They rightly point out that enrolling individuals with no risk of experiencing an endpoint in such trials may result in a greater likelihood of finding noninferiority. Some of the assumptions used in their model, however, are not appropriate for trials of TB-preventive therapy in people with HIV infection.

Stout and colleagues (1) used participant parameters from the BRIEF TB (Brief Rifapentine Isoniazid Efficacy for Tuberculosis) study, a large, phase-three randomized trial comparing 1 month of isoniazid and rifapentine (1HP) to 9 months of isoniazid in people with HIV infection (2) to assert that a trial in such a population would have an “unacceptably high” probability of declaring noninferiority even if the experimental regimen was in fact inferior to the control regimen. Their explanation for this contention is that a significant proportion of participants in the BRIEF TB study had negative or missing tests for latent TB infection and were, therefore, not at risk of developing TB.

The assumption that people with HIV infection and negative results of a tuberculin skin test (TST) or IFN-γ release assay (IGRA) are not at risk for TB and will not benefit from preventive therapy is incorrect. People with HIV infection are at greatly increased risk of developing TB, particularly in high-burden settings, and preventive therapy has been proved efficacious in the absence of a positive TST or IGRA (3, 4). In the trial of Rangaka and coworkers (3), individuals with advanced HIV infection and negative TSTs or IGRA who received a placebo experienced significantly higher rates of TB than those who received isoniazid. Of participants in the Temprano study tested by IGRA, only about one-third had positive results, yet those with negative tests who received isoniazid preventive therapy experienced similar reduction in the incidence of TB and death as those who were IGRA-positive (4).

In both arms of the BRIEF-TB trial, individuals with a negative TST or IGRA had rates of TB or death from an unknown cause that were substantially higher than those seen in TST-positive individuals without HIV infection enrolled in the PREVENT TB (Tuberculosis Trials Consortium Study 26) trial, demonstrating their increased risk (5). Additionally, the subgroup analysis of individuals in BRIEF-TB who had positive TSTs or IGRA demonstrated noninferiority of IHP to isoniazid, with an upper bound of the 95% confidence interval for the difference in rates being 0.73 per 100 person-years, which not only meets the noninferiority margin set for this trial (1.25 per 100 person-years) but also the noninferiority margin used in the PREVENT TB trial and the ongoing ASTERoID (Assessment of Safety, Tolerability, and Effectiveness of Rifapentine Given Daily for LTBI) trial (0.75 per 100 person-years) (5, 6).

TB-preventive treatment is essential for achieving global TB control. Although tests of latent TB infection are useful in nonimmunosuppressed patients, it is clear that some populations, such as people with HIV infection and young child household contacts, do not require testing before initiating preventive treatment, a recommendation now endorsed by the World Health Organization (7). Studies of TB-preventive therapy in people with HIV infection must enroll the population that will receive the therapy in real-world clinical practice. The BRIEF TB trial demonstrated noninferiority of IHP to isoniazid in both the overall population and the subset of those with a positive TST or IGRA, making the results generalizable to all HIV-infected adults and adolescents living in high-burden areas, as well as those with a positive test of latent infection anywhere. Requiring a positive TST or IGRA for enrollment into clinical trials of HIV-infected people seems to us like a step in the wrong direction.

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**References**

1. Stout JE, Turner NA, Belknap RW, Horsburgh CR, Sterling TR, Phillips PPJ. Optimizing the design of latent tuberculosis treatment trials: insights from mathematical modeling. *Am J Respir Crit Care Med* 2020;201:598–605.

2. Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N, et al.; BRIEF TB/A5279 Study Team. One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. *N Engl J Med* 2019;380:1001–1011.

3. Rangaka MX, Wilkinson RJ, Boule A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet* 2014;384:682–690.

4. Badjie A, Moh R, Gabillard D, Guéhi C, Kabran M, Ntakpé JB, et al.; Temprano ANRS 12136 Study Group. Effect of isoniazid preventive therapy on risk of death in West African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. *Lancet Glob Health* 2017;5:e1080–e1089.

5. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al.; TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med* 2011;365:2155–2166.

6. Assessment of the safety tolerability, and effectiveness of Rifapentine given daily for LTBI (ASTERoID). NCT03474029. [accessed 2020 Mar 3]. Available from: https://clinicaltrials.gov/ct2/show/NCT03474029.

7. World Health Organization. WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment. Geneva: World Health Organization; 2020.

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**Reply to Swindells et al.**

**From the Authors:**

We appreciate the interest in our recent manuscript (1) describing issues in noninferiority trials of latent tuberculosis infection (LTBI)
treatments. However, we believe that Swindells and colleagues are misinterpreting one of the fundamental points in the manuscript. Our model did not assume that people with HIV infection and a negative tuberculin skin test (TST) or IFN-γ release assay (IGRA) are not at risk for tuberculosis and do not benefit from LTBI treatment. On the contrary, we used reasonable estimates of test sensitivity and specificity from the best available evidence (2, 3) combined with a wide range of underlying population prevalence estimates to calculate the prevalence of LTBI among persons with negative tests, and then assumed that all of those persons were at risk to progress to active tuberculosis. For example, if the prevalence of LTBI in a population was 30% and we use the assumptions of 60% sensitivity and 70% specificity for the TST, then the prevalence of LTBI among persons with negative TST (i.e., false-negative TST) recruited from this population would be 

\[ 0.3 \times (0.4) + (0.3 \times 0.4 + 0.7 \times 0.7) = 19.6\% \]

our model assumed that persons with LTBI (i.e., persons with positive TST/IGRA or false-negative TST/IGRA) were at risk to progress to active tuberculosis, but that persons without LTBI (i.e., persons with false-positive TST/IGRA results and persons with true-negative TST/IGRA results) were not at risk to progress to active tuberculosis.

Understanding this point is fundamental to correct interpretation of our model, which explores the implications of the principle that recruiting on the basis of negative test results (TST/IGRA) reduces the prevalence of LTBI in the study population below the prevalence in the general population from which participants were recruited. This reduction, in turn, diminishes the number of participants at risk for the outcome of interest (active tuberculosis in this case) and results in fewer outcomes than might otherwise have been expected. Because the test performance does not depend on allocated treatment, test results should have no impact on the relative magnitude of event rates between arms, so the consistency in results between IGRA-negative and IGRA-positive participants in TEMPRANO (4) is entirely compatible with our model. However, in the setting of a noninferiority trial with an absolute noninferiority margin, fewer outcomes in both arms translate to lower absolute event rates, lower absolute differences in event rates, and a higher chance of falsely declaring an arm with low efficacy noninferior. In the case of BRIEF TB (Brief Rifapentine-Isoniazid Efficacy for Tuberculosis Prevention) (5), although the subgroup analysis of participants with a positive test met the presupposed absolute noninferiority margin, the low observed event rates in the trial and in this subgroup mean that one can only say with 95% confidence that the incidence rate ratio among persons with positive TST/IGRA in the 1-month arm was somewhere between 35% and 241% of that observed in the 9-month arm. With such a wide range of possible relative efficacies, a well-powered, well-designed study to confirm or refute the efficacy of the BRIEF-TB regimen using tests with high specificity to recruit participants would be a necessary step in the right direction.

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References

1. Stout JE, Turner NA, Belknap RW, Horsburgh CR, Sterling TR, Phillips PPJ. Optimizing the design of latent tuberculosis treatment trials: insights from mathematical modeling. Am J Respir Crit Care Med 2020;201:598–605.

2. Stout JE, Wu Y, Ho CS, Pettit AC, Feng PJ, Katz DJ, et al.; Tuberculosis Epidemiologic Studies Consortium. Evaluating latent tuberculosis infection diagnostics using latent class analysis. Thorax 2018;73:1062–1070.

3. Abubakar I, Drobniewski F, Southern J, Sitch AJ, Jackson C, Lipman M, et al.; PREDICT Study Team. Prognostic value of interferon-γ release assays and tuberculin skin test in predicting the development of active tuberculosis (UK PREDICT TB); a prospective cohort study. Lancet Infect Dis 2018;18:1077–1087.

4. Danel C, Moh R, Gabilard D, Badje A, Le Carrou J, Ouassa T, et al.; TEMPRANO ANRS 12136 Study Group. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med 2015;373:808–822.

5. Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N, et al.; BRIEF TB/A5279 Study Team. One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. N Engl J Med 2019;380:1001–1011.