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Annual Tuberculosis Preventive Therapy for Persons With HIV Infection

A Randomized Trial

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Background: Tuberculosis preventive therapy for persons with HIV infection is effective, but its durability is uncertain.

Objective: To compare treatment completion rates of weekly isoniazid–rifapentine for 3 months versus daily isoniazid for 6 months as well as the effectiveness of the 3-month rifapentine–isoniazid regimen given annually for 2 years versus once.

Design: Randomized trial. (ClinicalTrials.gov: NCT02980016)

Setting: South Africa, Ethiopia, and Mozambique.

Participants: Persons with HIV infection who were receiving antiretroviral therapy, were aged 2 years or older, and did not have active tuberculosis.

Intervention: Participants were randomly assigned to receive weekly rifapentine–isoniazid for 3 months, given either annually for 2 years or once, or daily isoniazid for 6 months. Participants were screened for tuberculosis symptoms at months 0 to 3 and 12 of each study year and at months 12 and 24 using chest radiography and sputum culture.

Measurements: Treatment completion was assessed using pill counts. Tuberculosis incidence was measured over 24 months.

Results: Between November 2016 and November 2017, 4027 participants were enrolled; 4014 were included in the analyses (median age, 41 years; 69.5% women; all using antiretroviral therapy). Treatment completion in the first year for the combined rifapentine–isoniazid groups (n = 3610) was 90.4% versus 50.5% for the isoniazid group (n = 404) (risk ratio, 1.78 [95% CI, 1.61 to 1.95]). Tuberculosis incidence among participants receiving the rifapentine–isoniazid regimen twice (n = 1808) or once (n = 1802) was similar (hazard ratio, 0.96 [CI, 0.61 to 1.50]).

Limitation: If rifapentine–isoniazid is effective in curing subclinical tuberculosis, then the intensive tuberculosis screening at month 12 may have reduced its effectiveness.

Conclusion: Treatment completion was higher with rifapentine–isoniazid for 3 months compared with isoniazid for 6 months. In settings with high tuberculosis transmission, a second round of preventive therapy did not provide additional benefit to persons receiving antiretroviral therapy.

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Tuberculosis preventive therapy reduces the risk for tuberculosis in persons with HIV infection (1–6). In settings with high tuberculosis transmission, the durability of protection may be limited, particularly when patients are not receiving antiretroviral therapy. Prolonged preventive therapy with isoniazid provides protection only for as long as the preventive therapy is taken (3, 4). Short-course tuberculosis preventive therapy with weekly rifapentine and isoniazid for 3 months has less toxicity, better treatment completion rates, and similar efficacy compared with 6 months or continuous isoniazid preventive therapy (7).

Adoption and scale-up of tuberculosis preventive therapy have been poor in most high-burden countries (8). Alternative strategies are needed to optimize protection from tuberculosis among persons with HIV infection in high-transmission settings. In the WHIP3TB trial (Weekly High Dose Isoniazid and rifapentine [P] Periodic Prophylaxis for TB trial), we hypothesized that, among persons with HIV infection receiving antiretroviral therapy, treatment completion of weekly rifapentine and isoniazid for 3 months would be superior to 6 months of daily isoniazid, and that annual weekly rifapentine and isoniazid for 3 months would be more effective than a single round.

Methods

Trial Design and Participants

We conducted a parallel, 2-part, open-label, individually randomized trial comparing 3 tuberculosis preventive therapy regimens in persons with HIV infection receiving antiretroviral therapy. Participants were assigned to 1 of 3 study groups: weekly rifapentine and isoniazid for 3

See also:

Editorial comment. 1462

Web-Only
Supplement

months given annually for 2 years (annual rifapentine–isoniazid group) or given once (single-round rifapentine–isoniazid group), or 6 months of daily isoniazid (isoniazid group). Participants in the rifapentine–isoniazid groups and the isoniazid group were followed for 24 and 12 months, respectively. Part A of the trial compared treatment completion in the combined rifapentine–isoniazid groups versus the isoniazid group during the first 12 months. Part B of the trial compared the effectiveness of rifapentine and isoniazid for preventing tuberculosis when given annually for 2 years versus once. The study was conducted in South Africa (5 sites), Ethiopia (2 sites), and Mozambique (1 site).

Persons with HIV infection aged 2 years or older were excluded if they had symptoms suggesting tuberculosis; had known exposure to isoniazid- or rifampin-resistant tuberculosis; received tuberculosis treatment or preventive therapy within the past year; reported intolerance to isoniazid or rifamycins; were taking nevirapine, HIV protease inhibitors, or integrase strand transfer inhibitors; had suspected or known liver disease; were pregnant or breastfeeding; or self-reported alcohol use exceeding 28 units per week for men or 21 units for women.

Eligible participants were randomly assigned in a 9:9:2 ratio to the annual rifapentine–isoniazid, single-round rifapentine–isoniazid, and isoniazid groups, stratified by country of residence and different block sizes.

Study Procedures

The study schedule and dosing of study medication are described in the Methods section of **Supplement 1** (available at Annals.org). Treatment was dispensed at months 0, 1, and 2 in all study groups, and 3 months of isoniazid was dispensed at month 3 in the isoniazid group (**Figure 1** of **Supplement 1**). In the annual rifapentine–isoniazid group, treatment was also dispensed at months 12, 13, and 14. Medication doses were directly observed at dispensing visits and were otherwise self-administered. Electronic medication monitors, if available, were offered to participants to support adherence. As monitors became available, distribution to South African sites was prioritized due to ease of importation and more rapid enrollment. Relatively few monitors were shipped to Ethiopia and Mozambique. Participants in the rifapentine–isoniazid groups were allowed 16 weeks to complete each 12-week course of treatment; those in the isoniazid group were allowed 32 weeks to complete the 26-week course. All women of childbearing potential had a pregnancy test before starting each treatment course or having a chest radiograph.

All participants were screened for tuberculosis symptoms (cough, fever, night sweats, or unintentional weight loss) at months 1 to 3 and 12. In addition, in both rifapentine–isoniazid groups, symptom screening was conducted at months 13 to 15 and 24. All participants had a chest radiograph and a sputum specimen collected for culture at month 12; the same was collected at month 24 in the rifapentine–isoniazid groups.

Participants with tuberculosis symptoms or those diagnosed with tuberculosis by the routine health service at any time during study follow-up were asked to provide a spot sputum sample for testing by Xpert MTB/RIF (Cepheid) and/or culture as soon as possible. Information on tuberculosis investigations and treatment was abstracted from routine clinic and laboratory records.

While receiving treatment, participants were screened at clinic and telephone visits (**Figure 1** of **Supplement 1**) for the following study-defined adverse events: hepatotoxicity, peripheral neuropathy, psychosis, seizures, flu-like reactions, and hypersensitivity reactions. Severity of adverse events was graded according to the Division of AIDS toxicity table (9).

Study Outcomes and Sample Size

The primary end point for part A was treatment completion, defined as having taken at least 11 doses of rifapentine–isoniazid or at least 167 doses of isoniazid. Treatment completion was based on doses directly observed at dispensing visits and self-report (see the Methods section of **Supplement 1**). For part B, the primary end point was the incidence of active (possible, probable, or definite) tuberculosis over 24 months (see the Methods section of **Supplement 1** for definitions). Secondary end points were all-cause mortality and permanent discontinuation of therapy due to treatment-related adverse events (parts A and B), tuberculosis incidence (part A only), and treatment completion and incidence of rifampin-resistant tuberculosis (part B only).

A sample size of 4000 participants (1800 each in the annual and single-round rifapentine–isoniazid groups and 400 in the isoniazid group) provided, in part A, at least 80% power to detect an increase in treatment completion from 85% in the isoniazid group to 90% in the combined rifapentine–isoniazid groups and, in part B, 80% power to detect a 50% reduction in tuberculosis incidence, from 3% in the single-round rifapentine–isoniazid group to 1.5% in the annual rifapentine–isoniazid group.

Statistical Analysis

Treatment completion was summarized as a percentage and compared by study group using a risk difference and risk ratio and associated 95% CIs, calculated using the generalized linear model with identity- and log-link functions, respectively. Time to tuberculosis, rifampin-resistant tuberculosis, and death were analyzed using Cox proportional hazards regression. Time to tuberculosis and mortality are displayed using Kaplan–Meier curves. Nonproportional hazards for the effect of study group on time to death over 24 months were assessed through a lexis expansion of follow-up time (0 to 12 vs. 12 to 24 months) and testing for interaction with the study group using a likelihood ratio test. A priori subgroup analyses of time to tuberculosis were conducted for country, sex, CD4 count strata (<0.250 vs. $\geq 0.250 \times 10^9$ cells/L), and baseline QuantiFERON-TB Gold Plus (QIAGEN) test status. Discontinuation of therapy was compared by study group using an odds ratio and the associated 95% CIs from logistic regression. Study-defined serious adverse events were summarized by study group. Comparisons were adjusted for country (3 levels) as a fixed effect.

For the analysis of tuberculosis incidence over the 12-month follow-up period, participants who were diagnosed with tuberculosis during this period were considered to have experienced the event at the date of their episode, defined as the date of collection of a specimen

that was positive for tuberculosis or the treatment start date, whichever was earlier. Participants who were not known to have died and who did not experience a tuberculosis event were censored at the last attended visit (up to and including the 12-month visit) or the enrollment date plus 392 days (scheduled date of 12-month visit [336 days] plus 8-week window [56 days]), whichever was earlier; those with no recorded follow-up visits were censored at the date of enrollment plus 28 days. Participants who were known to have died and who did not experience a tuberculosis event were censored at the date of death, the last attended visit (up to and including the 12-month visit), or the enrollment date plus 392 days (scheduled date of 12-month visit [336 days] plus 8-week window [56 days]), whichever was earliest. A similar approach was used for tuberculosis incidence over the 24-month follow-up period (part B). Hypothesis tests were based on the likelihood ratio and Wald test statistics (see the statistical analysis plan [Supplement 2, available at Annals.org] for more details).

Two post hoc analyses were also conducted. First, analysis of treatment completion in part A was restricted to participants who had pill counts recorded at the month 3 visit for the combined rifapentine–isoniazid groups and the month 6 visit for the isoniazid group. Second, time to a combined end point of tuberculosis or death over 12 and 24 months from enrollment was analyzed.

All analyses were conducted in Stata, version 16 (StataCorp).

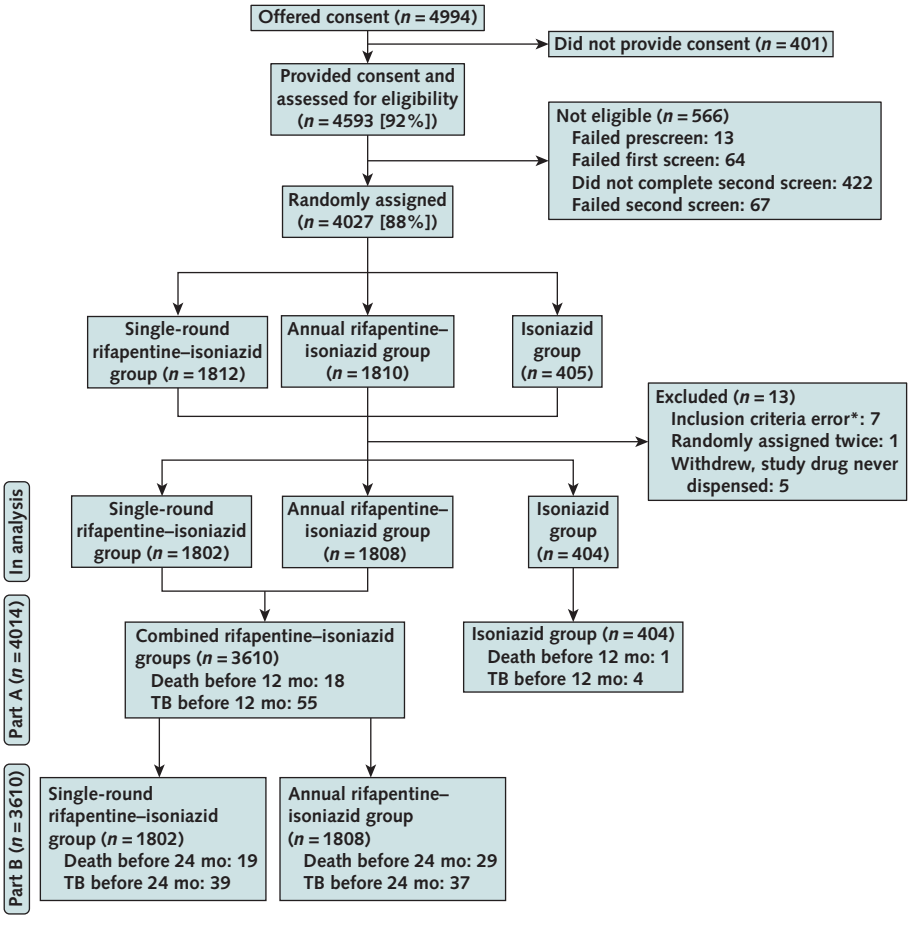
Trial Oversight

The investigators designed and implemented the study and analyzed the data. The authors vouch for the completeness and accuracy of the data and adherence to the protocol. The investigators' institutional review boards approved the protocol (Supplement 3, available at Annals.org). All participants or guardians gave written informed consent or witnessed verbal consent or assent where appropriate. Sanofi donated the rifapentine and isoniazid for the study but had no other role in the study design or conduct. An independent data safety and monitoring board monitored the study.

Role of the Funding Source

The U.S. Agency for International Development (USAID) had no role in study design, conduct, or analysis

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram for parts A and B.



The "combined" group refers to the annual and single-round rifapentine-isoniazid groups combined.* Incorrectly randomly assigned (did not satisfy enrollment criteria); no study dose taken.

Table 1. Summary of Participants at Baseline, by Study Group (n = 4014)

Characteristics	Annual Rifapentine–Isoniazid Group* (*n* = 1808)	Single-Round Rifapentine–Isoniazid Group† (*n* = 1802)	Isoniazid Group‡ (*n* = 404)
Country of enrollment, *n (%)*			
South Africa	1144 (63.3)	1139 (63.2)	257 (63.6)
Ethiopia	393 (21.7)	394 (21.9)	88 (21.8)
Mozambique	271 (15.0)	269 (14.9)	59 (14.6)
Age			
Median (IQR), *y*	42.0 (35.0–49.0)	41.0 (34.0–49.0)	40.5 (34.0–47.5)
<18 y, *n (%)*	6 (0.3)	11 (0.6)	2 (0.5)
Gender, *n (%)*			
Female	1258 (69.6)	1248 (69.3)	283 (70.0)
Male	550 (30.4)	554 (30.7)	121 (30.0)
ART			
Receiving ART, *n (%)*	1808 (100.0)	1802 (100.0)	404 (100.0)
Regimen, *n (%)*			
TDF + FTC/3TC + EFV§	1712 (94.7)	1710 (94.9)	386 (95.5)
ZDV + FTC/3TC + EFV	79 (4.4)	74 (4.1)	17 (4.2)
Other‖	17 (0.9)	18 (1.0)	1 (0.2)
Median time receiving ART, (IQR), *mo*	53.1 (27.4–86.9)	51.6 (26.4–83.7)	47.3 (26.7–78.9)
CD4 count¶			
Median (IQR), $\times 10^9$ *cells/L*	0.458 (0.300–0.641)	0.471 (0.301–0.649)	0.446 (0.315–0.666)
<0.250 $\times 10^9$ cells/L, *n/N (%)*	301/1702 (17.7)	310/1713 (18.1)	61/378 (16.1)
Previous TB, *n (%)*	436 (24.1)	427 (23.7)	94 (23.3)
Previous isoniazid preventive therapy, *n (%)*	272 (15.0)	276 (15.3)	67 (16.6)
Median BMI (IQR), *kg/m²*	24.0 (21.0–28.2)	24.1 (21.0–28.2)	23.8 (20.9–28.2)
QFT result, *n (%)***			
Positive	659 (38.8)	636 (37.2)	148 (39.3)
Negative	1033 (60.8)	1062 (62.2)	229 (60.7)
Indeterminate	6 (0.4)	10 (0.6)	0 (0)

3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; BMI = body mass index; D4T = stavudine; EFV = efavirenz; FTC = emtricitabine; IQR = interquartile range; QFT = QuantiFERON-TB Gold Plus; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine.
* Weekly rifapentine and isoniazid for 3 months given annually for 2 years.
† Single round of weekly rifapentine and isoniazid.
‡ Six months of daily isoniazid.
§ Fixed-dose combination.
‖ Includes ABC + FTC/3TC + EFV (*n* = 12 in the annual rifapentine–isoniazid group and 18 in the single-round rifapentine–isoniazid group) and D4T + FTC/3TC + EFV (*n* = 5 in the annual rifapentine–isoniazid group and 1 in the isoniazid group).
¶ Data were missing for 106 participants in the annual rifapentine–isoniazid group, 89 in the single-round rifapentine–isoniazid group, and 26 in the isoniazid group.
** Data were missing for 110 participants in the annual rifapentine–isoniazid group, 94 in the single-round rifapentine–isoniazid group, and 27 in the isoniazid group.

or in the decision to submit the manuscript for publication.

RESULTS

Between November 2016 and November 2017, 4994 persons with HIV infection were offered study enrollment; 4593 were screened, and 4027 were randomly assigned (Figure 1). Thirteen participants were excluded (Figure 1). Included in the analyses were 4014 participants in part A (3610 in the combined rifapentine–isoniazid groups and 404 in the isoniazid group) and 3610 participants in part B (annual [*n* = 1808] and single-round [*n* = 1802] rifapentine–isoniazid groups).

The median age of the participants was 41 years (19 [0.5%] were aged <18 years); 69.5% were female. All participants were receiving antiretroviral therapy; 17.7% (672 of 3793) had a CD4 count less than 0.250 $\times 10^9$ cells/L; 38.3% (1443 of 3767) had a positive result on the QuantiFERON-TB Gold Plus test; and 63.3%, 21.8%, and 14.9% were from South Africa, Ethiopia, and Mozambique, respectively. Baseline characteristics were similar among study groups (Table 1).

Part A

Treatment completion in the combined rifapentine–isoniazid groups was higher than in the isoniazid group overall (90.4% [95% CI, 89.4% to 91.3%] vs. 50.5% [CI,

45.5% to 55.5%]; adjusted risk ratio, 1.78 [CI, 1.61 to 1.95]; $P < 0.001$), with an adjusted risk difference of 39.6 percentage points (CI, 34.6 to 44.6 percentage points; $P < 0.001$) (**Table 2**; **Table 1** of **Supplement 1**). However, strong evidence indicated that the effect of study group on treatment completion differed by country (**Table 2** of **Supplement 1**).

Across all groups, 16.1% of participants (648 of 4014) used an electronic medication monitor in year 1 (**Table 6** of **Supplement 1**); of these, 96.0% (622 of 648), 2.3% (15 of 648), and 1.7% (11 of 648) were from South Africa, Ethiopia, and Mozambique, respectively. The analysis investigating whether use of electronic medication monitors modified treatment completion by study group was therefore restricted to South African sites. The risk difference in treatment completion for the combined rifapentine–isoniazid group versus the isoniazid group was 52.9 percentage points (CI, 46.1 to 59.7 percentage points) and 58.9 percentage points (CI, 46.2 to 71.7 percentage points), respectively, for participants not using and using the electronic medication monitor (*P* value for interaction = 0.42) (**Table 7** of **Supplement 1**).

During the first 12 months after randomization, 59 tuberculosis events (55 in the combined rifapentine–isoniazid groups and 4 in the isoniazid group) gave a tuberculosis incidence of 1.74 (CI, 1.34 to 2.28) and 1.12 (CI, 0.42 to 2.98) per 100 person-years in the rifapentine–isoniazid and isoniazid groups, respectively (adjusted hazard ratio [HR], 1.60 [CI, 0.58 to 4.42]) (**Table 2**; **Figure 2** of **Supplement 1**). Mortality in the first 12 months was low (0.57 [CI, 0.36 to 0.91] per 100 person-years for the combined rifapentine–isoniazid groups vs. 0.28 [CI, 0.04 to 1.99] per 100 person-years in the isoniazid group; HR, 2.07 [CI, 0.28 to 15.50]) (**Table 2**; **Figure 3** of **Supplement 1**). Twenty-six of 3610 (0.7% [CI, 0.5% to 1.1%]) participants in the combined rifapentine–isoniazid groups and 5 of 404 (1.2% [CI, 0.4% to 2.9%]) in the isoniazid group (odds ratio, 0.58 [CI, 0.22 to 1.94]) discontinued therapy due to treatment-limiting adverse events.

Part B

Overall, 89.4% (1548 of 1671) of participants in the annual rifapentine–isoniazid group attending the month 12 visit started a second round of rifapentine–isoniazid. By 24 months from randomization, 76 episodes of tuberculosis had occurred (37 and 39 in the annual and single-round rifapentine–isoniazid groups, respectively), giving an incidence of tuberculosis of 1.21 (CI, 0.87 to 1.66) and 1.26 (CI, 0.92 to 1.73) per 100 person-years, respectively (HR, 0.96 [CI, 0.61 to 1.50]) (**Table 3**; **Figure 2** [*top*]). The effect was similar when stratified by country, sex, CD4 count, and QuantiFERON-TB Gold Plus status (**Table 3** and **Figure 5** of **Supplement 1**) and when restricted to definite tuberculosis (**Table 4** of **Supplement 1**). Twenty-six of 30 participants (87.6%) at month 12 with bacteriologically confirmed tuberculosis were asymptomatic at the time sputum was collected.

Cumulative tuberculosis incidence over months 12 to 24 was similar in the annual and single-round rifapentine–isoniazid groups (HR, 1.02 [CI, 0.48 to 2.13]) (**Table 3**; **Figure 4** of **Supplement 1**). Overall, 8 tuberculosis episodes were rifampin resistant (10.5% [CI, 4.7% to 19.7%]) (**Table 5** of **Supplement 1**). The incidence of rifampin-resistant tuberculosis in the annual and single-round rifapentine–isoniazid groups was 0.13 per 100 person-years in each group (CIs, 0.05 to 0.35 and 0.05 to 0.34 in the annual and single-round rifapentine–isoniazid groups, respectively; HR, 1.01 [CI, 0.25 to 4.04]). All-cause mortality over 24 months was similar in the annual and single-round rifapentine–isoniazid groups (0.94 [CI, 0.66 to 1.36] and 0.61 [CI, 0.39 to 1.96] per 100 person-years; HR, 1.55 [CI, 0.87 to 2.76]) (**Table 3; Figure 2** [*bottom*]) and similar

Table 2. Primary and Secondary End Points: Part A (Combined Rifapentine and Isoniazid Groups vs. Isoniazid Group)

Part A Outcomes	Combined Rifapentine–Isoniazid Group (*n* = 3610)		Isoniazid Group (*n* = 404)		Combined Rifapentine–Isoniazid Group vs. Isoniazid Group	
	Participants, *n/N, % (95% CI)*	Events/PY, Rate per 100 PY (95% CI)	Participants, *n/N, % (95% CI)*	Events/PY, Rate per 100 PY (95% CI)	RR, HR, or OR (95% CI)	*P* Value
Primary						
Treatment completion*	3262/3610, 90.4 (89.4–91.3)	–	204/404, 50.5 (45.5–55.5)	–	RR, 1.78 (1.61–1.96)	<0.001
Secondary						
TB incidence from months 0–12†	–	55/3146, 1.74 (1.34–2.28)	–	4/357, 1.12 (0.42–2.98)	HR, 1.60 (0.58–4.42)	0.33
Mortality from months 0–12	–	18/3149, 0.57 (0.36–0.91)	–	1/357, 0.28 (0.04–1.99)	HR, 2.07 (0.28–15.50)‡	0.43
Discontinuation of therapy§	26/3610, 0.7 (0.5–1.1)	–	5/404, 1.2 (0.4–2.9)	–	OR, 0.58 (0.22–1.94)	0.26

HR = hazard ratio; OR = odds ratio; PY = person-years; RR = risk ratio; TB = tuberculosis.

* Risk difference, 39.6 percentage points (95% CI, 34.6 to 44.6 percentage points; $P < 0.001$). Doses taken were based on all available data. In the combined rifapentine–isoniazid groups, 331 of 3610 did not attend the month 3 visit, and 88 of 404 in the isoniazid group did not attend the month 6 visit.

† Measured over months 0 to 12. Fifty-nine tuberculosis events occurred (44 definite events [75%], 3 probable events [5%], and 12 possible events [20%]). A total of 87.6% of participants (26 of 30) with bacteriologically confirmed tuberculosis from sputum given at month 12 were asymptomatic at that visit.

‡ Not adjusted for country.

§ Discontinuation of therapy for treatment-limiting adverse events.

Table 3. Primary and Secondary End Points: Part B (Annual vs. Single-Round Rifapentine and Isoniazid Groups)

Part B Outcomes	Annual Rifapentine-Isoniazid Group (*n* = 1808)		Single-Round Rifapentine-Isoniazid Group (*n* = 1802)		Annual Versus Single-Round Rifapentine-Isoniazid Group	
	Events/PY, Rate per 100 PY (95% CI)	Participants, *n/N*, % *(95% CI)*	Events/PY, Rate per 100 PY (95% CI)	Participants, *n/N*, % *(95% CI)*	HR, RR, or OR (95% CI)	*P* Value
Primary						
TB incidence from months 0–24*	37/3070, 1.21 (0.87–1.66)	–	39/3094, 1.26 (0.92–1.73)	–	HR, 0.96 (0.61–1.50)	0.85
Secondary						
TB incidence from months 12–24†	14/1425, 0.98 (0.58–1.66)	–	14/1435, 0.98 (0.59–1.65)	–	HR, 1.02 (0.48, 2.13)	0.97
Rifampin-resistant TB incidence from months 0–24	4/3070, 0.13 (0.05–0.35)	–	4/3094, 0.13 (0.05–0.34)	–	HR, 1.01 (0.25–4.04)‡	0.99
Mortality from months 0–24§	29/3075, 0.94 (0.66–1.36)	–	19/3100, 0.61 (0.39–0.96)	–	HR, 1.55 (0.87–2.76)	0.134
Treatment completion	–	1310/1808, 72.5 (70.3–74.5)	–	1618/1802, 89.8 (88.3–91.1)	RR, 0.81 (0.78–0.83)	<0.001
Discontinuation of therapy‖	–	21/1808, 1.2 (0.7–1.8)	–	10/1802, 0.6 (0.3–10.2)	OR, 2.11 (0.99–4.49)	0.046

HR = hazard ratio; OR = odds ratio; PY = person-years; RR = risk ratio; TB = tuberculosis.
* Measured over months 0 to 24. Tuberculosis events (*n* = 76): definite, 68% (*n* = 52), probable, 4% (*n* = 3), possible, 28% (*n* = 21).
† Measured over months 12 to 24 using the actual date of the 12-month visit as the start date of the risk period.
‡ Not adjusted for country.
§ *P* value for nonproportional hazards = 0.86. In months 0 to 12, 13 deaths over 1745 PY (0.75 per 100 PY) occurred in the annual rifapentine–isoniazid group and 8 deaths over 1759 PY (0.45 per 100 PY) occurred in the single rifapentine–isoniazid group (HR, 1.64 [CI, 0.68 to 3.97]; *P* = 0.27). In months 12 to 24, 16 deaths over 1331 PY (1.20 per 100 PY) occurred in the annual rifapentine–isoniazid group and 11 deaths over 1341 PY (0.82 per 100 PY) occurred in the single-round rifapentine–isoniazid group (HR, 1.48 [CI, 0.69 to 3.19]; *P* = 0.31).
‖ Discontinuation of therapy for treatment-limiting adverse events.

when stratified by months 0 to 12 and 12 to 24 (*P* value for nonproportional hazards = 0.86). In a post hoc analysis, the incidence of tuberculosis and deaths combined from 0 to 24 months was similar by study group (HR, 1.10 [CI, 0.77 to 1.58]) (**Table 1** of **Supplement 1**).

Treatment completion in the annual rifapentine–isoniazid group (combined years 1 and 2) was lower than in the single-round rifapentine–isoniazid group (year 1) (risk ratio, 0.81 [CI, 0.78 to 0.83]) (**Table 3**; **Table 1** of **Supplement 1**). In the annual rifapentine–isoniazid group, the proportions completing treatment were similar in year 1 (90.9% [1644 of 1908]) and year 2 (89.3% [1359 of 1521]).

Treatment completion in year 1 among South African participants did not differ in the annual rifapentine–isoniazid group versus the single-round group by electronic medication monitor usage (*P* value for interaction = 0.90). The difference in tuberculosis incidence between the annual and single-round rifapentine–isoniazid groups was not modified by use of electronic medication monitors (*P* value for interaction = 0.31) (**Table 9** of **Supplement 1**).

The proportion of participants discontinuing therapy due to treatment-limiting adverse effects in the annual rifapentine–isoniazid group (over years 1 and 2) was greater than that in the single-round rifapentine–isoniazid group (year 1) (1.2% [CI, 0.7% to 1.8%] vs. 0.6% [CI, 0.3% to 10.2%]; odds ratio, 2.1 [CI, 0.95 to 5.02]) (**Table 3**). Overall, 37 participants experienced 39 grade 3 to 5 study-defined adverse events (**Table 4**). In the annual and single-round rifapentine–isoniazid groups and the isoniazid groups, 17, 12, and 8 participants had 19, 12, and 8 study-defined serious adverse events, respectively, and 4 of 19 events occurred during the second round of rifapentine and isoniazid. In the annual rifapentine–isoniazid group, 2 hypersensitivity reactions and 1 flu-like reaction occurred; however, none were experienced in the single-round rifapentine–isoniazid group.

DISCUSSION

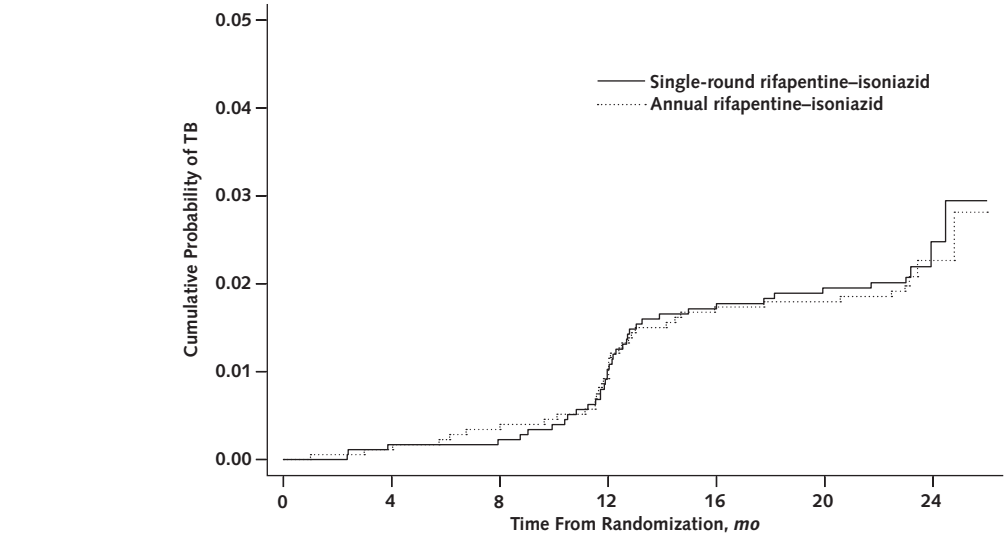
Among persons with HIV infection taking antiretroviral therapy in settings with high tuberculosis burden, treatment completion of tuberculosis preventive therapy with weekly rifapentine and isoniazid for 3 months was substantially higher than the standard 6-month course of isoniazid preventive therapy. Uptake and treatment completion of a second round of rifapentine and isoniazid were high but did not further reduce tuberculosis incidence.

Treatment completion is an important determinant of the effectiveness of tuberculosis preventive therapy. In published trials, treatment completion of directly observed short-course regimens was higher than that seen with 6 to 9 months of self-administered preventive therapy (7, 10, 11). In a systematic review of weekly rifapentine–isoniazid regimens, treatment completion of self-administered therapy was similar to that for directly observed treatment (12), and the World Health Organization (WHO) recommends self-administered short-course preventive therapy (13).

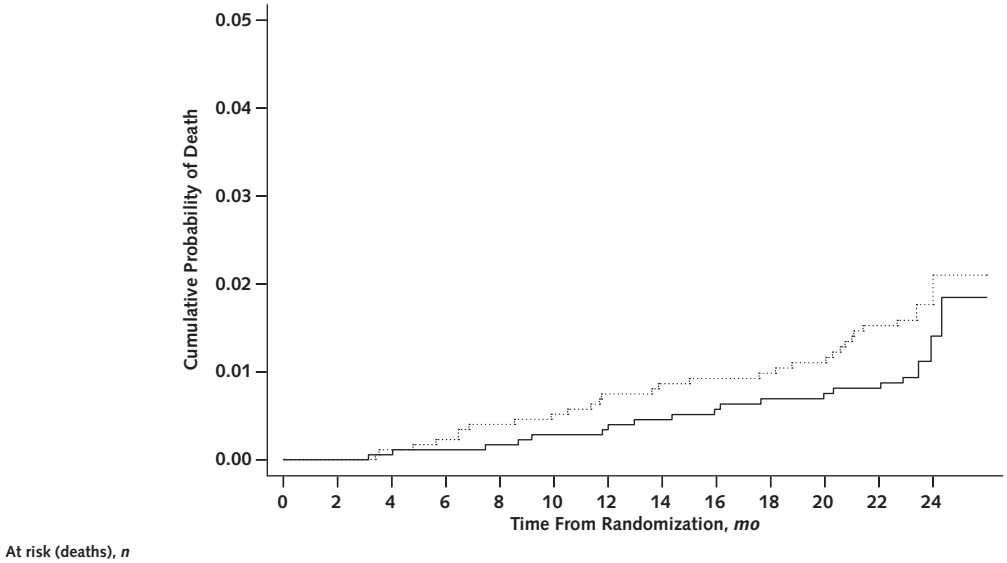
The duration of protection from 6 months of isoniazid preventive therapy among persons with HIV infection living in settings with high tuberculosis burden in the pre–antiretroviral therapy era was limited (1, 2). Many studies evaluated prolonged isoniazid preventive therapy as a means of extending the duration of protection among persons with HIV infection living in high-burden

countries at a time when antiretroviral therapy was starting to be used. Among persons with HIV infection with a positive tuberculin skin test result living in Botswana, 36 months of isoniazid was superior to 6 months of isoniazid preventive therapy. After completion of 36 months of isoniazid, the risk for tuberculosis grew despite increasing access to antiretroviral therapy (3, 4). In South Africa, among adults with HIV infection with a positive tuberculin skin test result, the majority of whom were not taking antiretroviral therapy, continuous isoniazid preventive therapy was not superior to 6 months of isoniazid or a single round of weekly isoniazid and rifapentine for 3 months (7). Furthermore, treatment completion was higher and serious adverse events were less frequent with short-course versus continuous isoniazid preventive therapy. In India, among adults with HIV infection with a positive tuberculin skin test result, 36 months of isoniazid showed a trend toward superiority compared with 6 months of isoniazid and ethambutol (14). On the basis of these data, the WHO made a conditional recommendation for isoniazid preventive therapy for at least 36 months for persons with HIV infection living in settings

Figure 2. Kaplan–Meier curves.



At risk (TB events), *n*													
Annual rifapentine–isoniazid	1808	(2)	1742	(5)	1725	(10)	1708	(13)	1659	(1)	1642	(5)	292
Single-round rifapentine–isoniazid	1802	(3)	1755	(1)	1748	(14)	1731	(12)	1662	(4)	1648	(4)	326



At risk (deaths), *n*													
Annual rifapentine–isoniazid	1808	(2)	1742	(5)	1729	(6)	1717	(3)	1663	(3)	1643	(9)	293
Single-round rifapentine–isoniazid	1802	(1)	1756	(2)	1750	(3)	1746	(4)	1662	(3)	1649	(5)	327

TB = tuberculosis. **Top.** Tuberculosis incidence from months 0 to 24, by annual and single-round rifapentine–isoniazid groups. **Bottom.** Mortality from months 0 to 24, by annual and single-round rifapentine–isoniazid groups.

Table 4. Study-Defined Adverse Events (Excluding Deaths), by Study Group

Study-Defined Adverse Events (Grades 3 to 5)	Single-Round Rifapentine–Isoniazid Group (*n* = 12)	Annual Rifapentine–Isoniazid Group (*n* = 17)	Isoniazid Group (*n* = 8)	Total (*n* = 37)
Total	12	19*†	8	39
Hypersensitivity reaction	0	2	0	2
Peripheral neuropathy	1	1	0	2
Psychosis	1	0	1	2
Seizure	2	2	0	4
Hepatitis	8	13	7	28
Flu-like illness	0	1	0	1
Serious‡	3	4	1	8

* One participant had 2 cases of hepatitis, and 1 participant had 2 seizures.
† Four of 19 events in the annual rifapentine–isoniazid group occurred during the second round of rifapentine–isoniazid (seizure, flu-like illness, drug-induced liver injury, and hypersensitivity reaction).
‡ Includes 2 life-threatening related events (1 case of hepatitis and 1 hypersensitivity reaction, both in the annual rifapentine–isoniazid group) and 6 hospitalizations (2 in the annual rifapentine–isoniazid group [1 case of peripheral neuropathy and 1 hypersensitivity reaction], 3 in the single-round rifapentine–isoniazid group [1 case of peripheral neuropathy, 1 psychotic episode, and 1 seizure], and 1 in the isoniazid group [1 psychotic episode]).

with high tuberculosis incidence in 2011 (8). In contrast to the studies of prolonged isoniazid preventive treatment, our trial evaluated a strategy of periodic tuberculosis preventive therapy using an annual, short-course regimen to achieve long-term protection while reducing the burden to patients and programs. An additional round of short-course preventive therapy given approximately 1 year after the first round did not provide additional benefit in preventing tuberculosis among persons receiving antiretroviral therapy.

The prevalence of rifampin-resistant tuberculosis among participants who developed tuberculosis was 10.5%, which is within the range of rifampin resistance seen in sub-Saharan Africa among previously treated patients with tuberculosis (**Table 10** of **Supplement 1**). A second round of rifapentine and isoniazid was not associated with a greater risk for rifampin-resistant tuberculosis.

Several factors may contribute to a lack of effectiveness of a second course of rifapentine and isoniazid. Trials have shown the benefit of tuberculosis preventive therapy combined with antiretroviral therapy for preventing tuberculosis (6, 10, 15–17). In contrast to the other studies evaluating prolonged isoniazid preventive therapy, all participants in our study were receiving antiretroviral therapy from enrollment and had a high median CD4 count at enrollment. The WHIP3TB participants may therefore have been less susceptible to reinfection and development of tuberculosis than participants in earlier trials. In low- to medium-burden countries, a single round of preventive therapy provides durable protection against tuberculosis (18, 19). More recently, the BRIEF-TB (Brief Rifapentine Isoniazid Efficacy for Tuberculosis) trial showed that among adolescents and adults with HIV infection, 1 month of daily rifapentine and isoniazid combined with ready access to antiretroviral therapy provides durable protection against tuberculosis in high-burden countries (16). Since the WHIP3TB trial was designed, the rates of HIV-associated tuberculosis have declined in all 3 participating countries, primarily due to the scale-up of antiretroviral therapy (20). Mathematical modeling suggests that, among persons with HIV infection, most tuberculosis that occurs after preventive therapy is due to reinfection (21). Annual short-course preventive therapy having little effect on tuberculosis incidence may therefore be the result of a lower risk for reinfection because of the reduced tuberculosis transmission in our participating countries (**Table 11** of **Supplement 1**).

Our study had several limitations. It was designed as a pragmatic clinical trial, which resulted in differences in the number of dispensing visits and observed doses in the short rifapentine–isoniazid groups compared with the long isoniazid group. The higher treatment completion rate in the combined rifapentine–isoniazid groups compared with the isoniazid group may have been due in part to study medication being directly observed at dispensing visits, which would have resulted in 25% (3 of 12) of rifapentine–isoniazid and 2% (4 of 182) of isoniazid doses being directly observed.

Completion of isoniazid preventive treatment was substantially lower in South Africa than in Ethiopia and Mozambique, consistent with routine program data over the same period. Among more than 500 000 persons with HIV infection who initiated isoniazid preventive therapy between 2017 and 2019 in 27 South African districts supported by the President's Emergency Plan For AIDS Relief, the proportion completing at least 6-month treatment was 38% in 2017, 47% in 2018, and 55% in 2019 (22). Due to limited availability, only a small proportion of participants used electronic medication monitors, which did not modify treatment completion by study group.

Because the study was a pragmatic clinical trial, tuberculosis screening at enrollment was aligned to the 2011 WHO 4-symptom screen, which had a sensitivity of 79%, and the in-country tuberculosis screening policies, which did not include chest radiographic screening (23). The WHO tuberculosis screening guidelines were updated in 2021 on the basis of a systematic review and meta-analysis that found that the 4-symptom screen among outpatients with HIV infection who were receiving antiretroviral therapy had a sensitivity of only 53% (24). Because all of our participants were receiving antiretroviral therapy at enrollment, on the basis of this recent analysis, symptom screening alone at enrollment may have missed a significant amount of active tuberculosis, which was subsequently detected at the 12-month screen.

Screening at month 12 identified a substantial number of participants with asymptomatic tuberculosis in both groups who would not have been identified using

routine symptom-based screening alone. If rifapentine–isoniazid is effective in curing subclinical tuberculosis, the intensive tuberculosis screening at month 12 may have reduced its effectiveness; however, it would not undermine the effectiveness of rifapentine–isoniazid in treating tuberculous infection, which is its predominant mechanism of action. The reasons for the higher mortality in the annual short-course preventive therapy group in the first year are not evident and may be due to chance. The measured tuberculosis incidence in the single-round rifapentine–isoniazid group was substantially lower than the assumed cumulative incidence of 5% over a 24-month period used in our sample size calculation.

In conclusion, treatment completion was much higher with 3 months of self-administered rifapentine and isoniazid compared with 6 months of isoniazid preventive therapy. In settings with high tuberculosis transmission and high antiretroviral therapy uptake, an additional round of short-course preventive therapy 1 year later did not provide additional benefit in reducing tuberculosis incidence.

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Data Sharing Statement: The following data will be made available with publication: deidentified participant data. The data are accessible at https://datacompass.lshtm.ac.uk. Requests to use the data should be sent to gchurchyard@auruminstitute.org. The data will be made available to researchers whose proposed use of the data has been approved. Data may be used as specified in the proposal after its approval.

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References

1. **Johnson JL, Okwera A, Hom DL, et al; Uganda-Case Western Reserve University Research Collaboration.** Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. AIDS. 2001;15:2137-47. [PMID: 11684933] doi:10.1097/00002030-200111090-00009
2. **Quigley MA, Mwinga A, Hosp M, et al.** Long-term effect of preventive therapy for tuberculosis in a cohort of HIV-infected Zambian adults. AIDS. 2001;15:215-22. [PMID: 11216930] doi:10.1097/00002030-200101260-00011
3. **Samandari T, Agizew TB, Nyirenda S, 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;377:1588-98. [PMID: 21492926] doi:10.1016/S0140-6736(11)60204-3
4. **Samandari T, Agizew TB, Nyirenda S, et al.** Tuberculosis incidence after 36 months' isoniazid prophylaxis in HIV-infected adults in Botswana: a posttrial observational analysis. AIDS. 2015;29:351-9. [PMID: 25686683] doi:10.1097/QAD.0000000000000535
5. **Churchyard GJ, Fielding KL, Lewis JJ, et al; Thibela TB Study Team.** A trial of mass isoniazid preventive therapy for tuberculosis control. N Engl J Med. 2014;370:301-10. [PMID: 24450889] doi:10.1056/NEJMoa1214289
6. **Rangaka MX, Wilkinson RJ, Boulle A, et al.** Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. Lancet. 2014;384:682-90. [PMID: 24835842] doi:10.1016/S0140-6736(14)60162-8
7. **Martinson NA, Barnes GL, Moulton LH, et al.** New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med. 2011;365:11-20. [PMID: 21732833] doi:10.1056/NEJMoa1005136
8. **World Health Organization.** Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. 2011. Accessed at https://apps.who.int/iris/handle/10665/44472 on 20 February 2021.
9. **National Institute of Allergy and Infectious Diseases.** Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. National Institutes of Health; 2017.
10. **Sterling TR, Villarino ME, Borisov AS, et al; TB Trials Consortium PREVENT TB Study Team.** Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011;365:2155-66. [PMID: 22150035] doi:10.1056/NEJMoa1104875

11. **Sterling TR, Scott NA, Miro JM, et al; Tuberculosis Trials Consortium, the AIDS Clinical Trials Group for the PREVENT TB Trial (TBTC Study 26ACTG 5259).** Three months of weekly rifapentine and isoniazid for treatment of Mycobacterium tuberculosis infection in HIV-coinfected persons. AIDS. 2016;30:1607-15. [PMID: 27243774] doi:10.1097/QAD.0000000000001098
12. **Njie GJ, Morris SB, Woodruff RY, et al.** Isoniazid-rifapentine for latent tuberculosis infection: a systematic review and meta-analysis. Am J Prev Med. 2018;55:244-252. [PMID: 29910114] doi:10.1016/j.amepre.2018.04.030
13. **World Health Organization.** Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. 2018. License: CC BY-NC-SA 3.0 IGO. Accessed at https://apps.who.int/iris/handle/10665/260233 on 20 February 2021.
14. **Swaminathan S, Menon PA, Gopalan N, et al.** Efficacy of a six-month versus a 36-month regimen for prevention of tuberculosis in HIV-infected persons in India: a randomized clinical trial. PLoS One. 2012;7:e47400. [PMID: 23251327] doi:10.1371/journal.pone.0047400
15. **Hakim J, Musiime V, Szubert AJ, et al; REALITY Trial Team.** Enhanced prophylaxis plus antiretroviral therapy for advanced HIV infection in Africa. N Engl J Med. 2017;377:233-245. [PMID: 28723333] doi:10.1056/NEJMoa1615822
16. **Swindells S, Ramchandani R, Gupta A, 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. [PMID: 30865794] doi:10.1056/NEJMoa1806808
17. **Danel C, Moh R, Gabillard D, et al; TEMPRANO ANRS 12136 Study Group.** A trial of early antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med. 2015;373:808-22. [PMID: 26193126] doi:10.1056/NEJMoa1507198
18. **Gordin F, Chaisson RE, Matts JP, et al.** Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health Organization, and the Centers for Disease Control and Prevention Study Group. JAMA. 2000;283:1445-50. [PMID: 10732934] doi:10.1001/jama.283.11.1445
19. **Golub JE, Cohn S, Saraceni V, et al.** Long-term protection from isoniazid preventive therapy for tuberculosis in HIV-infected patients in a medium-burden tuberculosis setting: the TB/HIV in Rio (THRio) study. Clin Infect Dis. 2015;60:639-45. [PMID: 25365974] doi:10.1093/cid/ciu849
20. **World Health Organization.** Global Tuberculosis Report 2019. License: CC BY-NC-SA 3.0 IGO. Accessed at https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf on 20 February 2021.
21. **Sumner T, Houben RM, Rangaka MX, et al.** Post-treatment effect of isoniazid preventive therapy on tuberculosis incidence in HIV-infected individuals on antiretroviral therapy. AIDS. 2016;30:1279-86. [PMID: 26950316] doi:10.1097/QAD.0000000000001078
22. **Motlhaoleng K, Ndlovu M, Chiliade P, et al.** Implementation of Tuberculosis Preventive Treatment (TPT) in South Africa: the urgent need to address gaps. Presented at the 51st Union World Conference on Lung Health, Virtual, 20–24 October 2020. Poster EP22-307-23.
23. **World Health Organization.** Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. 2011. Accessed at https://apps.who.int/iris/bitstream/handle/10665/44472/9789241500708_eng.pdf?sequence=1&isAllowed=y on 20 February 2021.
24. **World Health Organization.** WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease. 2020. Accessed at https://www.who.int/publications/i/item/9789240022676 on 20 February 2021.

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