WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment

ANNEX 2

GRADE summary of evidence tables (for new recommendations in 2018 & 2019 guidelines updates)

THE END TB STRATEGY

World Health Organization

WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment

Annex 2. GRADE summary of evidence tables (for new recommendations in 2018 & 2019 guidelines updates)

World Health Organization

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PICO 1: What is the prevalence of LTBI, risk of progression to active TB and cumulative prevalence of active TB among household contacts without HIV in different age groups in high TB incidence countries?

Is the prevalence of TB and LTBI higher among household contacts without HIV, compared to the general population, in different age groups in high TB incidence countries?

Quality assessment						No. LTBI+/No. tested		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	0–5 years	RR (95% CI)	Absolute per 1000 (95% CI)		
AGE GROUPS COMPARED: 5–10 YEARS VS 0–5 YEARS											
14 *(1–14)*	Cross-sectional	Not serious[1,2]	Serious[3]	Not serious	Not serious[4]	2265/ 8507	1298/ 9526	1.62 (1.25;2.11)	85.1 (34.2;151.1)	Moderate	Important
AGE GROUPS COMPARED: 10–15 YEARS VS 0–5 YEARS											
11 *(1,3,5,7–14)*	Cross-sectional	Not serious[5]	Serious[6]	Not serious	Not serious[7]	2616/ 6782	1093/ 9005	2.33 (1.55;3.50)	161.6 (67.2;303.3)	Moderate	Important
AGE GROUPS COMPARED: 5–15 YEARS VS 0–5 YEARS											
16 *(3,5,8, 10,12,15–25)*	Cross-sectional	Serious[8]	Serious[9]	Not serious	Not serious[10]	3709/ 8772	1605/ 5095	1.32 (1.11;1.56)	99.7 (34.9;176.5)	Low	Important
AGE GROUPS COMPARED: > 15 YEARS VS 0–5 YEARS											
19 *(3–5,8–10, 12–14,16,17, 19,20–26)*	Cross-sectional	Not serious[11]	Serious[12]	Not serious	Not serious[13]	13218/ 21962	1979/ 6763	2.04 (1.53;2.63)	293.9 (155.1;475.7)	Moderate	Important

1 Potential selection bias in *(2)*, as only 69% of participants were household contacts.
2 Potential misclassification: Eight studies *(3–5,7,10,11,13,14)* did not indicate whether household contacts with active TB were excluded from the analysis or did not provide sufficient data to calculate the number of household contacts with active TB per age stratum.
3 High heterogeneity among studies (I^2 = 94%) probably due to difference in background TB incidence. Risk ratios of two studies *(1,5)* showed opposite effect.
4 Small sample size in *(5)* (n < 50).
5 Potential misclassification: Seven studies *(3,5,6,10,11,13,14)* did not indicate whether household contacts with active TB were excluded from the analysis or did not provide sufficient data to calculate the number of household contacts with active TB per age stratum.
6 High heterogeneity among studies (I^2 = 97%) probably due to the differences in background TB incidence. Risk ratio of one study *(5)* showed opposite effect.
7 Wide confidence interval of pooled risk ratio. Small sample sizes in *(5)* (n < 50) and *(12)* (n < 100).
8 Potential selection bias in *(15)*, as only 89% of participants were household contacts.
9 High heterogeneity among studies (I^2 = 93%) probably due to differences in background TB incidence. Risk ratios in three studies showed opposite effects *(5,19,21)*.
10 Small sample size in *(5)* and *(18)* (n < 50).
11 Potential misclassification: Ten studies *(3–5,10,13,14,20,21,23,26)* did not indicate whether household contacts with active TB were excluded from the analysis or did not provide sufficient data to calculate the number of household contacts with active TB per age stratum.
12 High heterogeneity among studies (I^2 = 98%) probably due to differences in background TB incidence.
13 Small sample sizes in *(5)* and *(26)* (n < 100).

Development of active TB in household contacts with LTBI in high TB incidence countries

Quality assessment							No of contacts (active TB/no. LTBI)		Effect		Quality	Importance
No, of studies	Design	Risk of bias	Limitations	Inconsistency	Indirectness	Imprecision	Comparator	0–5 years	RR (95% CI)	Absolute per 1000 (95% CI)		
AGE GROUPS COMPARED: 5–15 YEARS VS 0–5 YEARS												
4 *(8,13,15,16)*	Cohort	Not serious	Not serious	Serious[1]	Not serious	Serious[2]	54/1329	73/630	0.28 (0.12;0.65)	83.8 (40.3;102.3)	Low	Critical
AGE GROUPS COMPARED: > 15 YEARS VS 0–5 YEARS												
3 *(8,13,16)*	Cohort	Not serious	Not serious	Serious[3]	Not serious	Not serious	186/4746	73/595	0.22 (0.08;0.60)	95.5 (49.1;112.6)	Moderate	Critical

Because of the small number of studies in the other categories, only data from studies with a follow-up of 1–2 years in high TB incidence countries are presented in the table.

1 Serious inconsistencies due to heterogeneity (I^2 = 71%): One study showed an increased risk in the age group 5–15 years. This was not observed in the other studies.

2 Small number of events.

3 High heterogeneity among studies probably due to differences in background TB incidence and methods used to diagnose active TB (I^2 = 89.3%).

Cumulative prevalence of active TB in household contacts irrespective of baseline LTBI status in high TB incidence countries

Quality assessment							No of contacts (active TB/total no. contacts)		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Limitations	Inconsistency	Indirectness	Imprecision	Comparator	0–5 years	RR (95% CI)	Absolute per 1000 (95%CI)		
AGE GROUPS COMPARED: 5–15 YEARS VS 0–5 YEARS												
6 *(8,13,15, 16,18,27)*[1]	Cohort	Not serious	Not serious	Serious[2]	Not serious	Not serious	131/4389	203/2903	0.39 (0.18;0.85)	42.9 (10.6;57.6)	Moderate	Important
AGE GROUPS COMPARED: >15 YEARS VS 0–5 YEARS												
4 *(8,13,16,27)*	Cohort	Not serious	Not serious	Not serious	Not serious	Not serious	417/10856	192/2764	0.68 (0.56;0.83)	22 (12.1;30.3)	High	Important

Owing to the small number of studies in the other categories, only data from studies with a follow-up of 1–2 years in high TB incidence countries are presented in the table.

1 One outlier *(28)* was excluded because of uncertainty about the cases included (co-prevalent vs incident cases).

2 High heterogeneity among studies (I^2 = 87.6%), probably due to the difference in background TB incidence.

Active TB in household contacts with LTBI and in the general population in high-TB incidence countries (12 months)

ACTIVE TB DISEASE IN HOUSEHOLD CONTACTS WITH LTBI INFECTION IN HIGH TB INCIDENCE COUNTRIES COMPARISON WITH THE GENERAL POPULATION (FOLLOW-UP OF 12 MONTHS)											
Quality assessment						No. of contacts (active TB/no. LTBI)		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	General population[1]	RR (95% CI)	Absolute per 1000 (95% CI)		
COMPARISON: HOUSEHOLD CONTACTS AGED 0–5 YEARS VS GENERAL POPULATION											
2 *(8,15)*	Cohort	Serious[2]	Serious[3]	Not serious	Very serious[4]	0/35	41/10 000	24.32 (0.73;811.02)	63 (–0.7;2187.1)	Very low	Critical
						32/230	13/10 000				
COMPARISON: HOUSEHOLD CONTACTS AGED 5–9 YEARS VS GENERAL POPULATION											
1 *(8)*	Cohort	Serious[2]	Not serious	Not serious	Serious[6]	12/298	13/10 000	30.98 (14.26;67.31)	39 (17.2;86.2)	Low	Critical
COMPARISON: HOUSEHOLD CONTACTS AGED 10–14 YEARS VS GENERAL POPULATION											
1 *(8)*	Cohort	Serious[2]	Not serious	Not serious	Serious[6]	26/363	13/10 000	55.1 (28.55;106.33)	70.3 (35.8;136.9)	Low	Critical
COMPARISON: HOUSEHOLD CONTACTS AGED 5–15 YEARS VS GENERAL POPULATION											
2 *(8,15)*	Cohort	Serious[2]	Not serious[5]	Not serious	Serious[6]	4/67	41/10 000	27.13 (17.47;54.07)	70.5 (21.3;220.7)	Low	Critical
						38/661	13/10 000				
COMPARISON: HOUSEHOLD CONTACTS AGED > 15 YEARS VS GENERAL POPULATION											
1 *(8)*	Cohort	Serious[3]	Not serious	Not serious	Serious[6]	155/3879	13/10 000	30.74 (17.46;54.07)	38.7 (21.4;69)	Low	Critical

1 LTBI does not apply to the general population.
2 Ascertainment bias highly likely, as TB cases in the general population detected passively, while TB cases in contacts detected actively. As a result, the relative and absolute risks might be overestimated. The composition of the general and the study population differed (general population of all ages versus a specific age group).
3 High heterogeneity among studies (I^2 = 83.9%), probably due to differences in background TB incidence.
4 Serious imprecision with a wide confidence interval for the effect estimates, probably due to small study size and number of outcome events.
5 I^2 = 72.5%, indicating moderate heterogeneity, probably due to differences in background TB prevalence; however, there is a trend across age groups and studies.
6 Few events and wide CI.

Active TB in household contacts with LTBI compared with general population in high-TB incidence countries (24 months)

ACTIVE TB DISEASE IN HOUSEHOLDS OF CONTACTS WITH LTBI INFECTION IN HIGH-TB INCIDENCE COUNTRIES COMPARISON WITH THE GENERAL POPULATION (FOLLOW-UP ≤ 24 MONTHS)[1]											
Quality assessment						No of contacts (active TB/no. LTBI)		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	General pop[2]	RR (95% CI)	Absolute per 1000 (95% CI)		
COMPARISON: HOUSEHOLD CONTACTS AGED 0–5 YEARS VS GENERAL POPULATION											
3 *(8,15,16)*	Cohort	Serious[3]	Serious[4]	Not serious	Serious[5]	0/35	82/10 000	22.87 (7.65;68.63)	108.6 (33;334.6)	Very low	Important
						26/320	41/10 000				
						32/230	26/10 000				
COMPARISON: HOUSEHOLD CONTACTS AGED 5–9 YEARS VS GENERAL POPULATION											
1 *(8)*	Cohort	Serious[3]	Not serious	Not serious	Serious[5]	12/298	26/10 000	15.49 (7.89;30.4)	37.7 (17.9;76.4)	Low	Important
COMPARISON: HOUSEHOLD CONTACTS AGED 10–14 YEARS VS GENERAL POPULATION											
1 *(8)*	Cohort	Serious[3]	Not serious	Not serious	Serious[5]	26/363	26/10 000	27.55 (16.16;46.96)	69 (39.4;119.5)	Low	Important
COMPARISON: HOUSEHOLD CONTACTS AGED 5–15 YEARS VS GENERAL POPULATION											
3 *(8,15,16)*	Cohort	Serious[3]	Serious[6]	Not serious	Serious[5]	4/67	82/10 000	8.22 (2.3;29.36)	35.8 (6.5;140.8)	Very low	Important
						6/475	41/10 000				
						38/661	26/10 000				
COMPARISON: HOUSEHOLD CONTACTS AGED OVER 15 YEARS VS GENERAL POPULATION											
2 *(8,16)*	Cohort	Serious[3]	Not serious[7]	Not serious	Not serious	26/571	41/10 000	13.35 (9.46;18.83)	41.4 (28.3;59.7)	Moderate	Important
						155/3879	26/10 000				

1 These comparisons included studies with a maximum follow-up of 24 months; therefore, TB incidence in the general population was multiplied by a factor of 2 to estimate the number of cases occurring during 24 months.
2 LTBI does not apply to the general population.
3 Ascertainment bias highly likely: TB cases in the general population detected passively, while TB cases in the contacts detected actively. As a result, relative and absolute risks might be overestimated. The composition of the general and study populations differs (general population of all ages versus a specific age group). TB incidence in the population was estimated by multiplying the yearly notification rate by a factor of 2.
4 High heterogeneity between studies probably due to difference in background TB incidence (I^2 = 84.4%).
5 Few events and wide CI.
6 I^2 = 88.1%, indicating high heterogeneity probably due to difference in background TB prevalence; however, there is a trend across age groups and studies.
7 I^2 = 16%.

Active TB in household contacts irrespective of LTBI status compared with general population in high TB incidence countries (12 months)

CUMULATIVE PREVALENCE OF ACTIVE TB IN HOUSEHOLD CONTACTS IRRESPECTIVE OF BASELINE LTBI STATUS IN HIGH TB INCIDENCE COUNTRIES COMPARISON WITH THE GENERAL POPULATION (FOLLOW-UP OF 12 MONTHS)											
Quality assessment						No. of contacts (active TB/total)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	General pop	RR (95% CI)	Absolute risk per 1000 (95% CI)		
COMPARISON: HOUSEHOLD CONTACTS AGED 0–5 YEARS VS GENERAL POPULATION											
3 *(8,15,18)*	Cohort	Serious[1]	Not serious[2]	Not serious	Serious[3]	2/31	28/10 000	25.86 (16.87;39.66)	68 (43.4;105.7)	Low	Important
						9/108	41/10 000				
						73/1791	13/10 000				
COMPARISON: HOUSEHOLD CONTACTS AGED 5–9 YEARS VS GENERAL POPULATION											
1 *(8)*	Cohort	Serious[1]	Not serious	Not serious	Serious[3]	35/1464	13/10 000	18.39 (9.75;34.68)	22.6 (11.4;43.8)	Low	Important
COMPARISON: HOUSEHOLD CONTACTS AGED 10–14 YEARS VS GENERAL POPULATION											
1 *(8)*	Cohort	Serious[1]	Not serious	Not serious	Serious[3]	45/1340	13/10 000	25.83 (13.97;47.76)	32.3 (16.9;60.8)	Low	Important
COMPARISON: HOUSEHOLD CONTACTS AGED 5–15 YEARS VS GENERAL POPULATION											
3 *(8,15,18)*	Cohort	Serious[1]	Not serious[2]	Not serious	Serious[3]	8/102	28/10 000	24.11 (16.89;34.43)	63.2 (43.4;91.4)	Low	Important
						16/161	41/10 000				
						80/2804	13/10 000				
COMPARISON: HOUSEHOLD CONTACTS AGED OVER 15 YEARS VS GENERAL POPULATION											
1 *(8)*	Cohort	Serious[1]	Not serious	Not serious	Not serious	301/9380	13/10 000	24.68 (14.18;42.98)	30.8 (17.1;54.6)	Moderate	Important

[1] Ascertainment bias highly likely, as TB cases in the general population detected passively, while TB cases in the contacts detected actively. As a result, the relative and absolute risk might be overestimated. The composition of the general and study populations differs (general population of all ages versus a specific age group).

[2] $I^2 = 0\%$.

[3] Few events and wide CI.

Active TB in household contacts irrespective of LTBI status compared with general population in high-TB incidence countries (24 months)

CUMULATIVE PREVALENCE OF ACTIVE TB IN HOUSEHOLD CONTACTS IRRESPECTIVE OF BASELINE LTBI STATUS IN HIGH-TB INCIDENCE COUNTRIES COMPARISON WITH THE GENERAL POPULATION (FOLLOW-UP OF 24 MONTHS)[1]											
Quality assessment						No of contacts (active TB/total no. contacts)		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	General population	RR (95% CI)	Absolute risk per 1000 (95% CI)		
COMPARISON: HOUSEHOLD CONTACTS AGED 0–5 YEARS VS GENERAL POPULATION											
5 *(8,15,16, 18,27)*	Cohort	Serious[2]	Not serious[3]	Not serious	Serious[4]	2/31	55/10 000	14.8 (9.82;22.3)	83.9 (53.6;129.5)	Low	Important
						37/335	100/10 000				
						9/108	82/10 000				
						55/508	41/10 000				
						73/1791	26/10 000				
COMPARISON: HOUSEHOLD CONTACTS AGED 5–9 YEARS VS GENERAL POPULATION											
1 *(8)*	Cohort	Serious[2]	Not serious	Not serious	Serious[4]	35/1464	26/10 000	9.2 (5.55;15.23)	21.3 (11.8;37)	Low	Important
COMPARISON: HOUSEHOLD CONTACTS AGED 10–14 YEARS VS GENERAL POPULATION											
1 *(8)*	Cohort	Serious[2]	Not serious	Not serious	Serious[4]	45/1340	26/10 000	12.92 (8.0;20.86)	31 (18.2;51.6)	Low	Important
COMPARISON: HOUSEHOLD CONTACTS AGED 5–15 YEARS VS GENERAL POPULATION											
5 *(8,15,16, 18,27)*	Cohort	Serious[2]	Serious[5]	Not serious	Not serious	8/102	55/10 000	6.29 (2.88;13.72)	32.2 (11.4;77.4)	Low	Important
						5/439	100/10 000				
						16/161	82/10 000				
						10/691	41/10 000				
						80/2804	26/10 000				
COMPARISON: HOUSEHOLD CONTACTS AGED OVER 15 YEARS VS GENERAL POPULATION											
3 *(8,16,27)*	Cohort	Serious[2]	Not serious[6]	Not serious	Not serious	34/432	100/10000	11.67 (7.55;18.02)	59.4 (36.5;94.7)	Moderate	Important
						49/719	41/10000				
						301/9380	26/10000				

[1] These comparisons are based on studies with a maximum follow-up of 24 months; therefore, TB incidence in the general population was multiplied by a factor of 2 to estimate the number of cases occurring during 24 months.
[2] Ascertainment bias highly likely, as TB cases in the general population detected passively, while TB cases in the contacts detected actively. As a result, the relative and absolute risks might be overestimated. The composition of the general and study populations differs (general population of all ages versus a specific age group). TB incidence in the population was estimated by multiplying the yearly notification rate by a factor of 2.
[3] Moderate heterogeneity among studies (I^2 = 67.1%) probably due to differences in background TB incidence.
[4] Few events and wide CI.
[5] High heterogeneity among studies (I^2 = 87.5%) probably due to differences in background TB incidence.
[6] Moderate heterogeneity among studies (I^2 = 72.5%) probably due to differences in background TB incidence.

PICO 2: What is the accuracy of WHO symptomatic screening to exclude active TB in individuals with HIV on antiretroviral treatment (ART)?

Four-symptom screening plus chest radiographic findings to exclude active TB in individuals with HIV

Population: Adults and adolescents with HIV on ART

Sensitivity	0.85 (95% CI: 0.70;0.93)				
Specificity	0.30 (95% CI: 0.26;0.33)	Prevalence	1%	5%	10%

Outcome	Nos of studies and patients	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients tested			Test accuracy Quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability, 1%	Pre-test probability, 5%	Pre-test probability, 10%	
True positives (patients with active TB)	2 studies 646 patients	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Serious[1]	None[2]	8 (7–9)	42 (35–46)	85 (70–93)	⨁⨁⨁◯ Moderate
False negatives (patients incorrectly classified as not having active TB)								2 (1–3)	8 (4–15)	15 (7–30)	
True negatives (patients without active TB)	2 studies 646 patients	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None[2]	295 (260–327)	283 (250–314)	268 (237–297)	⨁⨁⨁⨁ High
False positives (patients incorrectly classified as having active TB)								695 (663–730)	667 (636–700)	632 (603–663)	

From references *(29,30)*

[1] Imprecise estimate for sensitivity. Downgraded by one.

[2] The possibility of publication bias is not excluded, but it was not considered of sufficient concern to downgrade.

PICO 3: What is the accuracy of symptomatic screening and/or chest x-ray to exclude active TB in contacts of pulmonary TB cases without HIV in high TB incidence countries?

Chest radiographic findings for exclusion of active TB in contacts of TB cases without HIV in high-TB incidence countries

Index test: Chest X-ray. Any abnormality | Reference test: Sputum culture and/or smear
Place of testing: Triage
Test–treatment pathway: Chest X-ray positive → confirmatory test (mycobacterial culture or GeneXpert) → anti-TB chemotherapy (6–9 months' antibiotics)

Outcome	Nos of studies and patients	Study design	Factors that may decrease quality of evidence					Effect per 10 000 Sensitivity: 0.94 (95% CI: 0.86;0.98) Specificity: 0.87 (95% CI: 0.80;0.92)	Quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with active TB)	7 studies 251 410 patients	Cross-sectional (cohort type accuracy study)	Serious[1]	Not serious[2]	Not serious[3]	Not serious[4]	None[5]	Prevalence (2%): 1882 (1716;1954) Prevalence (5%): 4705 (4290;4885	⨁⨁⨁◯ Moderate
False negatives (patients incorrectly classified as not having active TB)								Prevalence (2%) : 118 (46;284) Prevalence (5%): 295 (115;710)	
True negatives (patients without active TB)	7 studies 251 410 patients	Cross-sectional (cohort type accuracy study)	Serious[1]	Not serious[2]	Not serious[3]	Not serious[4]	None[5]	Prevalence (2%) : 85 064 (78 106;89 866) Prevalence (5%): 82 460 (75 715;87 115)	⨁⨁⨁◯ Moderate
False positives (patients incorrectly classified as having active TB)								Prevalence (2%) : 12 936 (8134;19 894) Prevalence (5%): 12 540 (7 885;19 285)	

From references *(31–37)*

1 Limitations in study design (see QUADAS-2): High risk of selection bias in one study *(31)*. In all studies, less than half of participants received the reference standard; accuracy was calculated under the assumption that those who did not receive the reference standard were culture and/or smear negative (no active TB).
2 Indirectness (see QUADAS-2): Some concern about applicability of reference standard in 2 studies – no downgrading.
3 Inconsistency: Little heterogeneity for sensitivity and specificity (based on visual inspection of CIs).
4 Imprecision: Precise estimates for sensitivity and specificity.
5 Publication bias: Not applicable (the evidence base for publication bias in studies of diagnostic test accuracy is very limited).

Any symptom for exclusion of active TB in contacts of TB cases without HIV in high-TB incidence countries.

Index text: Any symptom | Reference test: Sputum culture and/or smear
Place of testing: Triage
Test–treatment pathway: Symptom positive → confirmatory test (mycobacterial culture or GeneXpert) → anti-TB chemotherapy (6–9 months' antibiotics)

Outcome	Nos of studies and patients	Study design	Factors that may decrease quality of evidence					Effect per 10 000 Sensitivity: 0.73 (95% CI: 0.64;0.80) Specificity: 0.77 (95% CI: 0.61;0.87)	Quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with active TB)	11 studies 357 609 patients	Cross-sectional (cohort type accuracy study)	Very serious[1]	Not serious[2]	Not serious[3]	Not serious[4]	None[5]	Prevalence (2%): 1460 (1282;1608) Prevalence (5%): 3650 (3205;4020)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having active TB)								Prevalence (2%): 540 (392;718) Prevalence (5%):1350 (980;1795)	
True negatives (patients without active TB)	11 studies 357 609 patients	Cross-sectional (cohort type accuracy study)	Very serious[1]	Not serious[2]	Serious[3]	Serious[4]	None[5]	Prevalence (2%):74 970 (60 074;85 260) Prevalence (5%):72 675 (58 235;82 650)	⨁◯◯◯ Very low
False positives (patients incorrectly classified as having active TB)								Prevalence (2%):23 030 (12 740;37 926) Prevalence (5%):22 325 (12 350;36 765)	

From references *(31–34,36,38–43)*

1 Limitations in study design (see QUADAS-2): high risk of selection bias in 1 study (den Boon, 2006) and in two studies unclear risk of bias for the reference standard. In 9 of the 11 studies less than half the participants received the reference standard; accuracy was calculated under the assumption that those who did not receive the reference standard were culture and/or smear negative (no active TB) .
2 Indirectness (see QUADAS-2): No major concern about applicability.
3 Inconsistency: Moderate heterogeneity for sensitivity and significant heterogeneity for specificity (based on visual inspection of CIs) – downgrading on specificity.
4 Imprecision: Precise estimates for sensitivity and imprecise estimate for specificity.
5 Publication bias: Not applicable (the evidence base for assessing publication bias in studies of diagnostic test accuracy is very limited.

PICO 4: Could interferon-gamma release assays be used as an alternative to tuberculin skin tests to identify individuals most at risk of progression from LTBI to active TB in high TB incidence settings?

TST or IGRA for identifying individuals at greatest risk of progression to active TB

Head-to head-evaluations of TST and IGRA (N = 5)
Review question: Among people at high risk of LTBI who are not treated with TB preventive therapy, which test (e.g. TST or IGRA), when positive, can best identify individuals most at risk of progression?
Outcome: Predictive utility of the TST vs commercial IGRAs for progression to active TB
Patients/population: Longitudinal studies of adults and children without active TB at baseline not treated with preventive therapy
Setting: Community cohorts, individuals attending outpatient clinics (e.g. people living with HIV), individuals participating in RCTs, household contacts; all in high-incidence countries
Index test: TST (RT23 purified protein derivative or purified protein derivative S) and/or commercial blood-based IGRAs (QuantiFERON®-TB Gold In-Tube and T-SPOT®.TB)
Importance: Longitudinal studies on the predictive value of a positive IGRA are still emerging in TB high-incidence countries (≥ 100/100 000). It is important to assess whether IGRA can be used as a replacement for the widely used TST.
Reference standard: All diagnoses of incident active TB (microbiologically confirmed or not)
Studies: Any longitudinal study design (e.g. prospective or retrospective cohort), in TB high-incidence countries, regardless of immunological status (e.g. HIV-infected or not) or BCG status. Average follow-up should be ≥ 1 year, but can be either active or passive.

Nos of studies and patients	Design	Quality				Effect		Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Relative (pooled)	Absolute effect	(GRADE)	
A. SR OUTCOME: PROGRESSION TO ACTIVE TUBERCULOSIS IN UNTREATED INDIVIDUALS									
5 (N = 7675 for TST, N = 7641 for IGRA) *(44–48)*	Prospectively followed cohorts	Serious (A1) (-1)	Serious TST: I^2 = 64.4% IGRA: I^2 = 49.6% (A2) (-1)	Not serious (A3)	TST: Serious imprecision IGRA: No serious imprecision (A4) (-1)	TST: RR = 1.49 (95% CI 0.79;2.80) I^2 = 64.4% IGRA RR = 2.03 (95% CI 1.18;3.50) I^2 = 49.6%	TST 10 more per 1000 (4 fewer to 37 more) IGRA 15 more per 1000 (3 more to 36 more)	Very low ⨁◯◯◯	Critical
B. SR OUTCOME (SUB-GROUP ANALYSIS): PROGRESSION TO ACTIVE TB IN IMMUNOCOMPROMISED PEOPLE (HIV AND OTHER IMMUNOSUPPRESSIVE CONDITIONS)									
2 (N = 725 for TST, N = 710 for IGRA) *(44, 45)*	Prospectively followed cohort of HIV-infected women pre- and post-delivery of ART Prospectively followed cohort of HIV-infected individuals	Serious (B1) (-1)	Serious TST: I^2 = 77.4% IGRA: I^2 = 78.7% (B2) (-1)	Serious (B3) (-1)	Very serious (B4) (-2)	TST: RR = 1.64 (95% CI 0.24;11.18) IGRA RR = 4.07 (95% CI 0.18;92.72)	TST 39 more per 1000 (46 fewer to 616 more) IGRA 149 more per 1000 (40 fewer to 4438 more)	Very low ⨁◯◯◯	Critical

Nos of studies and patients	Design	Quality				Effect		Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Relative (pooled)	Absolute effect	(GRADE)	
C. SR OUTCOME (SUB-GROUP ANALYSIS): PROGRESSION TO ACTIVE TB AMONG CONTACTS OF TB CASES									
1 (N = 1511 for TST, N = 1498 for IGRA) *(48)*	Prospective follow-up	Serious (C1) (-1)	Not assessed; single study (C2)	Serious C3 (-1)	Serious C4 (-1)	TST RR, single study = 1.31 (95% CI: 0.85;2.04) IGRA RR, single study = 1.87 (95% CI: 1.12;3.11)	TST 14 more per 1000 (7 fewer to 45 more) IGRA 28 more per 1000 (4 more to 69 more)	Very low ⨁◯◯◯	Critical
D. SR OUTCOME (SUB-GROUP ANALYSIS): PROGRESSION TO ACTIVE TB AMONG TB HEALTH-CARE WORKERS									
1 (N = 195 for TST, N = 189 for IGRA) *(47)*	Prospective follow-up	Serious risk of bias (D1) (-1)	Not assessed; single study. (D2)	Serious D3 (-1)	Very serious D4 (-2)	TST RR, single study = 0.40 (95% CI: 0.02;9.81) IGRA RR, single study = 3.10 (95% CI: 0.13;75.04)	TST 6 fewer per 1000 (9 fewer to 82 more) IGRA (A difference cannot be computed)	Very low ⨁◯◯◯	Critical
E. SR OUTCOME (SUB-GROUP ANALYSIS): PROGRESSION TO ACTIVE TB AMONG ADOLESCENTS IN A HIGH-INCIDENCE SETTING									
1 (N = 5244 for both tests) *(46)*	Prospective follow-up	Serious (E1) (-1)	Not assessed; single study (E2)	Serious E3 (-1)	No serious E4	TST RR, single study = 2.71 (95% CI: 1.42;5.15) IGRA RR, single study = 2.89 (95% CI: 1.55;5.41)	TST 9 more per 1000 (2 more to 21 more) IGRA 10 more per 1000 (3 more to 22 more)	Very low ⨁◯◯◯	Critical

Notes on GRADE summary table

Overall quality:

All studies start with one point docked off because none were RCTs. The lowest quality score achievable is 1 out of 4; no minus scores are given.

Quality assessment: Based on the relative effect measure (RR or IRR) for both TST and IGRA. Studies not marked down if estimates for both tests score high on a specific GRADE quality item.

Other study quality considerations: Newcastle-Ottawa Scale quality items were considered when assessing the risk of bias. One point will be docked if at least one concern is present.

A1: Risk of bias is possible. Issues in the studies include selection bias, risk of incorporation bias, ascertainment and publication bias. Methods for ascertaining TB included microbiological methods, but not all incident TB cases had a definite culture-confirmed diagnosis of TB. Publication bias not formally assessed, but expected to be likely. Several large prospective studies are ongoing and/or unpublished; their results were not included in this analysis. However, addition of results is not expected to change the overall conclusions of this review.

A2: Serious unexplained inconsistency of RR estimate for TST. Points docked if serious inconsistency identified in either estimate.

A3: Although the number of studies included is small, they involve a range of populations, including adults and children, immunocompromised people and TB contacts, providing direct evidence for these groups.

A4: Serious imprecision of RR estimate for TST. Lower limit of 95% CI indicates lack of predictive utility. Points docked if serious imprecision identified in either estimate.

B1: Risk of bias is possible. Issues include selection bias, risk of incorporation bias, ascertainment and publication bias. Incorporation bias could not be ruled out in the cohort that included antepartum and postpartum women because information was not available; moreover, there are concerns with selection. The ART cohort study reported reference standards that do not account for index tests; however, assessors were not blinded to baseline TST results that were recorded in patient records. Methods for ascertaining TB included microbiological methods, but not all incident TB cases had a definite diagnosis of TB. Publication bias not formally assessed, but expected to be likely. Several large prospective studies are ongoing and/or are unpublished; their results were not included in this analysis. However, addition of results is not expected to change the overall conclusions of this review.

B2: Serious unexplained inconsistency in RR estimates for both TST and IGRA.

B3: This pooled estimate is based on only two studies: one study of HIV-infected people on ART with a median CD4+ approximately 250, and one on HIV-infected antepartum and postpartum women. No direct evidence for treatment-naïve patients and/or HIV-infected patients with high CD4 counts or other sub-populations of HIV-infected individuals (e.g. children).

B4: Very serious imprecision of RR estimates for both TST and IGRA. CIs are wide and indicate both significant predictive performance and lack of predictive utility. Studies had few events.

C1: Risk of bias is possible. Issues include selection bias, risk of incorporation bias (no information) and publication bias. Publication bias not formally assessed, but expected to be likely. Several large prospective studies are ongoing and/or are unpublished; their results were not included in this analysis. However, addition of results is not expected to change the overall conclusions of this review.
C2: Inconsistency not assessed.
C3: This single study comprises household case contacts in a high-incidence country. No direct evidence for other subpopulations of case contacts.
C4: Serious imprecision of TST effect estimates. Lower limit of 95% CI indicates lack of predictive utility.

D1: Risk of bias is possible. Issues include selection bias, lack of use of microbiological tools in methods to ascertain TB, incorporation bias and publication bias. Publication bias not formally assessed, but expected to be likely. Several large prospective studies are ongoing and/or are unpublished; their results were not included in this analysis. However, addition of results is not expected to change the overall conclusions of this review.
D2: Inconsistency not assessed.
D3: This single study comprises health care workers at a primary health care clinic. No direct evidence for other subpopulations of health care workers or all settings of health care.
D4: Very serious imprecision of IGRA and TST effect estimates; CIs are wide and indicate both significant predictive performance and lack of predictive utility.

E1: Risk of bias is possible. Issues include selection bias, incorporation of index tests in methods to ascertain incident TB and publication bias. Publication bias not formally assessed, but expected to be likely. Several large prospective studies are ongoing and/or are unpublished; their results were not included in this analysis. However, addition of results is not expected to change the overall conclusions of this review.
E2: Inconsistency not assessed.
E3: This single study comprises adolescents in a high-incidence setting. No direct evidence for other subpopulations of children or adolescents.
E4: No serious imprecision: Few events with large sample size.

PICO 5: Should 3-month daily rifampicin plus isoniazid (3RH) be offered as a preventive treatment option for children and adolescents <15 years of age as an alternative to 6 or 9 months isoniazid (INH) monotherapy in high TB incidence countries?

3-month daily rifampicin and isoniazid in children and adolescents < 15 years

Overall quality: low

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3–4-month daily rifampicin and isoniazid	6–9-month isoniazid monotherapy	Relative (95% CI)	Absolute (95% CI)		
"RADIOLOGICAL" TB DISEASE: FOLLOW UP: RANGE 3–7 YEARS TO 7–11 YEARS; ASSESSED WITH: CHEST RADIOGRAPHY												
1 *(49)*	Randomised trial	Serious[1]	Not serious	Serious[2]	Not serious	None	26/220 (11.8%)	48/200 (24.0%)	RR 0.492 (0.318;0.762)	122 fewer per 1000 (from 57 fewer to 164 fewer)	⨁⨁◯◯ Low	Critical
MORTALITY												
0									Cannot be estimated		-	Important
ADVERSE EVENTS: FOLLOW UP: RANGE 3–7 YEARS TO 7–11 YEARS; ASSESSED BY: RECOGNITION OF SYMPTOMS AND ELEVATED LIVER ENZYMES												
1 *(49)*	Randomized trial	Very serious[1,3]	Not serious	Serious[4]	Not serious	None	27/650 (4.2%)	25/200 (12.5%)	RR 0.332 (0.197;0.559)	83 fewer per 1000 (from 55 fewer to 100 fewer)	⨁◯◯◯ Very low	Critical
ADVERSE EVENTS: FOLLOW UP: MEDIAN 97–197 DAYS; ASSESSED BY: LIVER TOXICITY TEST AND CLINICAL												
1 *(50)*	Observational study	Serious[5]	Not serious	Serious[4]	Serious[6]	None	1/220 (0.5%)	5/264 (1.9%)	RR 0.24 (0.03;2.04)	14 fewer per 1000 (from 18 fewer to 20 more)	⨁◯◯◯ Very low	Critical
COMPLETION RATE: FOLLOW UP: RANGE 3–7 YEARS TO 7–11 YEARS#												
1 *(49)*	Randomized trial	Serious[7]	Not serious	Serious[4]	Not serious	None	220/238 (92.4%)	200/232 (86.2%)	RR 1.07 (1.01;1.14)	60 more per 1000 (from 9 more to 121 more)	⨁⨁◯◯ Low	Critical
COMPLETION RATE: ASSESSED BY: COMPLETION OF > 80% OF TREATMENT WITHOUT INTERRUPTION OF > 2 MONTHS												
1 *(51)*	Observational study	Serious[5]	Not serious	Not serious	Serious[8]	None	48/72 (66.7%)	29/105 (27.6%)	RR 2.41 (1.70;3.43)	389 more per 1000 (from 193 more to 671 more)	⨁◯◯◯ Very low	Critical

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3–4-month daily rifampicin and isoniazid	6–9-month isoniazid monotherapy	Relative (95% CI)	Absolute (95% CI)		
DRUG-RESISTANT TB												
0									Cannot be estimated		–	Important

From references *(49–51)*

[1] Although there was a risk of selection bias, the characteristics of the two groups were similar. Patients with poor compliance were not included in the analysis of treatment outcomes. Downgraded by one level.

[2] There was no clinical disease. The outcome reported was new radiographic findings suggesting possible active disease. No data compared with 6H. Downgraded by one level.

[3] A high risk of detection bias due to lack of blinding. The RH group included participants enrolled during the second period, whose characteristics were different; they were not randomized between the RH group and the 9H group. Downgraded by two levels.

[4] No data compared with 6H. Downgraded by one level.

[5] Risk of bias due to poor comparability of the two groups. Downgraded by one level.

[6] Low event rate and wide 95% CI. Downgraded by one level.

[7] Lack of blinding. Medication adherence test was performed at home by parents. Although there was a risk of selection bias, the characteristics of the two groups were similar. Downgraded by one level.

[8] Wide 95% CI. Downgraded by one level.

The study reported adherence rates; compliance was considered to be poor if no medication was detected in urine strips or if patients did not return for follow-up visits or were lost to follow-up. Poor compliance was considered non-completion in the analysis.

PICO 6: In people of all ages at risk of active TB, does a 4-month daily rifampicin regimen safely prevent TB disease compared to other recommended TB preventive treatment regimens?

Overall quality: moderate

Bibliography: (see references *52–56*)

Menzies D, Adjobimey M, Ruslami R, Trajman A, Sow O, Kim H, et al. Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults. New Eng J Med. 2018 Aug 2;379(5):440–53.

Diallo T, Adjobimey M, Ruslami R, Trajman A, Sow O, Obeng Baah, J, et al. Safety and Side Effects of Rifampin versus Isoniazid in Children. N Engl J Med. 2018;379:454–463.

Menzies D, Long R, Trajman A, Dion MJ, Yang J, Al Jahdali H, et al. Adverse Events with 4 Months of Rifampin Therapy or 9 Months of Isoniazid Therapy for Latent Tuberculosis Infection: A Randomized Trial. Ann Intern Med. 2008;149(10):689–697.

Menzies D, Dion MJ, 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):445–449.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a regimen with four months of daily rifampicin	a regimen of nine months of daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
INCIDENCE OF ACTIVE TB (IN ALL FORMS) IN ADULTS (FOLLOW UP: MEAN 28 MONTHS; ASSESSED WITH: RCT EVIDENCE)												
1 [a]	randomised trials [b,c]	serious [d,e]	not serious	not serious [f]	not serious	none	8/3443 [g]	9/3416 [g]	Rate ratio 0.88 (0.34 to 2.28) [h]	0 fewer per 1000 patient(s) per years (from 2 fewer to 2 more) [i,j]	⨁⨁⨁◯ MODERATE	CRITICAL
INCIDENCE OF ACTIVE TB (MICROBIOLOGICALLY CONFIRMED) IN ADULTS (FOLLOW UP: MEAN 28 MONTHS; ASSESSED WITH: RCT EVIDENCE)												
1 [a]	randomised trials [b,c]	serious [d,e]	not serious	not serious [f]	not serious	none	4/3443 [g]	4/3416 [g]	Rate ratio 0.99 (0.25 to 3.96) [h]	0 fewer per 1000 patient(s) per years (from 1 fewer to 2 more) [i,j]	⨁⨁⨁◯ MODERATE	CRITICAL
MORTALITY (ALL CAUSE) IN ADULTS DURING TREATMENT (ASSESSED WITH: RCT EVIDENCE)												
2	randomised trials [b,c]	serious [d]	not serious	not serious [f]	not serious	none	0/3280 (0.0%) [k]	4/3205 (0.1%) k,l	RR 0.11 (0.01 to 2.02) [h,m]	1 fewer per 1,000 (from 3 fewer to 0 fewer) [n]	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a regimen with four months of daily rifampicin	a regimen of nine months of daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
MORTALITY (RELATED TO DRUG) IN ADULTS DURING TREATMENT (ASSESSED WITH: RCT EVIDENCE)												
2	randomised trials [b,c]	serious [d]	not serious	not serious [f]	not serious	none	0/3280 (0.0%) [k]	1/3205 (0.0%) k,l	RR 0.33 (0.01 to 8.00) [h,m]	0 fewer per 1,000 (from 1 fewer to 0 fewer) [n]	⨁⨁⨁◯ MODERATE	CRITICAL
ADVERSE EVENTS (GRADE 3-5) IN ADULTS (ASSESSED WITH: RCT EVIDENCE)												
2	randomised trials [b,c]	serious [d]	not serious	not serious [f]	not serious	none	53/3280 (1.6%) [k,o]	119/3205 (3.7%) [k,o]	RR 0.44 (0.32 to 0.60) [h]	21 fewer per 1,000 (from 25 fewer to 15 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
ADVERSE EVENTS (RELATED GRADE 3-5) IN ADULTS (ASSESSED WITH: RCT EVIDENCE)												
2	randomised trials [b,c]	serious [d]	not serious	not serious [f]	not serious	none	31/3280 (0.9%) [k,o]	75/3205 (2.3%) [k,o]	RR 0.40 (0.27 to 0.61) [h]	14 fewer per 1,000 (from 20 fewer to 8 fewer) [n]	⨁⨁⨁◯ MODERATE	CRITICAL
TREATMENT COMPLETION (EVER) IN ADULTS (ASSESSED WITH: RCT EVIDENCE)												
3	randomised trials [b,p]	serious [q]	not serious	not serious [f]	not serious	none	2763/3501 (78.9%) [r]	2188/3474 (63.0%) [r]	RR 1.25 (1.22 to 1.29) [h]	157 more per 1,000 (from 139 more to 183 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
INCIDENCE OF ACTIVE TB (IN ALL FORMS) IN PAEDIATRICS (FOLLOW UP: MEAN 16 MONTHS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials [s,t]	serious [u,v]	not serious	not serious [f]	not serious	none	0/422	2/407	Rate ratio 0.19 (0.01 to 4.02) [h,w]	4 fewer per 1000 patient(s) per years (from 9 fewer to 1 more) [i,x]	⨁⨁⨁◯ MODERATE	CRITICAL
INCIDENCE OF ACTIVE TB (MICROBIOLOGICALLY CONFIRMED) IN PAEDIATRICS (FOLLOW UP: MEAN 16 MONTHS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials [s,t]	serious [u,v]	not serious	not serious [f]	not serious	none	0/422	2/407	Rate ratio 0.19 (0.01 to 4.02) [h,w]	4 fewer per 1000 patient(s) per years (from 9 fewer to 1 more) [i,j]	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a regimen with four months of daily rifampicin	a regimen of nine months of daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
MORTALITY (ALL CAUSE) IN PAEDIATRICS DURING TREATMENT (ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials [s,t]	serious [v]	not serious	not serious [f]	not serious	none	1/422 (0.2%)	0/407 (0.0%)	RR 2.89 (0.12 to 70.82) [h,m]	2 more per 1,000 (from 2 fewer to 7 more) [n,y]	⨁⨁⨁◯ MODERATE	CRITICAL
MORTALITY (RELATED TO DRUG) IN PAEDIATRICS DURING TREATMENT (ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials [s,t]	serious [v]	not serious	not serious [f]	not serious	none	0/422 (0.0%)	0/407 (0.0%)	RR 0.96 (0.02 to 48.50) [h,m]	0 fewer per 1,000 (from 1 fewer to 1 more) [n,y]	⨁⨁⨁◯ MODERATE	CRITICAL
ADVERSE EVENTS (GRADE 3–5) IN PAEDIATRICS (ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials [s,t]	serious [v]	not serious	not serious [f]	not serious	none	1/422 (0.2%)	1/407 (0.2%)	RR 0.96 (0.06 to 15.37) [h]	0 fewer per 1,000 (from 6 fewer to 7 more) [n,y]	⨁⨁⨁◯ MODERATE	CRITICAL
ADVERSE EVENTS (RELATED GRADE 3–5) IN PAEDIATRICS (ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials [s,t]	serious [v]	not serious	not serious [f]	not serious	none	0/422 (0.0%)	0/407 (0.0%)	RR 0.96 (0.02 to 48.50) [h,m]	0 fewer per 1,000 (from 1 fewer to 1 more) [n,y]	⨁⨁⨁◯ MODERATE	CRITICAL
TREATMENT COMPLETION (EVER) IN PAEDIATRICS (ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials [s,t]	serious [q]	not serious	not serious [f]	not serious	none	365/422 (86.5%)	314/407 (77.1%)	RR 1.12 (1.05 to 1.20) [h]	136 more per 1,000 (from 79 more to 193 more) [n,z]	⨁⨁⨁◯ MODERATE	IMPORTANT
INCIDENCE OF ACTIVE TB (MICROBIOLOGICALLY CONFIRMED) IN HIV-POSITIVE ADULTS (FOLLOW UP: MEAN 28 MONTHS; ASSESSED WITH: RCT EVIDENCE)												
1 [a]	randomised trials [b,c]	serious [d]	not serious	not serious [f]	serious [aa]	none	1/132 [ab,g]	0/138 [ab]	Rate ratio 2.88 (0.12 to 70.67) [h,w]	8 more per 1000 patient(s) per years (from 7 fewer to 22 more) [ac]	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a regimen with four months of daily rifampicin	a regimen of nine months of daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
INCIDENCE OF ACTIVE TB (IN ALL FORMS) IN HIV-POSITIVE ADULTS (FOLLOW UP: MEAN 28 MONTHS; ASSESSED WITH: RCT EVIDENCE)												
1 [a]	randomised trials [b,c]	serious [d]	not serious	not serious [f]	serious [aa]	none	1/132 [ab,g]	2/138 [ab,g]	Rate ratio 0.48 (0.04 to 5.29) [h]	7 fewer per 1000 patient(s) per years (from 32 fewer to 18 more) [ac]	⨁⨁◯◯ LOW	CRITICAL
ADVERSE EVENTS (GRADE 3–5) IN HIV-POSITIVE ADULTS (ASSESSED WITH: RCT EVIDENCE)												
2	randomised trials [b,c]	serious [d]	not serious	not serious [f]	serious [aa]	none	2/130 (1.5%) [ab,ad]	8/138 (5.8%) [ab,ad]	RR 0.27 (0.06 to 1.23) [h]	43 fewer per 1,000 (from 87 fewer to 2 more) [ac]	⨁⨁◯◯ LOW	CRITICAL
ADVERSE EVENTS (RELATED GRADE 3–5) IN HIV-POSITIVE ADULTS (ASSESSED WITH: RCT EVIDENCE)												
2	randomised trials [b,c]	serious [d]	not serious	not serious [f]	serious [aa]	none	1/130 (0.8%) [ab,ad]	5/138 (3.6%) [ab,ad]	RR 0.21 (0.03 to 1.79) [h]	29 fewer per 1,000 (from 63 fewer to 6 more) [ac]	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

[a] The GDG decided that for efficacy outcomes the pooled outcomes for phase 2 and phase 3 studies be considered one trial as the same protocol was used for both phases conducted by the same investigating team, even if the number of sites increased in the phase 3 study. Although the quality was not downgraded for this, the GDG noted that Inconsistency could not be judged given that there was only a single trial. Ideally replication by other trials would be desirable. For adverse events the studies can be considered as two separate trials.

[b] Phase 2 *(54)* and Phase 3 *(52)* open-label trials conducted in nine countries, assigning adults with latent tuberculosis infection to receive treatment with a 4-month regimen of daily rifampicin or a 9-month regimen of daily isoniazid. The primary outcome in the phase 2 trial was incidence of grade 3 to 5 adverse events (superiority design), with secondary outcomes of treatment completion and incidence of active tuberculosis within 28 months of randomization. The primary outcome of the phase 3 trial was microbiologically confirmed active tuberculosis within 28 months after randomization (non-inferiority design), with secondary outcomes of clinically diagnosed active tuberculosis, grade 3 to 5 adverse events, and treatment completion. Outcomes of active tuberculosis and adverse events were adjudicated by three-member, blinded, independent review panels; treatment completion based on pill counts at routine follow-up visits.

[c] Between the phase 2 and phase 3 trials in adults, there were no significant changes in guidelines or risk profiling of latent TB reactivation in terms of judging 'increased risk for reactivation'. Randomization in both trials was stratified by site and centrally computer-randomized. Patients were randomized 1:1 in blocks of varying length (2 to 8) to isoniazid or rifampicin.

[d] Open label design but endpoints of active TB and adverse events adjudicated by three-member, independent, blinded review panels. There were 18 per protocol exclusions among those randomized to isoniazid and 19 per protocol exclusions among those randomized to rifampicin. These per protocol exclusions were due to being a household contact of a tuberculosis patient with resistance to isoniazid or rifampicin (proven post-randomization). There were nine individuals randomized to isoniazid and five individuals randomized to rifampicin who withdrew consent post-randomization. The GDG decided to downgrade by one level because of the open label design possibly leading to performance bias.

[e] Among those randomized to isoniazid and forming the modified intention-to-treat population, there were 260 individuals lost to follow-up. Among those randomized to rifampicin and forming the modified intention-to-treat population, there were 245 individuals lost to follow-up. Among all persons forming the modified intention-to-treat population, 7.4% of individuals were lost to follow-up.

[f] The quality was not downgraded for Indirectness, but the GDG noted that the trial compared 4R with 9H and therefore did not cover all other comparisons of the PICO, especially 6H, the most widespread standard of care in TB preventive treatment. Some study sites were low TB incidence settings for which a WHO recommendation for use of 4R already exists.

[g] All active TB events occurred within the phase 3 trial *(52)*.

[h] Unadjusted estimate.

[i] The rate difference was estimated by a Poisson model with the use of generalized estimating equations with a log link and the inclusion of the log of person-time as an offset. An exchangeable correlation structure with robust standard errors was used to account for the correlation of participants coming from the same household.

[j] Values reported as per Table 3 of *(52)*. Values include Phase 2 results *(54)* as well.

[k] Denominators are representative of the combined safety population of phase 2 *(54)* and phase 3 *(52)* as indicated in supplemental tables S2 and S3 of the phase 3 publication. From the phase 2 trial, 396 patients receiving isoniazid and 393 patients receiving rifampicin formed the safety population; from the phase 3 trial, 2809 patients receiving isoniazid and 2887 patients receiving rifampicin formed the safety population.

[l] All mortality events occurred in the phase 3 trial *(52)*.

[m] A zero cell correction of 0.5 has been used to calculate the risk ratio.

[n] The risk difference was estimated by a binomial distribution model with an identity link and generalized estimating equations. An exchangeable correlation structure and robust standard errors were used to account for correlation of patients coming from the same family. If no events occurred in one or both arms, confidence intervals were calculated based on *(56)*.

[o] Among adverse events from the phase 2 trial *(54)*, 10 patients receiving rifampicin experienced grade 3–5 adverse events which led to permanent discontinuation of the medication, of which 7 were deemed possibly/probably related to study drug; 19 patients receiving isoniazid experienced grade 3–5 adverse events which led to permanent discontinuation of the medication, of which 16 were deemed possibly/probably related to study drug. Among adverse events from the phase 3 trial *(52)*, 43 patients receiving rifampicin experienced grade 3–5 adverse events which led to permanent discontinuation of the medication, of which 24 were deemed possibly/probably related to study drug; 100 patients receiving isoniazid experienced grade 3–5 adverse events which led to permanent discontinuation of the medication, of which 59 were deemed possibly/probably related to study drug.

[p] Also included is the phase 1 trial *(55)*, a single center, open-label randomized trial assessing superiority of four months of daily rifampicin to nine-months of daily isoniazid for treatment completion.

[q] Open label trial, unblinded assessment of compliance judged on the basis of pill counts at monthly follow-up visits.

[r] Numerator and denominator values are derived from the Phase 1 trial *(55)*, Phase 2 trial *(54)*, and Phase 3 trial *(52)*. Treatment completion was defined as taking at least 80% of prescribed doses (i.e., at least 96 pills of rifampicin or 216 pills of isoniazid). In the phase 1 trial, 44 of 58 individuals randomized to isoniazid and 53 of 58 individuals randomized to rifampicin completed treatment. In the phase 2 trial, 254 of 427 individuals randomized to isoniazid and 328 of 420 individuals randomized to rifampicin completed treatment. In the phase 3 trial, 1890 of 2989 individuals randomized to isoniazid and 2382 of 3023 individuals randomized to rifampicin completed treatment.

[s] Open-label, non-inferiority trial conducted in seven countries, assigning children with latent tuberculosis infection to receive treatment with a 4-month regimen of rifampicin or a 9-month regimen of isoniazid for the incidence of grade 3 to 5 adverse events during treatment. Secondary outcomes were the incidence of microbiologically confirmed active tuberculosis within 16 months after randomization and completion of the treatment regimen. Outcomes of active TB and adverse events were adjudicated by two- or three-member, blinded, independent review panels; treatment completion based on pill counts at routine follow-up visits *(53)*.

[t] Randomization in the paediatric trial was stratified by country and centrally computer-randomized. Patients were randomized 1:1 in blocks of varying length (2 to 8) to isoniazid or rifampicin. Enrollment and randomization in this trial was completely separate from the adult trials.

[u] Among those randomized to isoniazid and forming the modified intention-to-treat population, there were 6 individuals lost to follow-up. Among those randomized to rifampicin and forming the modified intention-to-treat population, there were 5 individuals lost to follow-up. Among all children forming the modified intention-to-treat population, 1.3% of individuals were lost to follow-up.

[v] Open label design but endpoints of active TB and adverse events adjudicated by two-member and three-member, respectively, independent, blinded review panels. There were 9 per protocol exclusions among those randomized to isoniazid and 6 per protocol exclusions among those randomized to rifampicin. These per protocol exclusions were due to being tuberculin skin test negative at the end of the window period (two months after exposure). GDG decided to downgrade by one level because of the open label design and because some sites were not high burden.

[w] A zero cell correction of 0.5 has been used to calculate the rate ratio.

[x] Values as reported in the text of the paediatric trial *(53)*.

[y] Values as reported in Table 3 of the paediatric trial *(53)*.

[z] Values reported in Table 2 of the paediatric trial *(53)*.

[aa] Subgroup analysis within randomized trials that involved relatively small numbers of HIV-infected patients when compared to all patients included in the trials.

[ab] Denominators include HIV-positive patients known at the time of randomization as reported in Supplemental Table S1 of the phase 3 adult trial *(52)*, as well as patients diagnosed post randomization as a result of baseline assessment. This includes 130 patients and 8 patients receiving isoniazid with an HIV-diagnosis at time of randomization and post-randomization, respectively, and 125 patients and 7 patients receiving rifampicin with an HIV-diagnosis at time of randomization and post-randomization, respectively. This resulted in modified intention to treat population sizes of 132 for rifampicin and 138 for isoniazid. Among HIV-positive patients randomized to rifampicin, 2 did not receive a dose of therapy. Thus, the safety population sizes were 130 for rifampicin and 138 for isoniazid.

[ac] Unadjusted absolute estimate.

[ad] Among patients receiving rifampicin included in the safety population, 6 patients were HIV-positive in the phase 2 trial and 124 patients were HIV-positive in the phase 3 trial. All grade 3–5 adverse events among patients receiving rifampicin occurred in the phase 3 trial. Two patients experienced a grade 3–5 adverse event with rifampicin that resulted in permanent discontinuation of the study drug, only 1 was deemed possibly/probably related to the study drug. Among patients receiving isoniazid included in the safety population, 7 patients were HIV-positive in the phase 2 trial and 131 were HIV-positive in the phase 3 trial. One patient in the phase 2 trial and 7 patients in the phase 3 trial receiving isoniazid experienced a grade 3–5 adverse event resulting in permanent discontinuation of the study medication. The events were deemed possibly/probably related to the study drug for the one patient from the phase 2 trial and for 4 patients from the phase 3 trial.

PICO 7: In people of all ages at risk of active TB, does a 1-month daily rifapentine plus isoniazid regimen safely prevent TB disease compared to other recommended TB preventive treatment regimens?

Population: PLHIV at increased risk of active TB
Overall quality: low
Bibliography: (see reference 57)
Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, et.al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis, N Engl J Med. 2019 Mar 14;380(11):1001-1011. doi: 10.1056/NEJMoa1806808.[a]

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	one month daily rifapentine plus isoniazid	nine months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
INCIDENCE OF ACTIVE TB (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION); DEATHS OF UNKNOWN CAUSE OR NOT RELATED TO TB CENSORED)												
1	randomised trials	serious [b,c]	not serious	serious [d]	not serious	none	29/1488 (1.9%)	26/1498 (1.7%)	Incidence Rate Difference per 100 person-years 0.058 (-0.240 to 0.350)	-	⨁⨁◯◯ LOW	CRITICAL
INCIDENCE OF ACTIVE TB AMONG ART-NAIVE PARTICIPANTS AT ENTRY (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION); DEATHS OF UNKNOWN CAUSE OR NOT RELATED TO TB CENSORED)												
1	randomised trials	serious [b,c]	not serious	serious [d]	not serious	none	17/740 (2.3%)	15/746 (2.0%)	Incidence Rate Difference per 100 person-years 0.07 (-0.37 to 0.51)	-	⨁⨁◯◯ LOW	CRITICAL
INCIDENCE OF ACTIVE TB AMONG TST OR IGRA POSITIVE PARTICIPANTS AT ENTRY (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION); DEATHS OF UNKNOWN CAUSE OR NOT RELATED TO TB CENSORED)												
1	randomised trials	serious [b,c]	not serious	serious [d]	not serious	none	9/337 (2.7%)	10/349 (2.9%)	Incidence Rate Difference per 100 person-years -0.069 (-0.830 to 0.690)	-	⨁⨁◯◯	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	one month daily rifapentine plus isoniazid	nine months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
INCIDENCE OF BACTERIOLOGICALLY CONFIRMED TB (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION); DEATHS OF UNKNOWN CAUSE OR NOT RELATED TO TB CENSORED)												
1	randomised trials	serious [c,e]	not serious	serious [d]	not serious	none	18/1488 (1.2%)	14/1498 (0.9%)	Incidence Rate Difference per 100 person-years 0.08 (-0.15 to 0.31)	-	⨁⨁◯◯ LOW	CRITICAL
TIME TO TB DIAGNOSIS OR DEATH RELATED TO TB, WITH OTHER DEATHS TREATED AS COMPETING RISK (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION))												
1	randomised trials	serious [f]	not serious	serious [d]	not serious	none	1488 participants	1498 participants	HR 1.10 (0.65 to 1.87) [Time to TB diagnosis or death related to TB, with other deaths treated as competing risk]	2 more per 1,000 (from 6 fewer to 15 more)	⨁⨁◯◯ LOW	CRITICAL
							-	1.7% g		2 more per 1,000 (from 6 fewer to 15 more)		
INCIDENCE OF ACTIVE TB OR DEATH DUE TO UNKNOWN CAUSE (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION))H												
1	randomised trials	serious [i]	not serious	serious [d]	not serious	none	32/1488 (2.2%)	33/1498 (2.2%)	Incidence Rate Difference per 100 person-years -0.023 (-0.350 to 0.300)	-	⨁⨁◯◯ LOW	CRITICAL
INCIDENCE OF ACTIVE TB OR DEATH DUE TO UNKNOWN CAUSE (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (PER-PROTOCOL POPULATION))												
1	randomised trials	serious [i]	not serious	serious [d]	not serious	none	31/1456 (2.1%)	29/1381 (2.1%)	Incidence Rate Difference per 100 person-years 0.021 (-0.300 to 0.340)	-	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	one month daily rifapentine plus isoniazid	nine months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
INCIDENCE OF ACTIVE TB OR DEATH FROM ANY CAUSE (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION))												
1	randomised trials	serious [c]	not serious	serious [d]	not serious	none	45/1488 (3.0%)	51/1498 (3.4%)	Incidence Rate Difference per 100 person-years -0.13 (-0.52 to 0.27)	–	⨁⨁◯◯ LOW	CRITICAL
TIME TO DEATH FROM ANY CAUSE (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c,i]	not serious	serious [d]	not serious	none	1488 participants	1498 participants	HR 0.75 (0.42 to 1.31) [Time to death from any cause]	5 fewer per 1,000 (from 11 fewer to 6 more)	⨁⨁◯◯ LOW	CRITICAL
							–	1.9% [g,j]		5 fewer per 1,000 (from 11 fewer to 6 more)		
TIME TO DEATH FROM TUBERCULOSIS (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	serious [d]	serious [k]	none	3/1488 (0.2%)	3/1498 (0.2%)	HR 1.00 (0.20 to 4.93)	0 fewer per 1,000 (from 2 fewer to 8 more) l	⨁⨁◯◯ VERY LOW	CRITICAL
ADVERSE EVENTS (GRADE 3 OR HIGHER OF NAUSEA, VOMITING, RASH, DRUG-ASSOCIATED FEVER, ELEVATED LIVER-ENZYMES AND PERIPHERAL NEUROPATHY) (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	serious [d]	not serious	none	44/1488 (3.0%)	52/1498 (3.5%)	RR 0.86 (0.58 to 1.27)	5 fewer per 1,000 (from 15 fewer to 9 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	one month daily rifapentine plus isoniazid	nine months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
SERIOUS ADVERSE EVENTS (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	serious [d]	not serious	none	83/1488 (5.6%)	108/1498 (7.2%)	RR 0.79 (0.59 to 1.04)	15 fewer per 1,000 (from 30 fewer to 3 more)	⨁⨁◯◯ LOW	CRITICAL
TREATMENT COMPLETION (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c,m]	not serious	serious [d]	not serious	none	1444/1488 (97.0%)	1341/1498 (89.5%)	RR 1.04 (0.99 to 1.10)	36 more per 1,000 (from 9 fewer to 90 more)	⨁⨁◯◯ LOW	CRITICAL
TREATMENT COMPLETION AMONG ART-NAIVE PARTICIPANTS AT ENTRY (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c,m]	not serious	serious [d]	not serious	none	720/740 (97.3%)	656/743 (88.3%)	RR 1.05 (0.97 to 1.14)	44 more per 1,000 (from 26 fewer to 124 more)	⨁⨁◯◯ LOW	CRITICAL
EMERGENCE OF DRUG RESISTANCE TO ISONIAZID AMONG THOSE WITH CONFIRMED TB AND WITH DST (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	very serious [d,n]	very serious [o]	none	2/14 (14.3%)	1/12 (8.3%)	RR 1.63 (0.17 to 15.99)	52 more per 1,000 (from 69 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
EMERGENCE OF DRUG RESISTANCE TO RIFAMPICIN AMONG THOSE WITH CONFIRMED TB AND WITH DST (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	very serious [d,n]	very serious [o]	none	1/15 (6.7%)	1/12 (8.3%)	RR 0.81 (0.06 to 11.77)	16 fewer per 1,000 (from 78 fewer to 898 more)	⨁◯◯◯ VERY LOW	IMPORTANT
EMERGENCE OF DRUG RESISTANCE TO ETHAMBUTOL AMONG THOSE WITH CONFIRMED TB AND WITH DST												
1	randomised trials	serious [c]	not serious	very serious [d,n]	very serious [o]	none	0/7 (0.0%)	1/7 (14.3%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	one month daily rifapentine plus isoniazid	nine months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
EMERGENCE OF DRUG RESISTANCE TO PYRAZINAMIDE AMONG THOSE WITH CONFIRMED TB AND WITH DST (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	very serious [d,n]	very serious [o]	none	0/6 (0.0%)	0/6 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

[a] Randomized, open-label, phase 3 noninferiority trial comparing the efficacy and safety of a 1-month regimen of daily rifapentine plus isoniazid (1-month group) with 9 months of isoniazid alone (9-month group) in HIV-infected patients who were living in areas of high tuberculosis prevalence or who had evidence of latent tuberculosis infection. Primary end point was the first diagnosis of TB or death from TB or an unknown cause. Noninferiority would be shown if the upper limit of the 95% confidence interval for the between-group difference in the number of events per 100 person-years was less than 1.25. LTBI was not confirmed in about 80% of participants. Enrolment restricted to individuals ≥13 years old who were not pregnant or breastfeeding. Overall TB incidence observed in the trial was lower than expected. The number of patients with a CD4+ <250 cells per cu mm was small, and neither inferiority nor noninferiority of the 1-month regimen was shown in this stratum.

[b] Unknown cause of death censored in this analysis, which may cause bias in incidence rate difference if some of these deaths were related to TB (dependent censoring)

[c] The GDG decided to downgrade by one level because of the open label design possibly leading to performance bias. The quality was not downgraded for Indirectness, but the GDG noted that the trial compared 1HP with 9H and therefore did not cover all other comparisons of the PICO, especially 6H, the most widespread standard of care in TB preventive treatment. The GDG noted that Inconsistency could not be judged given that there was only a single trial; results from more trials would be desirable.

[d] Trial conducted only in PLHIV and not in all people at risk of active TB.

[e] Probable TB diagnoses and deaths with non-bacteriologically confirmed TB censored at the time of event

[f] When cause of death was determined to be unknown or not related to TB by blinded external reviewers, these were treated as a competing risk rather than endpoint. Some of these may have actually been due to TB, which may bias estimate.

[g] The proportion of events among controls

[h] Per-protocol population consisted of all participants who completed treatment, or who had died or received a TB diagnosis while they were receiving treatment.

[i] Deaths were reviewed by blinded external reviewers. Unknown causes of death were included as an endpoint, but misclassification of cause of death may bias estimate

[j] There were 21 deaths in the one-month arm, 3 related to TB. There were 28 deaths in the nine-month arm, 3 related to TB.

[k] Small number of events

[l] Incidence Rate Difference per 100 person-years of 0.00 (-0.10 to 0.10)

[m] Assessed via participant self-report at clinic visits

[n] Resistance may be non-emergent and coming from infecting strain

[o] Small sample of bacteriologically confirmed TB who had drug susceptibility test results

PICO 8: Should 3-month weekly rifapentine and isoniazid be offered as an alternative regimen to isoniazid monotherapy for treatment of LTBI in high TB incidence countries?

3-month weekly rifapentine plus isoniazid or daily isoniazid monotherapy for LTBI treatment in adults with HIV

Population: Adults with HIV
Comparison: 6 or 9 months of isoniazid monotherapy
Overall quality: high

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months weekly rifapentine + isoniazid	6 or 9 months isoniazid	Relative (95% CI)	Absolute (95% CI)		
ACTIVE TB												
2 *(58,59)*	RCTs	Not serious	Not serious	Not serious[1]	Serious[2]	None	26/534 (4.9%)	28/520 (5.4%)	RR 0.733 (0.234;2.295)	14 fewer per 1000 (from 41 fewer to 70 more)	⨁⨁⨁◯ Moderate	Critical
ALL-CAUSE MORTALITY												
2 *(58,59)*	RCTs	Not serious	Not serious	Not serious[1]	Serious[2]	None	23/535 (4.3%)	30/513 (5.8%)	RR 0.746 (0.438;1.270)	15 fewer per 1000 (from 16 more to 33 fewer)	⨁⨁⨁◯ Moderate	Important
ANY ADVERSE EVENTS (GRADE III OR IV)												
2 *(58,59)*	RCTs	Serious[3]	Not serious	Not serious[1]	Not serious	None	39/535 (7.3%)	59/513 (11.5%)	RR 0.627 (0.426;0.921)	43 fewer per 1000 (from 9 fewer to 66 fewer)	⨁⨁⨁◯ Moderate	Critical
HEPATOTOXICITY												
2 *(58,59)*	RCTs	Not serious[4]	Not serious	Not serious[1]	Not serious	None	8/535 (1.5%)	30/513 (5.8%)	RR 0.256 (0.118;0.553)	44 fewer per 1000 (from 26 fewer to 52 fewer)	⨁⨁⨁⨁ High	Critical
DRUG RESISTANT TB												
2 *(58,59)*	RCTs	Not serious	Not serious	Not serious[1]	Very serious[5]	None	3/534 (0.6%)	1/520 (0.2%)	RR 2.001 (0.259;15.436)	2 more per 1000 (from 1 fewer to 28 more)	⨁⨁◯◯ Low	Important

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months weekly rifapentine + isoniazid	6 or 9 months isoniazid	Relative (95% CI)	Absolute (95% CI)		
COMPLETION RATE												
2 *(58,59)*	RCTs	Not serious	Not serious	Not serious[1]	Not serious	None	497/534 (93.1%)	397/520 (76.3%)	RR 1.255 (1.014;1.553)	195 more per 1000 (from 11 more to 422 more)	⨁⨁⨁⨁ High	Critical

[1] Although one of the trials was conducted in low TB incidence countries, this is unlikely to affect the relative effect of rifapentine + isoniazid compared with isoniazid monotherapy. Not downgraded.
[2] 95% CIs of both relative and absolute effect include appreciable benefit and harm with 3HP.
[3] Both trials were open-label, which may have introduced bias in ascertainment of adverse events.
[4] Although the trials were open-label, this is unlikely to affect detection of hepatotoxicity, which is usually done by objective measurement (i.e. blood tests.). Not downgraded.
[5] Very low event rates. Upper limit of 95% CI of both relative and absolute effect include appreciable harm with 3HP. Downgraded by two levels.

3-month weekly rifapentine plus isoniazid or daily isoniazid monotherapy for treatment of LTBI in adults without HIV

Population: Adults without HIV
Comparison: 6 or 9 months of isoniazid monotherapy
Overall quality: moderate

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-month rifapentine + isoniazid	6 or 9 months isoniazid	Relative (95% CI)	Absolute (95% CI)		
ACTIVE TB												
1 *(60)*	RCT	Not serious	Not serious	Serious[1]	Not serious[2]	None	7/3986 (0.2%)	15/3745 (0.4%)	RR 0.438 (0.179;1.074)	2 fewer per 1000 (from 0 fewer to 3 fewer)	⨁⨁⨁◯ Moderate	Critical
ALL-CAUSE MORTALITY												
1 *(60)*	RCT	Not serious	Not serious	Serious[1]	Not serious[3]	None	31/3986 (0.8%)	39/3759 (1.0%)	RR 0.740 (0.462;1.183)	3 fewer per 1000 (from 2 more to 6 fewer)	⨁⨁⨁◯ Moderate	Important
ANY ADVERSE EVENTS (GRADE III OR IV)												
1 *(60)*	RCT	Serious[4]	Not serious	Serious[1]	Not serious	None	229/4040 (5.7%)	244/3759 (6.5%)	RR 0.873 (0.733;1.040)	8 fewer per 1000 (from 3 more to 17 fewer)	⨁⨁◯◯ Low	Critical
HEPATOTOXICITY												
1 *(60)*	RCT	Not serious[5]	Not serious	Serious[1]	Not serious	None	18/4040 (0.4%)	103/3759 (2.7%)	RR 0.163 (0.099;0.268)	23 fewer per 1000 (from 20 fewer to 25 fewer)	⨁⨁⨁◯ Moderate	Critical
DRUG-RESISTANT TB												
1 *(60)*	RCT	Not serious	Not serious	Serious[1]	Not serious[3]	None	1/3986 (0.0%)	2/3745 (0.1%)	RR 0.470 (0.043;5.179)	0 fewer per 1000 (from 1 fewer to 2 more)	⨁⨁⨁◯ Moderate	Important
COMPLETION RATE												
1 *(60)*	RCT	Not serious	Not serious	Serious[1]	Not serious	None	3273/3985 (82.1%)	2585/3745 (69.0%)	RR 1.190 (1.159;1.221)	131 more per 1000 (from 110 more to 153 more)	⨁⨁⨁◯ Moderate	Critical

[1] No comparison with 6 months of isoniazid. The study included 2.7% HIV-positive participants. Although the trial was conducted in low TB incidence countries, this is unlikely to affect relative effect of rifapentine + isoniazid compared with isoniazid monotherapy. Downgraded by one level.
[2] Although the 95% CI of RR is wide, the number of events was small and the CI of absolute effect is narrow. The result also met pre-stated non-inferiority margin. Not downgraded.
[3] Although the 95% CI of RR is wide, the number of events was small and the CI of absolute effect is narrow. Not downgraded.
[4] An open-label design of the trial may have introduced ascertainment bias.
[5] Although the trial was open-label, this is unlikely to affect detection of hepatotoxicity, which is usually done by objective measurement (i.e. blood tests). Not downgraded.

3-month weekly rifapentine plus isoniazid or daily isoniazid monotherapy for treatment of LTBI in children and adolescents

Population: Children and adolescents
Comparison: 6 or 9 months isoniazid
Overall quality: moderate

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-month rifapentine + isoniazid	6 or 9 months isoniazid	Relative (95% CI)	Absolute (95% CI)		
ACTIVE TB												
1 *(61)*	RCT	Not serious	Not serious	Serious[1]	Not serious[2]	None	0/471 (0.0%)	3/434 (0.7%)	RR 0.132 (0.007;2.542)	6 fewer per 1000 (from 7 fewer to 11 more)	⨁⨁⨁◯ Moderate	Critical
ALL-CAUSE MORTALITY												
1 *(61)*	RCT	Not serious	Not serious	Serious[1]	Not serious[3]	None	0/539 (0.0%)	2/493 (0.4%)	RR 0.183 (0.009;3.802)	3 fewer per 1000 (from 4 fewer to 11 more)	⨁⨁⨁◯ Moderate	Important
ANY ADVERSE EVENTS (GRADE III OR IV)												
1 *(61)*	RCT	Serious[4]	Not serious	Serious[1]	Not serious[3]	None	7/539 (1.3%)	8/493 (1.6%)	RR 0.875 (0.320;2.396)	2 fewer per 1000 (from 11 fewer to 23 more)	⨁⨁◯◯ Low	Critical
HEPATOTOXICITY												
1 *(61)*	RCT	Not serious[5]	Not serious	Serious[1]	Not serious	None	0/539 (0.0%)	0/493 (0.0%)	Cannot be estimated	0 fewer per 1000 (from 4 fewer to 4 more)	⨁⨁⨁◯ Moderate	Critical
DRUG-RESISTANT TUBERCULOSIS												
0									Cannot be estimated		–	Important
COMPLETION RATE												
1 *(61)*	RCT	Not serious	Not serious	Serious[1]	Not serious	None	415/471 (88.1%)	351/434 (80.9%)	RR 1.089 (1.030;1.153)	72 more per 1000 (from 24 more to 124 more)	⨁⨁⨁◯ Moderate	Critical

[1] No comparison against 6 months of isoniazid. Although the trial was conducted in low TB incidence countries, this is unlikely to affect relative effect of rifapentine + isoniazid compared with isoniazid monotherapy. Downgraded by one level.
[2] Although the 95% CI of the RR is wide, the number of events was small and the CI of absolute effect is narrow. The result also met pre-stated non-inferiority margin. Not downgraded.
[3] Although the 95% CI of the RR is wide, the number of events was small and the CI of absolute effect is narrow. Not downgraded.
[4] An open-label design of the trial may have introduced ascertainment bias.
[5] Although the trial was open-label, this is unlikely to affect detection of hepatotoxicity, which is usually done by objective measurement (i.e. blood tests). Not downgraded.

PICO 9: In pregnant and postpartum women, is isoniazid preventive treatment for TB as safe as other preventive treatment regimens?

Population: Isoniazid Preventive Therapy (IPT) compared to no IPT or placebo in pregnant women with HIV.
Bibliography:[1] (see references *62–65*)
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Overall quality of evidence rating: low

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT	no IPT or placebo	Relative (95% CI)	Absolute (95% CI)		
COMPOSITE PREGNANCY OUTCOMES (LOW BIRTH WEIGHT, PRETERM DELIVERY SPONTANEOUS ABORTION, STILLBIRTH, OR CONGENITAL ANOMALY												
1	randomised trials *(62)*	not serious	not serious	not serious	serious [a]	none	106/449 (23.6%)	78/460 (17.0%)	OR 1.51 (1.09 to 2.10)	66 more per 1,000 (from 12 more to 131 more)	⨁⨁⨁◯ MODERATE	CRITICAL
COMPOSITE PREGNANCY OUTCOMES (LOW BIRTH WEIGHT, PRETERM DELIVERY, SPONTANEOUS ABORTION, STILLBIRTH, NEONATAL MORTALITY, OR CONGENITAL ANOMALY)												
2	observational studies *(64,65)*	very serious [b]	not serious	not serious	serious [a]	none	43/172 (25.0%)	63/175 (36.0%)	OR 0.471 (0.199 to 0.742)	151 fewer per 1,000 (from 259 fewer to 66 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
MATERNAL DEATH												
1	randomised trials *(62)*	not serious	not serious	not serious	very serious [c]	none	1/477 (0.2%)	3/479 (0.6%)	RR 0.33 (0.03 to 3.21)	4 fewer per 1,000 (from 6 fewer to 14 more)	⨁⨁◯◯ LOW	CRITICAL
MATERNAL DEATH												
2	observational studies *(63,64)*	very serious [b]	not serious	not serious	not serious	none	18/10786 (0.2%)	105/41311 (0.3%)	RR 0.65 (0.39 to 1.07)	1 fewer per 1,000 (from 2 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT	no IPT or placebo	Relative (95% CI)	Absolute (95% CI)		
GRADE 3 OR 4 ADVERSE EVENTS RELATED TO STUDY TREATMENT												
1	randomised trials *(62)*	not serious	not serious	not serious	serious [a]	none	34/477 (7.1%)	22/479 (4.6%)	RR 1.55 (0.92 to 2.61)	25 more per 1,000 (from 4 fewer to 74 more)	⨁⨁⨁◯ MODERATE	CRITICAL
HEPATOTOXICITY												
1	randomised trials *(62)*	not serious	not serious	not serious	serious [a,d]	none	18/477 (3.8%)	11/479 (2.3%)	RR 1.64 (0.78 to 3.44)	15 more per 1,000 (from 5 fewer to 56 more)	⨁⨁⨁◯ MODERATE	CRITICAL
HEPATOTOXICITY												
1	observational studies *(63)*	very serious [e]	not serious	not serious	not serious [f]	none	30/17015 (0.2%)	114/41227 (0.3%)	RR 1.01 (0.68 to 1.51)	0 fewer per 1,000 (from 1 fewer to 1 more)	⨁⨁◯◯ LOW	CRITICAL
DISCONTINUATION OF STUDY DRUG DUE TO TOXICITY												
1	randomised trials *(62)*	not serious	not serious	not serious	serious [d]	none	11/477 (2.3%)	8/479 (1.7%)	RR 1.38 (0.56 to 3.40)	6 more per 1,000 (from 7 fewer to 40 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **OR:** Odds ratio; **RR:** Risk ratio

[a] Optimal information size not met.
[b] Bias due to confounding is considered serious. Important confounders are not fully accounted for.
[c] Large CI including both appreciable benefits and harms and very few events d. CI includes both appreciable benefits and harms
[e] Confounding was not accounted for. Bias due to measurement of hepatotoxicity is considered serious since liver function tests were performed only if clinically indicated, which was likely to be influenced by knowledge of the receipt of IPT.
[f] Very large sample size and CI of absolute effect is very narrow.

Population: Immediate Isoniazid Preventive Therapy (IPT) compared to deferred IPT (12 weeks at post-partum) in pregnant women with HIV
Bibliography: (see reference *62*)
Gupta A, Montepiedra G, Aaron L, Theron G, McCarthy K, Bradford S, et al. Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women. N Engl J Med. 2019 Oct 3;381(14):1333–46.
Overall quality of evidence rating: moderate

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immediate IPT	deferred IPT	Relative (95% CI)	Absolute (95% CI)		
ADVERSE PREGNANCY OUTCOME (COMPOSITE)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	106/449 (23.6%)	78/460 (17.0%)	OR 1.51 (1.09 to 2.10)	66 more per 1,000 (from 12 more to 131 more)	⨁⨁⨁◯ MODERATE	CRITICAL
MATERNAL DEATH (ANY CAUSE)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	2/477 (0.4%)	4/492 (0.8%)	RR 0.50 (0.09 to 2.73)	4 fewer per 1,000 (from 7 fewer to 14 more)	⨁⨁◯◯ LOW	CRITICAL
HEPATOTOXICITY												
1	randomised trials	not serious	not serious	not serious	serious [c]	none	29/477 (6.1%)	34/479 (7.1%)	RR 0.86 (0.53 to 1.38)	10 fewer per 1,000 (from 33 fewer to 27 more)	⨁⨁⨁◯ MODERATE	CRITICAL
ANY GRADE 3 OR 4 ADVERSE EVENTS RELATED TO TREATMENT												
1	randomised trials	not serious	not serious	not serious	serious [c]	none	70/477 (14.7%)	70/479 (14.6%)	RR 1.00 (0.74 to 1.36)	0 fewer per 1,000 (from 38 fewer to 53 more)	⨁⨁⨁◯ MODERATE	CRITICAL
DISCONTINUATION DUE TO ADVERSE DRUG REACTIONS												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	16/477 (3.4%)	28/479 (5.8%)	RR 0.57 (0.31 to 1.05)	25 fewer per 1,000 (from 40 fewer to 3 more)	⨁⨁⨁◯ MODERATE	CRITICAL

[a] Optimal information size not met.
[b] Large CI including both appreciable benefits and harms. Very few events.
[c] CI includes both appreciable benefit and harm.

PICO 10: Should preventive treatment be recommended for contacts of patients with multidrug-resistant or rifampicin-resistant TB?

Preventive treatment for contacts of patients with multidrug- or rifampicin-resistant TB

Five studies that included fewer than 20 participants who completed preventive TB treatment were excluded. In addition, the study by Kritski was excluded as only isoniazid monotherapy was given.

Overall quality: very low

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preventive treatment	No treatment	Relative (95% CI)	Absolute (95% CI)		
INCIDENCE OF ACTIVE TB DISEASE (BOTH DRUG-SUSCEPTIBLE AND DRUG-RESISTANT TB)												
4 *(66–69)*	Observational	Very serious[1]	Not serious	Not serious	Very serious[3]	None	2/41 (4.9%)	13/64 (20.3%)	0.20 (0.04;0.94)[4]	154 fewer per 1000 (273 fewer to 36 fewer)	⨁◯◯◯ Very low	Critical
							0/93 (0%)	3/15 (20%)	0.02 (0.00;0.39)[5]	200 fewer per 1000 (403 fewer to 3 more)		
							0/21 (0%)	0/10 (0%)	–[6]	0 more per 1000 (138 fewer to 138 more)		
							0/30 (0%)	0/166 (0%)	–[7]	0 more per 1000 (45 fewer to 45 more)		
INCIDENCE OF MDR-TB												
3[2] *(66, 67, 69)*	Observational	Very serious[1]	Not serious	Not serious	Very serious[3]	None	0/93 (0%)	3/15 (20%)	0.02 (0.00;0.39)[5]	200 fewer per 1000 (403 fewer to 3 more)	⨁◯◯◯ Very low	Critical
							0/21 (0%)	0/10 (0%)	–[6]	0 more per 1000 (138 fewer to 138 more)		
							0/30 (0%)	0/166 (0%)	–[7]	0 more per 1000 (45 fewer to 45 more)		
MORTALITY												
0	No evidence								Cannot be estimated		–	Important

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preventive treatment	No treatment	Relative (95% CI)	Absolute (95% CI)		
ADVERSE EVENTS												
0	No evidence								Cannot be estimated		–	Critical
DEVELOPMENT OF DRUG RESISTANCE												
0	No evidence											Important

[1] Risk of bias in selection of the control group, and none of the studies adjusted for confounders. Downgraded by two levels.
[2] The study by Shaaf et al. was excluded, as the incidence of MDR-TB was not reported.
[3] Small sample sizes and wide 95% CIs. Downgraded by two levels.
[4] Reference *(68)*
[5] Reference *(66)*
[6] Reference *(67)*
[7] Reference *(69)*

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World Health Organization

For further information, please contact:

World Health Organization
20, Avenue Appia CH-1211 Geneva 27 Switzerland
Global TB Programme
Web site: www.who.int/tb