Published in final edited form as:

Curr HIV/AIDS Rep. 2012 September ; 9(3): 259–266. doi:10.1007/s11904-012-0120-1.

Treatment of Latent Tuberculosis Infection in HIV: Shorter or Longer?

Anna K. Person and

Division of Infectious Diseases, Vanderbilt Comprehensive Care Clinic, One Hundred Oaks, 719 Thompson Lane, Suite 37189, Nashville, TN 37204, USA

Timothy R. Sterling

Division of Infectious Diseases, A2209 Medical Center North, 1161 21st Avenue South, Nashville, TN 37232, USA

Anna K. Person: anna.k.person@Vanderbilt.Edu; Timothy R. Sterling: timothy.sterling@vanderbilt.edu

Abstract

Nine months of daily isoniazid is efficacious in treating latent *M. tuberculosis* infection, but completion rates are low, limiting treatment effectiveness. In 2011, three important studies were published involving novel regimens for the treatment of latent *M. tuberculosis* infection. At least 36 months of isoniazid was more effective than 6 months of isoniazid in one study, but not in another—both of which were conducted among tuberculin skin test positive HIV-infected adults living in high tuberculosis incidence settings. Three months of once-weekly isoniazid plus rifapentine or twice-weekly isoniazid plus rifampin (both given under direct observation) resulted in tuberculosis rates similar to those seen with 6 months of isoniazid among HIV-infected persons in high tuberculosis incidence settings. Three months of once-weekly, directly-observed isoniazid plus rifapentine was at least as effective as 9 months of daily isoniazid among predominantly HIV-uninfected persons living in low and medium tuberculosis incidence countries. The 3-month once-weekly isoniazid plus rifapentine regimen demonstrates promise for treatment of latent *M. tuberculosis* infection in HIV-infected persons.

Keywords

Latent *M. tuberculosis* infection; Treatment; HIV; Co-infections

Introduction

Persons infected with both human immunodeficiency virus (HIV) and *M. tuberculosis* develop active tuberculosis (TB) at much higher rates than HIV-uninfected persons, with an annual incidence of 8–10 % among those with untreated HIV infection [1, 2]. The World Health Organization (WHO) estimated that in 2010 approximately 13 % of tuberculosis cases worldwide occurred in HIV-infected individuals [3]. Thus, prevention of TB disease is critical. A recent Cochrane review found that treatment of latent *M. tuberculosis* infection (LTBI) in HIV-infected persons with a positive tuberculin skin test prevents tuberculosis and improves survival [4]. However, acceptance and completion of isoniazid (INH) preventive therapy is low in both HIV-uninfected and HIV-infected persons [5, 6]. The

World Health Organization (WHO) recommends screening all persons with HIV for four symptoms: current cough, fever, weight loss, and night sweats. If these symptoms are absent, INH preventive therapy is recommended even in the absence of skin testing [7]. Challenges to this strategy include the lack of proven effectiveness of INH in tuberculin skin test negative persons. Further, it is critically important to identify other safe, efficacious treatment regimens that have high completion rates and therefore high effectiveness.

The standard recommended treatment for LTBI is 9 months of daily INH. Completion rates of INH are lower than with shorter regimens [5, 6, 8–10]. Given this, several recent studies have examined possible alternative regimens for the treatment of LTBI, evaluating the optimal duration of therapy, tolerability, efficacy, durability of protective effect, and cost. Here we review the literature from the past year (2011) on treatment of *M. tuberculosis* in HIV-infected persons.

Recent Studies of Latent *M. tuberculosis* Treatment

In 2011, three important studies of regimens to treat LTBI were published. All three studies included HIV-infected adults, and are included in this review. Another study assessed a strategy of prolonged isoniazid therapy among HIV-infected and HIV-uninfected but exposed infants [11]. That study is not included in this review because it evaluated a general strategy rather than a regimen directed against LTBI. The characteristics of all four studies are described in Table 1.

Six vs. 36 Months of INH, Botswana

Because of concerns that the protective effect of a 6-month course of INH may wane after treatment completion in areas of high tuberculosis prevalence (and possible *M. tuberculosis* re-infection) [12, 13], a study of 6 versus 36 months of INH was conducted among HIV-infected adults in Botswana [14••].

This randomized, placebo-controlled, double-blind trial enrolled 1995 HIV-infected adults from 2004 to 2009; persons were eligible for inclusion regardless of tuberculin skin test status. Participants were enrolled into one of two groups: 1) the continued treatment group, which consisted of open-label INH for 6 months, followed by 30 additional months of INH, or 2) the control group, which consisted of 6 months of INH followed by 30 months of placebo. TB incidence was 0.72 % per year in the group randomized to 36 months of INH vs 1.26 % per year in persons receiving 6 months of INH (HR 0.57, 95 % CI 0.33–0.99, *P*0.047). Approximately 1 year after study enrollment, TB incidence increased in the control group compared to persons who continued to receive INH. The protective effect of continued INH was greatest among persons with a positive tuberculin skin test; the TB incidence was 1.6 % in the 36INH group vs. 6.0 % in the 6INH group, demonstrating a 74 % reduction in TB incidence. There was no significant protective effect of 36 months of INH among tuberculin skin test-negative persons. Notably, among tuberculin skin test positive persons there was a three-fold lower mortality risk for those who received 36INH compared to 6INH, and additional protective benefit with antiretroviral therapy, as described in detail below.

Three Alternative Regimens Compared Against 6 Months of INH, South Africa

This open-label trial was conducted from 2002 to 2009 in Soweto, South Africa and evaluated four regimens in a population of HIV-infected adults with positive tuberculin skin tests [15••].

Participants were randomized to one of 4 groups: 1) rifapentine 900 mg plus isoniazid 900 mg once weekly for 12 weeks, 2) rifampin (RIF) 600 mg plus isoniazid 900 mg twice

weekly for 12 weeks, 3) isoniazid 300 mg daily for the duration of the study (6 years, continuous INH), or 4) isoniazid 300 mg daily for 6 months (6INH; control group). Those in the rifapentine/INH group and rifampin/INH group received directly-observed therapy (DOT) in the clinic; the INH-only groups did not. Of note, this trial was designed to assess the potential superiority of the three investigational regimens compared to the control regimen (6INH).

Incidence rates of TB per 100 person-years were 2.0 in the rifapentine/INH group, 2.0 in the RIF/INH group, 1.4 in the continuous INH group, and 1.9 in the 6INH group; none of these rates were statistically significantly different, and none were superior to 6INH. In a post-hoc as-treated analysis there was a 58 % lower risk of TB or death in the continuous INH group compared to the group that received 6 months of INH, but the tuberculosis risk increased markedly after discontinuation of continuous INH. There was a trend towards more adverse events in the continuous INH group when compared with the two rifamycin-containing regimens, and adherence rates were higher for those taking the 12-week regimens. Among those who developed TB, there were 2 cases of rifampin resistance in the rifapentine/INH arm, none in the RIF/INH arm, and one in the continuous INH arm.

Three Months of Once-Weekly Rifapentine and INH Versus 9 Months INH, U.S, Canada, Brazil, and Spain

In this prospective non-inferiority trial, participants were randomized to open-label, directly-observed, once-weekly rifapentine 900 mg plus INH (max dose 900 mg) for 12 weeks (combination-therapy group) vs. self-administered INH 300 mg daily for 9 months (control group) [16••]. Subjects were at high risk for TB; individuals had to have been a close contact to a case of TB and have a positive tuberculin skin test, have HIV infection and a positive tuberculin skin test or close contact, have conversion of tuberculin skin test from negative to positive, or chest radiograph changes consistent with previous TB disease. The study took place from 2001 to 2010. Overall, a small proportion of the study population was HIV-infected; 100 (2.7 %) in the INH group and 105 (2.6 %) in the combination therapy group. Three months of once-weekly rifapentine plus INH was at least as effective as 9 months of INH, with TB rates in the former group half that of the 9INH group. Completion rates were 82 % in the combination therapy group and 69 % in the 9INH group ($P<0.001$). Enrollment was extended among HIV-infected persons to obtain additional tolerability and effectiveness data in this population; results are pending.

Taken together, the information provided in these three studies is important, but must be placed in the context of several other issues. We discuss these issues below.

Role of Antiretroviral Therapy

It has previously been shown that antiretroviral therapy decreases the incidence of tuberculosis among HIV-infected persons in countries with high or low TB incidence [17–19]; in a meta-analysis antiretroviral therapy reduced TB incidence by 67 % [20]. This finding is further supported by the studies discussed above. Notably, in the Botswana trial, only 2 % of participants were on antiretroviral therapy at enrollment and 45 % started antiretroviral therapy during the course of the study [14••]. Persons receiving antiretroviral therapy had a lower risk of TB; for those with a positive tuberculin skin test, the greatest protective effect was seen among those who received both antiretroviral therapy and continuous INH. Interestingly, persons with negative tuberculin skin tests had lower TB risk with antiretroviral therapy, but not with continuous INH [14••]. This reduction in TB disease with antiretroviral therapy regardless of tuberculin skin test result may be due to an improved ability to control LTBI, including after recent TB exposure [21]. Antiretroviral therapy is also associated with lower TB recurrence rates, and decreased mortality [21].

For the benefits of antiretroviral therapy on TB incidence to fully be realized, further scale-up of ART is needed, but limitations on resources will no doubt diminish the feasibility of widespread test-and-treat initiatives. There are ongoing trials investigating the use of INH preventive therapy given in conjunction with antiretroviral therapy or of INH preventive therapy given prior to starting antiretroviral therapy [22, 23]. Regardless, it is clear that neither antiretroviral therapy nor INH preventive therapy alone is sufficient; best results for reduction in TB incidence has been shown when the two are implemented in concert [24, 25].

Safety and Tolerability

Given that persons with LTBI are not sick or able to transmit disease, it is paramount that treatment regimens have minimal adverse events. This is particularly important in HIV-infected persons, who may receive several concomitant medications, and therefore be subject to drug-drug interactions and pharmacokinetic variability.

Six months of INH preventive therapy appears to be largely safe in HIV-infected persons. In the trial comparing 36 vs. 6 months of INH, overall rates of adverse events and death were similar in both groups. However, for the sub-population of those with negative tuberculin skin tests who received 36 months of INH, there were significantly more deaths—though most of these deaths were not related to INH [14••]. In the South African trial, in those who were tuberculin skin test positive and received continuous INH, adverse events were more common compared to the other, shorter regimens, with 28 % of persons in the continuous INH group experiencing grade 3 or 4 elevations in liver enzymes during the treatment phase, compared to 5.5 % in the 6INH arm [15••].

Rifamycin-containing regimens must also be critically evaluated in terms of safety. For HIV-infected individuals, however, potential drug-drug interactions between antiretroviral therapy and rifampin or rifapentine must be a consideration. In South Africa, serious adverse events occurred at 8.7 per 100 person-years in the rifapentine/INH group, 10.6 per 100 person-years in the rifampin/INH group, versus 15.4 and 18.4 per 100 person-years in the 6 months of INH group and continuous INH groups, respectively [15••].

When weekly rifapentine/INH for 12 weeks was compared with daily INH for 9 months among a largely HIV-uninfected population, however, safety results were somewhat mixed. There was greater hepatotoxicity in the INH group, but higher rates of permanent drug discontinuation due to an adverse event in the rifapentine/INH group (4.9 % vs. 3.7 %). This was thought to be due in part to a possible hypersensitivity reaction; however, a potential confounder could have been the more frequent interaction of participants with study staff in this arm, given that this arm was administered via directly-observed therapy [16••].

Hypersensitivity reactions had not been previously reported with rifapentine/INH regimen. Of note, this study had very few HIV-infected individuals and further data regarding safety in the HIV-infected participants are forthcoming.

Role of Tuberculin Skin Test

The benefit (or lack thereof) of LTBI treatment according to tuberculin skin test result has been investigated previously. In the United States, HIV-infected individuals with anergy did not benefit from treatment of LTBI [26•]. In a recent systematic review of several different preventive regimens in HIV-infected individuals, there was a 62 % reduction in the risk of active TB for those who were skin test positive but no benefit for those who were skin test negative [4]. The lack of benefit of INH preventive therapy in tuberculin skin test-negative individuals seen in the Botswana trial (and the *possible* trend toward increased mortality for those who received continuous INH and were skin test negative), leads some to suggest that

the 2011 WHO recommendation for INH preventive therapy regardless of skin test result should be reevaluated [27].

Duration of Protective Effect and Possible Reinfection

For those without HIV infection, INH provides protection against active TB for up to 19 years [28]. However, the duration of protective effect of any regimen depends on host factors (e.g., immune status), and on the prevalence of TB in the region. In high incidence settings, increased rates of TB seen following treatment of LTBI may be due to either reinfection or to activation of partially treated *M. tuberculosis*. However, few trials have assessed duration of protective effect, and the data are limited by duration of follow-up for these studies [4]. One study suggested that for HIV-infected individuals with positive skin tests in Uganda the duration of protective effect was for only 1 year after receiving 6 months of INH. The protective effect was approximately 3 years for a 3-month regimen of INH, rifampicin, and pyrazinamide, or 3 months of INH and rifampicin [13]. In Zambia, the protective effect of two different regimens (6 months of INH or 3 months of rifampicin plus pyrazinamide) in HIV-infected adults was approximately 2.5 years [12]. In another Zambian study of 6 months of INH versus 3 months of rifampicin plus pyrazinamide (both taken twice weekly), both arms had rates of TB similar to those in the placebo group at 18 months [29].

In the 2011 trial in Botswana, increasing rates of TB were observed at just over 6 months after completion of 6INH when compared to 36 H [14•]. However, in South Africa, rates of TB increased after discontinuation of continuous INH as well (6 years) [15•]. When 3 months of rifapentine/INH were compared to 9INH, almost all cases of TB in the rifapentine/INH arm occurred during the first 500 days; only one case occurred in the second 500 days of follow-up. In the 9INH arm of this study, TB cases occurred throughout the follow-up period [30]. There has not yet been a comparison of the duration of protection of 3 months of rifapentine/INH versus 36 H. Rifapentine-containing regimens may have greater sterilizing activity than regimens containing isoniazid alone, which could influence duration of protection.

Drug Resistance

One key potential concern is drug resistance among those who develop active TB after completing preventive therapy. In the Botswana trial of 6INH versus 36INH, 5 of the 29 cases of TB for which drug susceptibility testing was available were INH resistant; this was not thought to differ from expected rates of drug resistance in the region [14•]. In the South African study of rifapentine/INH or rifampin/INH (both for 12 weeks) versus INH-only containing regimens, there was one case of INH-resistant TB, 2 cases of rifampin-resistant TB, and one case resistant to both INH and rifampin in the rifapentine/INH group. Again, the overall rate of drug-resistant TB in this study was comparable to that found elsewhere in the area [15•]. Though there were few HIV-infected individuals in the trial comparing weekly rifapentine plus INH versus 9 months of INH, one case of rifampin-resistant TB occurred and it was in a HIV-infected person randomized to the rifapentine plus INH arm [16•]. This was a case of *M. bovis*, resistant to pyrazinamide (which is characteristic of *M. bovis*) as well as rifampin.

So what can be made of the resistance data from these trials? Other studies suggest that those who develop TB after INH preventive therapy do not appear to have an increased risk of resistance to INH [31]. In a systematic review of those receiving INH preventive therapy who subsequently developed TB, the relative risk of INH resistance was 1.45 (95 % CI 0.85–2.47), with similar results for both HIV-infected and HIV-uninfected individuals [32]. However, for those on rifamycin-containing preventive regimens, there may be more reason

to give pause—particularly if the patient did not have latent infection but instead had active disease that was not suspected or detected. This is possible given the frequent occurrence of asymptomatic or subclinical tuberculosis in HIV-infected persons [33]. In a study of weekly INH/rifapentine (600 mg dose) for the continuation phase of active TB treatment, among HIV-infected individuals there were more relapses of TB disease when compared with those who received twice-weekly INH and rifampin in the continuation phase. Of those who relapsed in the weekly INH/rifapentine group, 4 of 5 had rifamycin resistance [34]. The risk of rifamycin-resistance developing in INH/rifapentine preventive regimens may be due to a “pharmacokinetic mismatch.” In a pharmacokinetic study of weekly rifapentine in patients with TB, 54 % of patients had detectable rifapentine levels 36 h after clearance of INH, when both drugs were given at the same time [35].

Because of the overall low burden of organisms in LTBI, the risk of selecting for drug-resistance is likely low. However, the critical factor is ruling out active disease before starting preventive therapy. If active TB disease is missed and preventive therapy is initiated, the higher burden of organisms will increase the likelihood of selecting for drug-resistance. The WHO system for symptom-based screening (ruling out cough, fever, weight loss, and night sweats) had a negative predictive value of 97.7 % for active TB in settings where TB prevalence among HIV-infected individuals was at least 5 % [36], and should aid clinicians in assessing for active disease prior to starting preventive therapy. As rifamycin-containing short-course preventive regimens are embraced, prevention of drug-resistance will hinge on ruling out active disease.

What These Studies Add

In considering the issues above, the three studies published in 2011 of different regimens for the treatment of LTBI demonstrate a few key points. Thirty-six months of INH was more effective than 6 months of INH only among HIV-infected persons with positive tuberculin skin tests [14•]; it was not more effective in tuberculin skin test-negative individuals. However, in a second study, continuous INH for up to 6 years was not significantly more effective than 6 months of INH [15•]. Prolonged INH provided perhaps greater durability of protective effect than 6INH [14•, 15•], but protection waned when INH was discontinued [15•]. A 12-week course of directly-observed rifapentine plus INH had higher adherence rates and similar TB incidence rates when compared with 6 months of INH in HIV-infected persons [15•], and when compared with 9 months of INH in mostly HIV-uninfected persons [16•]. In the study of once-weekly rifapentine and INH vs. 9INH, there were more permanent discontinuations in the combination therapy group [16•], but there was no significant difference in adverse events seen with this regimen compared to 6 months of INH [15•]. However, safety will have to be closely monitored as this regimen is given to a broader population. The effectiveness and tolerability of this regimen will also need to be evaluated more closely in HIV-infected persons. One advantage of the once or twice-weekly rifamycin-based regimens is higher completion rates; a disadvantage is the requirement of directly-observed therapy. The Centers for Disease Control (CDC) has now recommended the use of once-weekly rifapentine and INH for 12 weeks for the treatment of LTBI as an alternative to 9INH in the United States [37]. However, this regimen is not recommended for HIV-infected persons receiving antiretroviral therapy, due to concerns regarding drug interactions with rifapentine [38].

Unresolved Issues

Many questions remain about the preventive therapy regimens discussed here. Additional data are needed on the ability to implement the once-weekly rifapentine/INH regimen. While this regimen was given via directly-observed therapy, it will be important to assess in

clinical trials whether it can be given as self-administered therapy. Though convenience would be increased via self-administration, this may lead to lower treatment completion rates and therefore lower effectiveness. Finally, there are numerous studies on cost-effectiveness of various LTBI regimens [39, 40]. None of these cost-effectiveness analyses, however, have focused specifically on *M. tuberculosis* preventive regimens for HIV-infected individuals, and information on this unique patient population is needed.

Conclusions

Three studies in 2011 examined regimens for the treatment of latent tuberculosis infection in HIV-infected adults. Shorter, rifamycin-based regimens given under direct observation have the advantage of greater adherence. Longer regimens of INH may decrease the risk of subsequent TB that has been seen with just 6 months of INH, but the benefit wanes shortly after INH is discontinued. When deciding on the optimal regimen, however, efficacy and safety are paramount. The role of tuberculin skin testing, the contribution of antiretroviral therapy, the emergence of resistance, and cost-effectiveness data will all be important when identifying the optimal regimen for HIV-infected individuals. While the regimens highlighted in 2011 hold promise, further evaluation is needed as they are used for the treatment of HIV-infected persons with latent *M. tuberculosis* infection.

Acknowledgments

Funding support: NIAID K24 AI 65298 (TRS).

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

- 1•. Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE, Vermund SH, Klein RS, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med*. 1989; 320(9):545–50. Often-cited paper on the high annual risk of progression to active tuberculosis among HIV-infected persons with *M. tuberculosis* infection who do not receive treatment for either infection. [PubMed: 2915665]
2. Wood R, Maartens G, Lombard CJ. Risk factors for developing tuberculosis in HIV-1-infected adults from communities with a low or very high incidence of tuberculosis. *J Acquir Immune Defic Syndr*. 2000; 23(1):75–80. [PubMed: 10708059]
3. WHO Report 2011. Geneva, Switzerland: 2011 Nov 7. Global Tuberculosis Control 2011; p. 1-258. Available from: http://www.who.int/tb/publications/global_report/en/
4. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev*. 2010; 1:CD000171. [PubMed: 20091503]
5. Diaz A, Diez M, Bleda MJ, Aldamiz M, Camafort M, Camino X, et al. Eligibility for and outcome of treatment of latent tuberculosis infection in a cohort of HIV-infected people in Spain. *BMC Infect Dis*. 2010; 10:267. [PubMed: 20840743]
6. Horsburgh CR, Goldberg S, Bethel J, Chen S, Colson PW, Hirsch-Moverman Y, et al. Latent TB infection treatment acceptance and completion in the United States and Canada. *Chest*. 2010; 137(2):401–9. [PubMed: 19793865]
7. Guidelines for intensified tuberculosis case finding and isoniazid preventive therapy for people living with HIV in resource constrained settings. Geneva, Switzerland: WHO; 2011.
8. Menzies D, Dion M-J, Rabinovitch B, Mannix S, Brassard P, Schwartzman K. Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months. *Am J Respir Crit Care Med*. 2004; 170(4):445–9. [PubMed: 15172892]

9. Lardizabal A, Passannante M, Kojakali F, Hayden C, Reichman LB. Enhancement of treatment completion for latent tuberculosis infection with 4 months of rifampin. *Chest*. 2006; 130 (6):1712–7. [PubMed: 17166986]
10. Page KR, Sifakis F, Montes de Oca R, Cronin WA, Doherty MC, Federline L, et al. Improved adherence and less toxicity with rifampin vs isoniazid for treatment of latent tuberculosis: a retrospective study. *Arch Intern Med*. 2006; 166(17):1863–70. [PubMed: 17000943]
11. Madhi SA, Nachman S, Violari A, Kim S, Cotton MF, Bobat R, et al. Primary isoniazid prophylaxis against tuberculosis in HIV-exposed children. *N Engl J Med*. 2011; 365(1):21–31. [PubMed: 21732834]
12. Quigley MA, Mwinga A, Hosp M, Lisse I, Fuchs D, Porter JDH, et al. Long-term effect of preventive therapy for tuberculosis in a cohort of HIV-infected Zambian adults. *AIDS*. 2001; 15 (2):215–22. [PubMed: 11216930]
13. Johnson JL, Okwera A, Hom DL, Mayanja H, Mutuluza Kityo C, Nsubuga P, et al. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. *AIDS*. 2001; 15 (16): 2137–47. [PubMed: 11684933]
- 14•. Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Shang N, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011; 377(9777):1588–98. A study of the effect of prolonged isoniazid treatment among HIV-infected persons in a high tuberculosis incidence area (Botswana), where the risk of *M. tuberculosis* re-infection is high. Also assessed tuberculosis risk according to tuberculin skin test status and receipt of antiretroviral therapy. [PubMed: 21492926]
- 15•. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*. 2011; 365(1):11–20. Conducted among HIV-infected persons in South Africa, this study demonstrated no significant difference in the protective effect of four regimens: 3 months of once-weekly isoniazid +rifapentine (directly-observed), 3 months of twice-weekly isoniazid+rifampin (directly-observed), 6 months of daily isoniazid (self-administered), and up to 6 years of daily isoniazid (self-administered). The continuous isoniazid regimen was poorly tolerated. [PubMed: 21732833]
- 16•. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011; 365(23):2155–66. Although most of the study population was HIV-uninfected, this study conducted in low and medium tuberculosis incidence countries demonstrated that 3 months of once-weekly isoniazid+rifapentine (directly-observed) was at least as effective as 9 months of daily isoniazid (self-administered). The tolerability of both regimens was similar. [PubMed: 22150035]
17. Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet*. 2002; 359(9323):2059–64. [PubMed: 12086758]
18. Santoro-Lopes G, de Pinho AMF, Harrison LH, Schechter M. Reduced risk of tuberculosis among Brazilian patients with advanced human immunodeficiency virus infection treated with highly active antiretroviral therapy. *Clin Infect Dis*. 2002; 34 (4):543–6. [PubMed: 11797184]
19. Jones JL, Hanson DL, Dworkin MS, DeCock KM. Adult/Adolescent Spectrum of HIV Disease Group. HIV-associated tuberculosis in the era of highly active antiretroviral therapy. The Adult/Adolescent Spectrum of HIV Disease Group. *Int J Tuberc Lung Dis*. 2000; 4(11):1026–31. [PubMed: 11092714]
20. Lawn SD, Wood R, De Cock KM, Kranzer K, Lewis JJ, Churchyard GJ. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. *Lancet Infect Dis*. 2010; 10(7):489–98. [PubMed: 20610331]
21. Lawn SD, Harries AD, Williams BG, Chaisson RE, Losina E, De Cock KM, et al. Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? *Int J Tuberc Lung Dis*. 2011; 15(5):571–81. [PubMed: 21756508]
22. www.clinicaltrials.gov [Internet]. [cited 2012 Mar. 29]. Available from: <http://clinicaltrials.gov/ct2/show/NCT00463086?term0Isoniazid+Plus+%28Highly+Active>

+Antiretroviral+Therapy%29+HAART+to+Prevent+Tuberculosis+%28TB%29+in+HIV-infected+Persons+%28HAART-IPT%29&rank01

23. www.clinicaltrials.gov [Internet]. [cited 2012 Mar. 29]. Available from: <http://clinicaltrials.gov/ct2/results?term0Early+Antiretroviral+Treatment+and%2For+Early+Isoniazid+Prophylaxis+Against+Tuberculosis+in+HIV-infected+Adults+>
24. Golub JE, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, King BS, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS*. 2007; 21 (11):1441–8. [PubMed: 17589190]
25. Golub JE, Pronyk P, Mohapi L, Thsabangu N, Moshabela M, Struthers H, et al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. *AIDS*. 2009; 23(5):631–6. [PubMed: 19525621]
26. Gordin FM, Matts JP, Miller C, Brown LS, Hafner R, John SL, et al. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. Terry Beinr Community Programs for Clinical Research on AIDS. *N Engl J Med*. 1997; 337(5):315–20. As has been subsequently demonstrated in other studies, there was no significant decrease in tuberculosis risk among anergic HIV-infected persons who received isoniazid preventive therapy. [PubMed: 9233868]
27. Dodd LE, Wilkinson RJ. Isoniazid preventive therapy in HIV infection. *Lancet*. 2011; 377(9777):1548–50. [PubMed: 21492928]
28. Comstock GW, Baum C, Snider DE. Isoniazid prophylaxis among Alaskan Eskimos: a final report of the betel isoniazid studies. *Am Rev Respir Dis*. 1979; 119(5):827–30. [PubMed: 453704]
29. Mwinga A, Hosp M, Godfrey-Faussett P, Quigley M, Mwaba P, Mugala BN, et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. *AIDS*. 1998; 12(18):2447–57. [PubMed: 9875583]
30. sterlit. Supplementary Appendix. *New England Journal of Medicine* [Internet]. 2011 Dec 8; 365(23):1–23. Available from: <http://nejm.org>.
31. van Halsema CL, Fielding KL, Chihota VN, Russell EC, Lewis JJC, Churchyard GJ, et al. Tuberculosis outcomes and drug susceptibility in individuals exposed to isoniazid preventive therapy in a high HIV prevalence setting. *AIDS*. 2010; 24(7):1051–5. [PubMed: 20299958]
32. Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. *Emerg Infect Dis*. 2006; 12(5):744–51. [PubMed: 16704830]
33. Mtei L, Matee M, Herfort O, Bakari M, Horsburgh CR, Waddell R, et al. High rates of clinical and subclinical tuberculosis among HIV-infected ambulatory subjects in Tanzania. *Clin Infect Dis*. 2005; 40(10):1500–7. [PubMed: 15844073]
34. Vernon A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. *Tuberc Trials Consortium Lancet*. 1999; 353(9167):1843–7.
35. Weiner M, Bock N, Peloquin CA, Burman WJ, Khan A, Vernon A, et al. Pharmacokinetics of rifapentine at 600, 900, and 1,200 mg during once-weekly tuberculosis therapy. *Am J Respir Crit Care Med*. 2004; 169(11):1191–7. [PubMed: 14962821]
36. Getahun H, Kittikraisak W, Heilig CM, Corbett EL, Ayles H, Cain KP, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLoS Med*. 2011; 8(1):e1000391. [PubMed: 21267059]
37. Centers for Disease Control and Prevention: CDC. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent mycobacterium tuberculosis infection. *MMWR Morb Mortal Wkly Rep*. 2011; 60:1650–3. [PubMed: 22157884]
38. [Accessed March 26, 2012.] Short-Course (3-Month) Therapy with Weekly Isoniazid-Rifapentine Is NOT RECOMMENDED for HIV-Infected Patients Receiving Antiretroviral Therapy. Dec 20. 2011 <http://aidsinfo.nih.gov/Guidelines/Default.aspx>
39. Ziakas PD, Mylonakis E. 4 months of rifampin compared with 9 months of isoniazid for the management of latent tuberculosis infection: a meta-analysis and cost-effectiveness study that focuses on compliance and liver toxicity. *Clin Infect Dis*. 2009; 49(12):1883–9. [PubMed: 19911936]

40. Holland DP, Sanders GD, Hamilton CD, Stout JE. Costs and cost-effectiveness of four treatment regimens for latent tuberculosis infection. *Am J Respir Crit Care Med*. 2009; 179(11):1055–60. [PubMed: 19299495]

Table 1

Recent studies of regimens for the treatment of latent tuberculosis infections

Citation	Regimen	Study population	Findings
Sterling et al. [16••]	3 months RPT-INH DOT weekly vs 9 months daily INH	<ul style="list-style-type: none"> Mainly HIV-negative individuals in the US, Canada, Brazil, and Spain There were 3,986 in RPT- INH group and 3,745 in INH group 105 HIV-infected persons in RPT-INH group, and 100 in the INH group. Follow-up was 33 months 	<ul style="list-style-type: none"> Open label, RCT, noninferiority trial RPT-INH was as effective as INH with better completion rates There were higher rates of drug discontinuation due to an adverse event in RPT-INHT group vs INH
Martinson et al. [15••]	Randomized to one of 4 groups: <ol style="list-style-type: none"> 1 RPT (900 mg) plus INH (900 mg) weekly for 12 weeks 2 RIF (600 mg) plus INH (900 mg) twice weekly for 12 weeks 3 INH (300 mg) daily for up to 6 years (continuous INH) 4 INH (300 mg) daily for 6 months (control group) 	<ul style="list-style-type: none"> Adults in South Africa with HIV infection (not on ART) with a positive TST 1,148 patients randomized Trial was designed to demonstrate superiority of the 3 regimens over 6 months of INH 	<ul style="list-style-type: none"> Incidence rates of TB or death were 3.1 per 100 person-years in the RPT-INH group, 2.9 per 100 person-years in the RIF-INH group, and 2.7 per 100 person- years in the continuous-INH group, as compared with 3.6 per 100 person-years in the control group The continuous INH group had the most adverse events Regimen 1 and 2 had higher adherence rates There were 2 cases of RIF- resistant TB that developed in the RPT-INH group
Samandari et al. [14••]	Randomized to: <ol style="list-style-type: none"> 1 6 months open-label INH followed by 30 months masked placebo (control group) or 2 6 months open-label INH followed by 30 months masked INH (continued INH group) 	<ul style="list-style-type: none"> HIV-infected adults in Botswana No prior tuberculin skin testing done On ART only if CD4 <200 989 patients in control group 1,006 in continuous INH group 	<ul style="list-style-type: none"> RCT, double-blind, placebo-controlled trial TB incidence of 1.26 % per year vs. 0.72 % for control vs. continuous INH group (HR 0.57, 95 % CI 0.33–0.99) Those who had positive TST had greater benefit from INH than those who were TST negative 36 months more effective than 6 months in this setting, especially for those with positive TST Adverse events were similar in both groups
Madhi et al. [11]	Randomized to: <ol style="list-style-type: none"> 1 INH daily x 96 weeks 2 Placebo x 96 weeks 	<ul style="list-style-type: none"> 548 HIV-infected and 804 HIV-uninfected infants (exposed to HIV during perinatal period) Ages ranged from 91 to 120 days All infants received BCG vaccine within 30 days of birth 	<ul style="list-style-type: none"> RCT, double-blind, placebo-controlled trial No difference in deaths or TB disease in HIV-infected infants between INH and placebo groups No difference in deaths, TB disease, TB infection in HIV- uninfected infants between INH and placebo groups

ART, antiretroviral therapy; BCG, bacille Calmette–Guérin; DOT, directly-observed therapy; INH, isoniazid; RCT, randomized controlled trial; RIF, rifampin; RPT, rifapentine; TST, tuberculin skin test