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RESPIRATORY INFECTIONS (CL DALEY, SECTION EDITOR)

Diagnosis and treatment of latent tuberculosis infection: an update

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Abstract It is estimated that more than two billion people have latent *M. tuberculosis* infection, and this population serves as an important reservoir for future tuberculosis cases. Prevalence estimates are limited by difficulties in diagnosing the infection, including the lack of an ideal test, and an incomplete understanding of latency. Current tests include the tuberculin skin test and two interferon-γ release assays: QuantiFERON Gold In-Tube and T-SPOT.TB. This update focuses on recent publications regarding the ability of these tests to predict tuberculosis disease, their reproducibility over serial tests, and discordance between tests. We also discuss recent advances in the treatment of latent *M. tuberculosis* infection, including the three-month regimen of once-weekly rifapentine plus isoniazid, and prolonged isoniazid therapy for HIV-infected persons living in high-tuberculosis-incidence settings. We provide an update on the tolerability of the three-month regimen.

Keywords Latent tuberculosis infection · Tuberculin skin test · Interferon gamma release assay · QuantiFERON-TB gold in tube assay · T-SPOT. TB assay

Abbreviations

TST	Tuberculin skin test
QFT-GIT	QuantiFERON TB Gold In-Tube test
Mm	Millimeters
BCG	Bacillus Calmette–Guerin
HCW	Healthcare worker
IGRA	Interferon-γ release assay
PPV	Positive predictive value
NPV	Negative predictive value
IRR	Incidence rate ratio

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Introduction

Persons infected with *Mycobacterium tuberculosis* have immune responses to *M. tuberculosis* antigens, but no signs or symptoms of disease. However, there is much debate regarding the actual state of latency, and the degree of metabolic activity associated with this disease state. There is probably a continuum between latent (or dormant) *M. tuberculosis* infection and active tuberculosis, rather than two distinct disease states. This is best illustrated by HIV-infected persons, who can undergo a relatively rapid transition between latent infection, sub-clinical tuberculosis, and active (symptomatic) tuberculosis disease [1].

It is estimated that at least two billion people in the world have latent *M. tuberculosis* infection [2]; approximately 10 million persons in the United States are infected [3]. However, such estimates are approximate, in large part because of difficulties in diagnosing latent infection. There is no ideal test for detecting *M. tuberculosis* infection. Current tests assess the host immune response to *M. tuberculosis*, but do not detect the infection itself. Previously, only the tuberculin skin test (TST) was available for diagnosis of latent tuberculosis infection; the introduction of the interferon-γ release assay (IGRA) was an advance in diagnostic technology. Recent research has improved our understanding of the ability of IGRA results to predict tuberculosis disease

and also addressed several shortcomings of these assays, including reproducibility over serial testing and discordance between tests.

The large number of persons with latent *M. tuberculosis* infection is an important reservoir of future tuberculosis cases. Treatment of latent tuberculosis infection is very effective in preventing progression to active disease, thereby reducing the tuberculosis burden [4]. As with the diagnosis of latent infection, there have been recent advances in the treatment of *M. tuberculosis* infection. Short-course alternatives to the standard nine-month course of isoniazid are now available. However, questions remain regarding the tolerability of regimens, including three months of isoniazid and rifapentine (3HP). In this review we emphasize data published since late 2011 on the diagnosis and treatment of latent tuberculosis infection. Recent studies of the diagnosis of latent *M. tuberculosis* infection are listed in Table 1.

Diagnosis of latent *M. tuberculosis* infection

Available tests

There are currently three commercially available tests to diagnose latent *M. tuberculosis* infection: the tuberculin skin test, the QuantiFERON-TB Gold In-Tube assay, and the T-SPOT.TB test. Each has advantages and disadvantages, as discussed below.

The oldest method of diagnosis, the tuberculin skin test (TST), has been in use for over 100 years. The TST requires intradermal injection of purified protein derivative: a mixture of approximately 200 mycobacterial antigens, including antigens from *M. tuberculosis* and other mycobacterial species. For persons with *M. tuberculosis* infection, a delayed-type hypersensitivity reaction results in induration at the site of the injection. The American Thoracic Society and Centers for Disease Control and Prevention have established criteria for the number of millimeters of induration required for a positive test [5]. These criteria vary according to the risk of acquiring infection (e.g. close contacts of an infectious case vs. persons without recent exposure). The advantages of this test include low cost, and extensive experience with its use. The latter has resulted in established cut-offs for a positive test on the basis of risk of subsequent active disease, evidence for the benefit of treating persons with a positive test, and evidence regarding the risk of active disease after conversion from negative to positive [5]. The disadvantages of this test include the need for two visits (to place the TST, and to read it 48–72 hours later), inter-reader variability in measuring millimeters of induration, diminished response caused by immunosuppression, boosting on repeat testing, and potential cross-reaction with nontuberculous mycobacteria and *M. bovis* Bacillus Calmette–Guerin (BCG) vaccine [6].

There are two sources of purified protein derivative for the TST in the United States: Aplisol (JHP Pharmaceuticals, LLC) and Tubersol (Sanofi Pasteur Limited); each has a slightly different composition, but both are injected in a standard five-tuberculin unit dose [7]. Although both Aplisol and Tubersol have been associated with false-positive tests, a randomized, controlled, double-blinded trial comparing both tests on 1555 persons at low risk for tuberculosis reported comparable specificity [8]. However, observational data have suggested that switching from Tubersol to Aplisol may result in a greater proportion of positive tests [9–12].

In April 2013, the Centers for Disease Control and Prevention (CDC) were notified of a shortage of Tubersol, and a subsequent reliance on (and relative shortage of) Aplisol [13]. This led some institutions to temporarily suspend tuberculin skin testing of their employees. CDC provided guidance on addressing the shortage, recommending substitution of IGRAs for TST, using TSTs only for public health priorities including tuberculosis contact investigations, and substituting Aplisol for Tubersol [13]. In the absence of a shortage, however, recommendations for tuberculosis screening programs are to use one antigen consistently and to recognize the possible difficulties in interpreting serial testing when switching from one product to another [14].

IGRAs measure interferon-γ or interferon-γ-producing cells, which respond to synthetic peptides present in *M. tuberculosis* but not in most nontuberculous mycobacterial species, particularly *M. bovis* BCG. These peptides include ESAT-6 (early secretory antigen-6), CFP-10 (culture filtrate protein-10), and TB7.7. Two IGRAs are commercially available: the QuantiFERON-TB Gold In-Tube assay (Cellestis Ltd, Carnegie, Australia) and the T-SPOT.TB assay (Oxford Immunotec, Abingdon, UK). QuantiFERON-TB Gold In-Tube uses an enzyme-linked immunosorbent assay (ELISA) to quantify interferon-γ responses to the above peptides [15]. The T-SPOT.TB test incubates peripheral blood mononuclear cells with the above peptides, and then measures interferon-γ-producing T-cells via an enzyme-linked immunospot assay technique (ELISPOT) [16].

Ability to predict progression to TB disease

Despite their benefits, including the convenience of a one-time visit, if IGRAs are to supplant more than 100 years of experience with the TST it is important to understand their ability to predict progression to subsequent tuberculosis disease. Since the first appearance of IGRAs in 2001, there have been several studies published on the relative ability of IGRAs and the TST to predict disease progression; here we review the recently published data.

A recent meta-analysis [17••] included 28 studies with data on positive and/or negative predictive value for predicting progression to tuberculosis disease; 23 included data on

Table 1 Recent studies of the diagnosis of latent *M. tuberculosis* infection

Ref.	Diagnostic test	Study population	Findings
Gran G, Aßmus J, Dyrhol-Riise AM. Screening for latent tuberculosis in Norwegian health care workers: high frequency of discordant tuberculin skin test positive and interferon-gamma release assay negative results. BMC Public Health 2013;13(1):353	TST and the QuantiFERON TB Gold In-Tube test	387 healthcare workers with possible exposure to TB in Norway History of BCG vaccination reported for 97.9 %	4.7 % had both positive TST and positive QFT-GIT 55.3 % had a positive TST (≥6 mm) and 13.7 % a TST ≥15 mm 3.4 % had a positive QFT-GIT In mostly BCG-vaccinated population: high incidence of discordant TST/QFT-GIT results, with most TST+/QFT-GIT−
Park JS, Lee JS, Kim MY. Monthly follow-ups of interferon-γ release assays among health-care workers in contact with patients with TB. Chest 2012 vol. 142 (6) pp. 1461-1468	QuantiFERON TB Gold In-Tube assays were performed monthly for one year	Forty-nine healthcare workers in South Korea; contacts to patients with active pulmonary TB 91.7 % had BCG scars 40 % rarely wore N95 masks	25 % had baseline positive QFT-GIT tests (>0.35 IU mL^{-1}) 52 % had conversions/reversions when single cut-point of 0.35 IU mL^{-1} used on monthly testing. 10 % had conversions or reversions to 0.7 IU mL^{-1} ≥ 2 times during one year Frequent fluctuations around the single cut-point were seen, indicating possible variability of the assay, difficulty processing of the specimens, or varying individual T-cell responses to true TB exposure
Fong KS, Tomford JW, Teixeira L, et al. Challenges of interferon-γ release assay conversions in serial testing of health-care workers in a TB control program. Chest 2012;142(1):55–62	QuantiFERON-TB Gold In-Tube	Retrospective chart review of 7,374 newly hired health care workers receiving QGT-GIT testing for screening at the Cleveland Clinic	6.6 % had positive results, 4.1 % had indeterminate results. 52 HCWs later converted with no known TB exposure (median value was 0.63 IU mL^{-1}). Of those, 10 had repeat QFT-GIT testing; eight had reversion. Single cut-point for positivity on serial testing may lead to conversions/reversions of unclear clinical significance
Diel R, Loddenkemper R, Nienhaus A. Predictive value of interferon-γ release assays and tuberculin skin testing for progression from latent TB infection to disease state: a meta-analysis. Chest 2012;142(1):63–75	TST, "in-house" IGRAs, QuantiFERON-TB Gold In-Tube, and T-SPOT.TB	Meta-analysis of 28 studies evaluating PPV or NPV for progression to active TB. No participant had received preventive therapy.	Overall PPV for progression to TB was 2.7 % for the IGRAs vs. 1.5 % for the TST (p <0.0001). When the high-risk groups were considered in a sub-analysis, the PPV was 6.8 % [95 % CI, 5.6–8.3 %] for the IGRA vs. 2.4 % [95 % CI, 1.9–2.9 %] for the TST (p <0.0001) For high-risk individuals in particular, there was a suggestion of higher PPV for the IGRAs compared with TST
Mancuso JD, Mazurek GH, Tribble D, et al. Discordance among commercially available diagnostics for latent tuberculosis infection. Am J Respir Crit Care Med 2012;185(4):427–34	QuantiFERON-TB Gold In-Tube test, T-SPOT.TB test, TST, and Battey skin test using purified protein derivative from the Battey bacillus	Cross-sectional comparison study of 2,017 low-risk military recruits in South Carolina; simultaneous testing performed (tests listed at left). 1,826 recruits completed all tests	Specificity estimates were 99.3 % for TST, 98.7 % for the T-SPOT.TB, and 98.8 % for the QFT-GIT: no statistical difference Modest agreement was seen between the T-SPOT.TB and the QFT-GIT, kappa statistic=0.39 (95 % CI, 0.24–0.54) 77 % of those with a positive result were positive on only one test
Zwerling A, van den Hof S, Scholten J, Cobelens F, Menzies D, Pai M. Interferon-gamma release assays for tuberculosis screening of	TST, "in-house" IGRAs, QuantiFERON-TB Gold In-Tube, Quantiferon Gold, and T-SPOT.TB	A systematic review of all IGRA studies in HCWs. 50 studies were included, five in high-TB-incidence areas	24 of 25 studies comparing IGRA to TST had lower prevalence of positive IGRA than positive TST, with BCG vaccination not accounting for all difference

Table 1 (continued)

Ref.	Diagnostic test	Study population	Findings
healthcare workers: a systematic review. Thorax 2012;67(1):62–70			Concordance was not strong between TST and IGRAs; k values ranged from 0.05 to 0.56
Rangaka MX, Wilkinson KA, Glynn JR, et al. Predictive value of interferon-γ release assays for incident active tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis 2012;12(1):45–55	"In-house" IGRAs, and QuantiFERON-TB Gold In-Tube, and T-SPOT.TB	A systematic review and meta-analysis assessing ability of IGRAs and TST to predict development of active TB. 15 studies with >26,000 participants, including infants/ children and those with HIV-infection or other co-morbidities. Those who had taken preventive therapy were not excluded	Unadjusted IRR for positive vs. negative IGRA was 2.11 (95 % CI, 1.29–3.46). For TST >10 mm, the unadjusted IRR was 1.60 (95 % CI, 0.94–2.72) Unadjusted IRR for the ELISPOT assays (including T-SPOT.TB) was 2.64 [95 % CI, 1.41–4.93] vs. 1.82 [95 % CI, 1.11–2.97] for whole blood ELISA assays (including QuantiFERON-TB Gold In-Tube), when compared with negative IGRA results

commercially available IGRAs (QuantiFERON-TB Gold In-Tube and T-SPOT.TB), and 18 included data on the TST. Only studies in which participants did not receive preventive treatment for tuberculosis were included. Studies from high-incidence countries (six studies), intermediate-incidence countries (12 studies), and low-incidence countries (10 studies) were included. Follow-up for progression to active tuberculosis ranged from 12–46 months. For nine studies involving direct comparison of the positive predictive value of IGRA and TST (one study was of QuantiFERON-TB Gold, the rest of QuantiFERON-TB Gold In-Tube and T-SPOT.TB test), the combined positive-predictive value of the IGRA was 2.1 % (95 % CI, 1.7–2.5 %), versus 1.4 % (95 % CI, 1.2–1.8 %) for the TST. Including all studies, the overall positive predictive value for progression to tuberculosis was 2.7 % for the IGRAs versus 1.5 % for the TST ($p < 0.0001$). When high-risk groups (per American Thoracic Society/Centers for Disease Control Criteria [5]) were considered in a sub-analysis, the positive predictive value was 6.8 % (95 % CI, 5.6–8.3 %) for the IGRA versus 2.4 % (95 % CI, 1.9–2.9 %) for the TST ($p < 0.0001$) [17••]. Although there was substantial heterogeneity in the patient populations and type of IGRAs analyzed, this meta-analysis found a greater positive predictive value for progression to tuberculosis for IGRAs than for the TST; the increase in positive predictive value for high-risk individuals supports targeted testing.

Another recent systematic review and meta-analysis also evaluated the predictive value of several IGRAs versus TST for progression to tuberculosis disease [18•]. The analysis covered fifteen studies with over 26,000 participants, including infants and/or children and those with HIV-infection or other co-morbidities; nearly 12,000 individuals came from one study in South Africa. All study cohorts were at high risk of TB disease; this analysis differs from the previously mentioned meta-analysis [17••], in that persons receiving chemoprophylaxis were not excluded (0–76 % of individuals received INH preventive therapy). The specific IGRAs included were QuantiFERON-TB Gold In Tube, T-SPOT.TB, and several in-house assays. The primary endpoint was active tuberculosis.

In this analysis, five studies stratified risk of incident tuberculosis on the basis of baseline TST and IGRA results; the studies included different TST cut-offs for positivity. The unadjusted incidence rate ratio (IRR) for positive versus negative IGRA was 2.11 (95 % CI, 1.29–3.46). For TST >10 mm, the unadjusted IRR was 1.60 (95 % CI, 0.94–2.72); for TST >5 mm the value was 1.43 (95 % CI, 0.75–2.72). These results suggest only modest, non-significant differences in IRR for incident tuberculosis on the basis of positive IGRA compared with positive TST. When the ELISPOT assays (including T-SPOT.TB) were compared with the whole-blood ELISA assays (including QuantiFERON-TB Gold In-Tube), the unadjusted IRR for

the ELISPOT assay was 2.64 (95 % CI, 1.41–4.93) and 1.82 (95 % CI, 1.11–2.97) for whole-blood ELISA assays when compared with negative IGRA results. Overlapping confidence intervals suggest no dramatic difference between assay types. The authors attempted to compare patient populations; after excluding studies on the grounds of a variety of biases, only eight studies remained, all from low-to-middle income countries. No differences were seen across multiple subgroups, including isoniazid-preventive treatment, whole-blood ELISA versus ELISPOT assay, HIV prevalence, or BCG scar. The authors concluded that neither the IGRA nor the TST had high accuracy for predicting progression to TB disease. Although no difference was seen between IGRA and TST for predicting progression to tuberculosis, several notable factors—for example, inclusion of those who had received preventive therapy for tuberculosis, and the wide range of "in-house" assays used—may have affected the outcome.

Serial testing

Among the benefits of using IGRAs for diagnosis of latent tuberculosis infection is that it requires just one blood draw and provides a quantifiable result with established guidelines for interpretation. However, there have been concerns about the variability of results around this single "cut-point" for a positive or negative IGRA result, and questions about how to interpret these data. This is especially true with serial IGRA testing, which may be performed among healthcare workers. There may be reversion of a positive result to a negative result; and there can also be conversion of a negative result to positive, leading to imaging or treatment. This often occurs when the initial positive test is close to the cut-off value [19, 20]. Existing guidelines (published in 2010) on the use of IGRAs note that fluctuations in interferon-γ response in serial testing are largely unexplained [6]. However, in the last year several studies have revealed variable results in serial testing with IGRAs, and these studies reveal convincingly that a single cut-off value denoting a positive IGRA can lead to significant reversion and/or conversion in serial testing [21••, 22•, 23]. This was also observed by two systematic reviews on the subject [24, 25].

Because serial testing can result in conversion of 1–21 % [24, 25] and reversion of 40–50 % [26] of results, an expert panel was convened to discuss how best to address variability in serial testing [27]. Guidelines are being developed. Others have recommended that a "gray zone" be established around the single cut-off value for QuantiFERON-TB Gold In-Tube, similar to that used for T-SPOT.TB (the FDA-approved "borderline value") [28], or account for the magnitude of change of the interferon-γ response as a marker of a conversion [26]. Others have suggested that serial IGRA testing not be performed until these problems are resolved [29].

Discordant test results

Another factor complicating the diagnosis of latent tuberculosis infection is discordant results between the TST and IGRAs. A meta-analysis has noted discordance among results for persons with different risks of tuberculosis infection [20, 30]. Several recent publications add to the data regarding this phenomenon. Four studies, included in the recent systematic review and meta-analysis discussed above [18•], investigated tuberculosis incidence among those with discordant TST and IGRA results. These studies were conducted in Senegal, India, Turkey, and the Gambia. With the exception of the Gambia, the highest incidence of progression to tuberculosis was found in those with concordant positive TST and IGRA results (TST+/IGRA+), compared with those with negative IGRAs and either positive or negative TSTs [18•]. Although overall numbers of individuals with paired TST and IGRA testing were small in this subset of the analysis, there was a trend toward a slightly stronger association with tuberculosis disease when the IGRA was positive and TST negative than when the TST was positive and IGRA negative; however, confidence intervals overlap. These results are difficult to interpret in light of the presumed differences between populations of these four countries and the use of different TST cut-offs. The Tuberculosis Epidemiologic Studies Consortium (TBESC) is currently conducting a study that might provide further information regarding discordant results and subsequent risk of active TB [31].

In a study of US military recruits, individuals received simultaneous testing with QuantiFERON-TB Gold In-Tube, T-SPOT.TB, and tuberculin skin testing [32••]. Given the lack of an ideal method, test specificity was estimated by assuming that those with no risk factors did not have latent tuberculosis infection. Of 1,826 recruits who completed all three tests, only 88 had any positive test, and 10 were positive on all three tests. The specificities of the three tests ranged from 98.7–99.3 % and there were no statistically significant differences. Notably, 77 % of those with a positive result were positive on only one test: 1.1 % of recruits had a positive T-SPOT.TB but negative QuantiFERON-TB Gold In-Tube, and 1.2 % had a positive QuantiFERON-TB Gold In-Tube but negative T-SPOT.TB test; 0.8 % were positive for both. In this study, those who were TST positive but IGRA negative tended to have responses to nontuberculous mycobacteria skin testing, or a history of BCG vaccine, or were born in countries with higher tuberculosis prevalence. In this low-prevalence setting, notable findings were that the lower the risk for tuberculosis, the lower the quantitative results; and that those with lower quantitative results tended to have single positive tests. Lower tuberculosis risk also increased the incidence of test disagreement. All of these findings argue for the use of targeted testing, especially in low-prevalence settings.

In a systematic review investigating the use of IGRAs to screen healthcare workers, 25 studies comparing TST with IGRAs in countries with varying rates of BCG vaccination were analyzed [25]. Concordance between the TST and IGRA ranged from 0.05 to 0.56, and discordance was found even in countries with low BCG vaccination. Among all studies analyzed, there was a lower prevalence of positive IGRA than positive TST in lower and moderate-tuberculosis-incidence countries; this difference was not seen in higher-incidence countries.

In another study, Norwegian healthcare workers who were contacts of known or suspected tuberculosis cases were tested by use of both the TST and the QuantiFERON TB Gold In-Tube test. Of these healthcare workers, 97.9 % had previously received BCG vaccination. In this study, 3.4 % of the healthcare workers had a positive IGRA, 55.3 % had a positive TST (cut-off for positivity ≥ 6 mm), and 13.7 % had TST ≥ 15 mm [33]. Discordance here was probably caused in large part by almost universal BCG vaccination, with all individuals probably having had a tuberculosis exposure.

Previous research on high-risk individuals in three locations in the United States revealed moderate concordance (kappa=0.53) between the TST and QuantiFERON TB Gold In-Tube test [34]. Those tested were either homeless, HIV-infected, foreign-born refugees recently arrived, or seeking treatment for substance abuse. Although information about BCG vaccination may have been inaccurate, the strongest risk factor for a positive TST but a negative QuantiFERON TB Gold In-Tube test was being foreign born.

Considered together, these studies are often difficult to interpret because of the wide variation in interpretive criteria for both TST and IGRAs, and the disparate tuberculosis risk and personal characteristics of the individuals studied. For all the examples cited above, the possible effect of BCG vaccination causing discordance between TST and IGRA must be noted. However: even for individuals, agreement between QuantiFERON TB Gold In-Tube and T-SPOT.TB is not high. In the study of military recruits, only modest agreement was seen between T-SPOT.TB and the QuantiFERON TB Gold In-Tube, with a kappa statistic of 0.39 (95 % CI, 0.24–0.54) [32••].

Given the frequency of discordant results, one approach would be to regard any positive test as a positive (i.e. if an individual has a positive TST and a negative IGRA, he or she would be regarded as having a positive test). This would probably result in more false positives. Another approach would be to require both a TST and an IGRA to be positive to count as a "positive" test. Requiring two tests would increase the time and expense of testing, reduce convenience, and result in some true infections being missed because of diminished sensitivity [6]. Still others have argued for a step-wise approach, starting with a TST and following up with IGRA if the TST is positive. Existing guidance recommends avoidance of a possible discordant result, stating that "an IGRA may be used in place of (*but not in addition to*) a TST in all situations in which CDC recommends tuberculin skin testing as an aid in diagnosing *M. tuberculosis* infection" [6] (emphasis ours).

In summary, although use of IGRAs has been much studied, their ability to predict progression to active tuberculosis is not yet well established. Serial testing by use of IGRAs is problematic because of conversions and reversions, and interpretation of low-positive results in the absence of corresponding clinical risk; guidance on serial testing is forthcoming. Problems of discordance between TST and IGRAs also merit further investigation, as does discordance between the commercially available IGRAs. Currently, testing by use of both TST and IGRA is discouraged. Thus, despite (or perhaps because of) large amounts of recent data, diagnosis of latent tuberculosis infection remains a challenge.

Treatment of latent *M. tuberculosis* infection

Treatment of latent tuberculosis infection has also been the subject of recent scientific advances. There were several important papers in 2011, and new guidelines were published in December 2011 from the Centers for Disease Control and Prevention (CDC) regarding use of the three-month once-weekly regimen of rifapentine + isoniazid given under direct observation (3HP) [35]. Over the subsequent 18 months additional data on the tolerability of this new regimen have been presented, and shortages of isoniazid have affected treatment of latent tuberculosis infection.

Summary of recent clinical trials of 3HP

An open-label trial was performed in Soweto, South Africa to evaluate four regimens for preventing tuberculosis among HIV-infected adults with positive tuberculin skin tests [36•]. Participants were randomized to either:

1) rifapentine 900 mg plus isoniazid 900 mg, once weekly for 12 weeks (3HP; directly-observed);
2) rifampin 600 mg plus isoniazid 900 mg, twice weekly for 12 weeks (3HR; directly-observed);
3) isoniazid 300 mg daily for the duration of the study (continuous H; ≤six years; self-administered); or
4) isoniazid 300 mg daily for six months (6H; self-administered).

This study was designed to assess the potential superiority of the three trial regimens to 6H. Incidence of TB per 100 person-years was 2.0 for the 3HP group, 2.0 for the 3HR group, 1.4 for the continuous H group, and 1.9 for the 6H group; none of these differences were statistically significant, and no regimen was superior to 6H. There was a trend towards

more adverse events in the continuous H group when compared with the two rifamycin-containing regimens, and adherence was higher for those taking the 12-week regimens. Among those who developed TB, there were two cases of rifampin resistance in the 3HP group, none in the 3HR group, and one in the continuous H group.

In a large prospective open-label non-inferiority trial (the PREVENT TB Study), 3HP (directly-observed) was compared with daily isoniazid for nine months (9H; self-administered). This study was conducted on high-risk tuberculin skin test reactors, in settings with low-to-medium TB incidence: the United States, Canada, Brazil, and Spain [37••]. Less than 3 % of the study population was HIV-infected. The study revealed that 3HP was at least as effective as 9H, with TB incidence in the 3HP group half that of the 9H group. Completion rates were 82 % with 3HP and 69 % with 9H ($P<0.001$). Both regimens were well tolerated; permanent drug discontinuation caused by an adverse event was 4.9 % for the 3HP group vs. 3.7 % for the 9H group ($P=0.009$). Possible hypersensitivity was more common in the 3HP group (3.8 % vs. 0.5 %) and hepatotoxicity was more common in the 9H group (2.7 % vs. 0.4 %).

Additional tolerability data on 3HP presented since January 2012

Enrollment into the PREVENT TB study was extended to young children and HIV-infected persons to obtain tolerability data for these important sub-populations. For children aged 2–17 years, treatment completion was higher with 3HP (88 % vs. 80 %) and there was no significant difference in drug discontinuation caused by an adverse event: 1.3 % for the 3HP group vs. 0.8 % for the 9H group. Possible hypersensitivity occurred in 1.3 % of the children receiving 3HP; there were no cases of hepatotoxicity in either group [38]. Although there were few tuberculosis cases, 3HP was as effective as 9H [38]. For HIV-infected persons, the tolerability of 3HP was also comparable to that of 9H. Treatment completion was higher with 3HP (89 % vs. 65 %), and there was no difference in treatment discontinuation caused by an adverse event (4 % for each group) [39]. Hepatotoxicity was more common in the 9H group (6 % vs. 2 %) and there was no difference by group in possible hypersensitivity (0.5 % for 3HP vs. 0 % for 9H) [39]. Data on effectiveness are pending.

The CDC has performed surveillance regarding the safety of 3HP under field conditions at 18 sites since the recommendation for its use was published in December 2011. Among 1,102 persons who started 3HP, the incidence of permanent drug discontinuation caused by an adverse event was 5.7 %, and possible hypersensitivity was 2.3 %; similar to the 4.9 % and 3.8 % incidences, respectively, in the PREVENT TB Study [40].

Extended duration of INH for HIV-infected persons in high-TB-incidence settings

There are concerns that the protective effect of a six-month course of INH may wane after treatment completion in areas of high tuberculosis prevalence, as the result of possible *M. tuberculosis* re-infection [41, 42]. In a placebo-controlled, double-blind trial involving HIV-infected adults in Botswana, participants were randomized to six versus 36 months of INH [43•]. TB incidence was 0.72 % per year for the group randomized to 36 months of INH vs. 1.26 % per year for persons receiving six months of INH (HR 0.57, 95 % CI 0.33–0.99, $P=0.047$). The protective effect of continued INH was greatest for persons with a positive tuberculin skin test. Among this sub-set, TB incidence was 1.6 % for the 36INH group vs. 6.0 % for the 6INH group—a 74 % reduction. There was no significant protective effect of 36 months of INH for tuberculin-skin-test-negative persons. Among tuberculin skin test positive persons there was a threefold lower mortality risk for those who received 36INH compared with those who received 6INH.

The World Health Organization recommends that in resource-constrained settings, HIV-infected persons without signs or symptoms of tuberculosis on TB screening should be offered isoniazid for at least six months. Tuberculin skin testing is not required, although those with a positive TST are most likely to benefit from isoniazid [44]. For HIV-infected persons living in settings with high tuberculosis transmission, 36 months of isoniazid is conditionally recommended [44].

Isoniazid shortage

In November 2012 the United States and other countries began to experience an interruption in the supply of isoniazid, with 79 % of health departments surveyed noting difficulties in procuring this medication. This has resulted in prioritization of treatment of active tuberculosis over latent tuberculosis infection, and use of alternative latent infection treatment regimens [45]. The CDC is working to ensure an uninterrupted supply of anti-tuberculosis drugs in the United States.

Conclusion

Tools for the diagnosis of latent tuberculosis infection have increased with the addition of the IGRAs to the TST, and much scientific data has been published on their use. However, substantial questions remain regarding their optimum use. Recent studies suggest that the data regarding the ability of IGRAs to predict progression to TB disease is not yet robust. In addition, problems regarding serial testing

with IGRAs and discordant results require further study. Treatment of latent tuberculosis infection has been improved by the introduction of an effective three-month regimen. Additional data on the tolerability of this regimen as it is implemented in operational settings will be beneficial.

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Compliance with Ethics Guidelines

Conflict of Interest Anna K. Person and April C. Pettit declare that they have no conflicts of interest. Timothy R. Sterling's institution receives grants from Bristol Myers Squibb, Pfizer, and Janssen for HIV observational cohort studies and receives payment from Otsuka for a data safety monitoring committee.

Human and Animal Rights and Informed Consent This article contains studies with human subjects performed by the authors. Informed consent was obtained.

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