosis case in 522 p-y of follow-up in the rifampin + pyrazinamide arm (0.5 vs 0.2 per 100 p-y; $p = 0.66$).[64] The same isoniazid + rifapentine regimen is being compared against daily self-administered isoniazid 300 mg for 9 months in a multinational study being conducted by the Tuberculosis Trials Consortium of the CDC (U.S. Public Health Service Study 26; NCT00023452). As of February 2008 the target enrollment of 8000 patients had been achieved; the analysis will be performed after all patients have been followed for 33 months after enrollment.

HIV-Seropositive Persons There have been no studies published to date of isoniazid + rifapentine in HIV-infected persons, but one study in South Africa has completed enrollment (NCT00057122).[65] In this study of 1148 HIV-infected adults, patients were randomized to receive once-weekly directly observed isoniazid + rifapentine for 3 months versus twice-weekly directly observed isoniazid + rifampin for 3 months versus daily self-administered isoniazid for 6 months versus daily self-administered isoniazid continuously. The analysis is under way.

If effective and well tolerated, isoniazid + rifapentine would provide a relatively simple short-course regimen for the treatment of latent tuberculosis infection, with presumably good treatment completion rates.

TOLERABILITY

HIV-Seronegative Persons In the study from Brazil, one of 206 (0.5%) patients discontinued isoniazid + rifapentine due to drug toxicity, compared with six of 193 (3.1%) in the rifampin + pyrazinamide arm. The rates of grade 3 or 4 hepatotoxicity were 1% versus 10%, respectively ($p < 0.001$).[64]

HIV-Seropositive Persons There are currently no published data on the safety of this regimen in HIV-seropositive persons.

Rifampin + Pyrazinamide for Two Months

The 2-month regimen of rifampin + pyrazinamide was initially evaluated for effectiveness and tolerability in HIV-infected persons. Although the regimen was effective and safe in this population, the risk of severe hepatotoxicity subsequently reported when this regimen was used in the general population was unacceptably high. This regimen is therefore no longer recommended.[66]

EFFECTIVENESS

There are very limited data on the effectiveness rifampin + pyrazinamide in HIV-seronegative persons. In HIV-seropositive persons, rifampin + pyrazinamide was similar in effectiveness to isoniazid.[49,67,68] In the largest study conducted, the effectiveness of daily rifampin + pyrazinamide for 2 months was similar to 12 months of daily isoniazid, with tuberculosis rates of 0.8 and 1.1 per 100 person-years, respectively ($p = 0.28$).[67]

TOLERABILITY

Drug discontinuation due to toxicity has ranged from 2.0 to 17.6% in HIV-seronegative persons[69–77] and 0 to 9.5% in HIV-seropositive persons.[49,67,68,78,79] After the initial reports of severe and fatal liver injury among persons treated with rifampin + pyrazinamide, the Centers for Disease Control and Prevention (CDC) conducted a survey of state and city tuberculosis programs in the United States. Among 8087 persons initiating therapy between January 2000 and June 2002, the rate of symptomatic hepatitis was 18.7 per 1000 persons initiating therapy. There were seven hepatitis-associated fatalities, for a rate of 0.9 per 1000 treatment starts.[80] Although concomitant data among persons initiating isoniazid were not obtained, the risk of hepatitis-associated death was ~10-fold greater than has been reported with isoniazid. A subsequent report noted a total of 50 cases of severe liver injury attributable to rifampin + pyrazinamide, including 12 deaths.[81]

Although the regimen was well tolerated in the clinical trials conducted among HIV-seropositive persons,[49,67,68] because the studies all had less than 1000 persons per arm, and given the above event rate of severe hepatotoxicity of ~1 per 1000, it is possible that such serious events were not detected because of relatively small sample size.

Special Situation

CONTACTS OF PERSONS WITH DRUG-RESISTANT TUBERCULOSIS

If persons are infected with a strain of *M. tuberculosis* that is resistant to rifampin but susceptible to isoniazid, isoniazid is effective for treatment. For persons exposed to a case of tuberculosis resistant to isoniazid, treatment with rifampin is recommended, as discussed earlier.[1] If persons with evidence of latent *M. tuberculosis* infection

have been exposed to multidrug resistant tuberculosis (MDR-TB; defined as resistance to at least isoniazid + rifampin), the optimal treatment is unknown. There have been no randomized, controlled trials performed to date to assess specific regimens, and observational data are limited.[82] In a prospective cohort study among children in South Africa who were household contacts of MDR-TB cases, preventive treatment individualized according to the drug susceptibility pattern of the source case was effective compared with no treatment (OR = 0.20; 95% CI: 0.04 to 0.94).[83] The Centers for Disease Control and Prevention recommends considering regimens that include a fluoroquinolone + pyrazinamide or ethambutol + pyrazinamide.[84] Although a 6- to 12-month treatment duration is recommended, the optimal duration is unknown; they are often poorly tolerated.[85]

FUTURE PROSPECTS FOR IMPROVEMENTS IN THE TREATMENT OF LATENT *M. TUBERCULOSIS* INFECTION

Data from the mouse model of tuberculosis have demonstrated that moxifloxacin, a newer fluoroquinolone, has excellent activity against *M. tuberculosis*. This drug may allow for shorter and more effective treatment of active tuberculosis[86,87]and may also be effective for the treatment of latent tuberculosis infection. In a murine model of latent infection, a 3-month once-weekly regimen of rifapentine plus moxifloxacin was as effective as 6 to 9 months of daily isoniazid.[88] The combination of moxifloxacin plus the experimental nitroimidazopyran PA-824 was active, as was the combination of the heat shock protein 65 DNA vaccine plus moxifloxacin.[88] With the ongoing evaluation of additional new drugs for tuberculosis (e.g., the diarylquinoline TMC-207, the nitroimidazole OPC-67683, and the diamine SQ-109), there may be additional future options for the treatment of latent tuberculosis infection.[89]

ACKNOWLEDGMENTS

Funding support: National Institutes of Allergy and Infectious Diseases K24 AI65298.

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