SUPPLEMENTARY TABLES: Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence and references

Question: Should 6 months of isoniazid compared to placebo be used in HIV-uninfected children and adults?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**6 months of isoniazid**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
4 [1,2,3,4]	randomised trials	serious [a]	not serious	not serious	not serious	none	298/11395 (2.6%)	465/11182 (4.2%)	**RR 0.59** (0.51 to 0.68)	**17 fewer per 1,000** (from 13 fewer to 20 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Hepatotoxicity												
2 [2,3*]	randomised trials	serious [b]	not serious	not serious	not serious	strong association	44/11066 (0.4%)	7/10897 (0.1%)	**RR 6.35** (2.86 to 14.10)	**3 more per 1,000** (from 1 more to 8 more)	⊕⊕⊕⊕ HIGH	CRITICAL

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

Explanations

a. Possible selection and performance bias.

b. Possible performance, detection, and attrition bias.

References

1. Xie Q-B, Wen F-Q, Yin G. [Isoniazid prophylaxis for pulmonary tuberculosis in Chinese patients with rheumatoid arthritis receiving long-term methotrexate therapy]. *Sichuan Da Xue Xue Bao Yi Xue Ban*; 2009.

2. Horwitz O, Payne PG, Wilbek E. Epidemiological Basis of Tuberculosis Eradication. 4. Isoniazid Trial in Greenland. *Bull World Health Organ*; 1966.

3. International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow up in the IUAT trial. *Bull World Health Organ*; 1982.

4. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. *Am Rev Respir Dis*; 1992.

*Partly estimated by authors from data provided in the IUAT study.

Question: Should 9 months of isoniazid compared to no treatment be used HIV-uninfected children and adults?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**9 months of isoniazid**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
2 [1,2]	randomised trials	serious [a]	not serious	serious [b]	not serious	strong association	10/1650 (0.6%)	27/1583 (1.7%)	**RR 0.36** (0.17 to 0.73)	**11 fewer per 1,000** (from 5 fewer to 14 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Hepatotoxicity												
0									not estimable		-	CRITICAL

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

Explanations

a. Possible selection, performance, and detection bias.

b. Kim et al. targeted kidney and pancreas transplant recipients.

References

1. Kim SH, Lee So, Park IA, Kim SM, Park SJ, Yun SC, et al. Isoniazid treatment to prevent TB in kidney and pancreas transplant recipients based on an interferon-gamma releasing assay: an exploratory randomized controlled trial. *J Antimicrob Chemother*; 2015.

2. Debre R, Perdrizet S, Lotte A, Naveau M, Lert F. Isoniazid chemoprophylaxis of latent primary tuberculosis. *Int J Epidemiol*; 1972.

Question: Should 12 months of isoniazid compared to placebo or no treatment be used in HIV-uninfected adults and children?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**12 months of isoniazid**	**placebo or no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
15 [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15]	randomised trials	serious [a]	not serious	not serious	not serious	strong association	258/41415 (0.6%)	605/41125 (1.5%)	**RR 0.48** (0.37 to 0.62)	**8 fewer per 1,000** (from 6 fewer to 9 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Hepatotoxicity												
5 [1,11,12,14,16*]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	99/7599 (1.3%)	53/7631 (0.7%)	**RR 1.90** (0.64 to 5.63)	**6 more per 1,000** (from 3 fewer to 32 more)	⨁⨁◯◯ LOW	CRITICAL

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

Explanations

a. Possible selection, performance, and detection bias.

b. Wide 95% CI that crosses line of no effect.

References

1. John GT, Thomas PP, Thomas M, Jeyaseelan L, Jacob CK, Shastry JC. A double-blind randomized controlled trial of primary isoniazid prophylaxis in dialysis and transplant patients. *Transplantation*; 1994.

2. Ma L, Lin B, Wang L, Wang D, Li G, Wang G. [Preventive therapy for iatrogenic active tuberculosis in systemic lupus erythematosus patients]. *Zhonghua Yi Xue Za Zhi*; 2014.

3. Falk A, Fuchs GF. Prophylaxis with isoniazid in inactive tuberculosis. A Veterans Administration Cooperative Study XII. *Chest*; 1978.

4. Egsmose T, Ang'awa JO, Poti SJ. The use of isoniazid among household contacts of open cases of pulmonary tuberculosis. *Bull World Health Organ*; 1965.

5. Comstock GW, Ferebee SH, Hammes LM. A controlled trial of community-wide isoniazid prophylaxis in Alaska. *Am Rev Respir Dis*; 1967.

6. Bush OB Jr, Sugimoto M, Fujii Y, Brown FA Jr. Isoniazid prophylaxis in contacts of persons with known tuberculosis. Second report. *Am Rev Respir Dis*; 1965.

7. Del Castillo H, Bautista LD, Jacinto CP, Lorenzo CE, Lapuz S, Legaspi B. Chemoprophylaxis in the Philippines: A controlled pilot study among household contacts of tuberculosis cases. *Bull Quezon Inst*; 1965.

8. Mount FW, Ferebee SH. The effect of isoniazid prophylaxis on tuberculosis morbidity among household contacts of previously known cases of tuberculosis. *Am Rev Respir Dis*; 1962.

9. Ferebee SH, Mount FW. Tuberculosis morbidity in a controlled trial of the prophylactic use of isoniazid among household contacts. *Am Rev Respir Dis*; 1962.

10. Ferebee SH, Mount FW,Murray FJ, Livesay VT. A controlled trial of isoniazid prophylaxis in mental institutions. *Am Rev Respir Dis*; 1963.

11. International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow up in the IUAT trial. *Bull World Health Organ*; 1982.

12. Madhi SA, Nachman S, Violari A, et al. Primary isoniazid prophylaxis against tuberculosis in HIV-exposed children. *N Engl J Med*; 2011.

13. Naqvi R, Navqi , Akhtar S, et al. Use of isoniazid chemoprophylaxis in renal transplant recipients. *Nephrol Dial Transplant*; 2010.

14. Vikrant S, Agarwal SK,Gupta S,et al.. Prospective randomized control trial of isoniazid chemoprophylaxis during renal replacement therapy. *Transpl Infect*; 2005.

15. Debre R, Perdrizet S, Lotte A, Naveau M, Lert F. Isoniazid chemoprophylaxis of latent primary tuberculosis. *Int J Epidemiol*; 1972.

16. Bailey WC. The effect of isoniazid on transaminase level. *Ann Intern Med*; 1974.

*Partially estimated based on data from IUAT study.

Question: Should 6 months of isoniazid compared to placebo or no treatment be used in HIV-infected adults?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**6 months of isoniazid**	**placebo or no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
5 [1,2,3,4,5,6]	randomised trials	not serious [a]	not serious	not serious	not serious	none	135/2915 (4.6%)	191/2762 (6.9%)	**RR 0.67** (0.53 to 0.85)	**23 fewer per 1,000** (from 10 fewer to 33 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Hepatotoxicity												
3 [1,4,5,6]	randomised trials	serious [b]	not serious	not serious	serious [c]	none	23/1439 (1.6%)	24/1747 (1.4%)	**RR 1.38** (0.60 to 3.18)	**5 more per 1,000** (from 5 fewer to 30 more)	⨁⨁◯◯ LOW	CRITICAL

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

Explanations

a. Possible attrition bias.

b. Possible selection or attrition bias.

c. Wide 95% CI that crosses line of no effect.

References

1. Gordin FM, Matts JP, Miller C, et al. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. *N Engl J Med*; 1997.

2. Hawken MP, Meme HK, Elliott LC, et al. Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: results of a randomized controlled trial. *AIDS*; 1997.

3. Mwinga A, Hosp M, Godfrey-Faussett P, et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. *AIDS*; 1998.

4. Johnson JL, Okwera A, Hom DL, Mayanja H, Mutuluuza KC, Nsubuga P, et al. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. *AIDS*; 2001.

5. Whalen CC, Johnson JL, Okwera A, Hom DL, Huebner R, Mugyenyi P, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. *N Engl J Med*; 1997.

6. Danel C, Moh R, Gabillard D, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med*; 2015.

Question: Should 12 months of isoniazid compared to placebo be used HIV-infected children?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**12 months of isoniazid**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
3 [1,2,3]	randomised trials	serious [a]	not serious	not serious	not serious	none	40/490 (8.2%)	58/487 (11.9%)	**RR 0.70** (0.47 to 1.04)	**36 fewer per 1,000** (from 5 more to 63 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Hepatotoxicity												
1 [3]	randomised trials	serious [a]	not serious	not serious	not serious	none	1/273 (0.4%)	5/274 (1.8%)	**RR 0.20** (0.02 to 1.71)	**15 fewer per 1,000** (from 13 more to 18 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

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

Explanations

a. Possible selection, detection, and attrition bias.

References

1. Gray DM, Workman LJ, Lombard CJ, et al. Isoniazid preventive therapy in HIV-infected children on antiretroviral therapy: a pilot study. *Int J Tuberc Lung Dis*; 2014.

2. Zar HJ, Cotton MF, Strauss S, et al. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV. *BMJ*; 2007.

3. Madhi SA, Nachman S, Violari A, et al. Primary isoniazid prophylaxis against tuberculosis in HIV-exposed children. *N Engl J Med*; 2011.

Question: Should 12 months of isoniazid compared to placebo be used in HIV-infected adults and children?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**12 months of isoniazid**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
5 [1,2,3,4,5]	randomised trials	not serious	not serious	not serious	not serious	none	86/1200 (7.2%)	122/1204 (10.1%)	**RR 0.72** (0.52 to 0.99)	**28 fewer per 1,000** (from 1 fewer to 49 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Hepatotoxicity												
3 [1,4,5]	randomised trials	not serious	not serious	not serious	serious [a]	none	20/983 (2.0%)	15/991 (1.5%)	**RR 1.34** (0.69 to 2.61)	**5 more per 1,000** (from 5 fewer to 24 more)	⊕⊕⊕◯ MODERATE	CRITICAL

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

Explanations

a. Wide 95% CI that crosses line of no effect.

References

1. Mohammed A, Myer L, Ehrlich R,et al. Randomized controlled trial of isoniazid preventive therapy in South African adults with advanced HIV disease. *Int J Tuberc Lung Dis*; 2007.

2. Zar HJ, Cotton MF, Strauss S, et al. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV. *BMJ*; 2007.

3. Gray DM, Workman LJ, Lombard CJ, et al. Isoniazid preventive therapy in HIV-infected children on antiretroviral therapy: a pilot study. *Int J Tuberc Lung Dis*; 2014.

4. Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomized double-blind, placebo-controlled trial. *Lancet*; 2014.

5. Madhi SA, Nachman S, Violari A,et al. Primary isoniazid prophylaxis against tuberculosis in HIV-exposed children. *N Engl J Med*; 2011.

Question: Should 12 months of isoniazid compared to no treatment be used in HIV-infected adults?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**12 months of isoniazid**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
2 [1,2]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	10/184 (5.4%)	15/171 (8.8%)	**RR 0.68** (0.20 to 2.32)	**28 fewer per 1,000** (from 70 fewer to 116 more)	⨁⨁◯◯ LOW	CRITICAL
Hepatotoxicity												
0									not estimable		-	

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

Explanations

a. Possible selection, performance, and detection bias

b. Wide 95% CI that crosses line of no effect.

References

1. Fitzgerald DW, Severe P, Mellon LR, et al. No effect of isoniazid prophylaxis for purified protein derivative-negative HIV-infected adults living in a country with endemic tuberculosis: results of a randomized trial. *J Acquir Immune Defic Syndr*; 2001.

2. Pape JW, Jean SS, Ho JL, et al. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. *Lancet*; 1993.

Question: Should 3 months of isoniazid plus rifampin compared to no treatment or placebo be used in HIV-uninfected adults and children?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**3 months of isoniazid plus rifampin**	**no treatment or placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
2 [1,2]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	30/252 (11.9%)	53/252 (21.0%)	**RR 0.46** (0.15 to 1.36)	**114 fewer per 1,000** (from 76 more to 179 fewer)	⨁⨁◯◯ LOW	CRITICAL
Hepatotoxicity												
0									not estimable		-	

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

Explanations

a. Possible selection bias.

b. 95% CI crosses the line of no effect.

References

1. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. *Am Rev Respir Dis*; 1992.

2. Gupta DK, Kumar R, Nath N, Kothari AK. Chemoprophylaxis in high-risk children-analysis of 8 years' follow-up: preliminary report. *Indian J Tuberc*; 1993.

Question: Should 3 months of isoniazid plus rifampin compared to 6 months of isoniazid be used in HIV-uninfected adults and children?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**3 months of isoniazid plus rifampin**	**6 months of isoniazid**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
3 [1,2,3]	randomised trials	serious [a]	not serious	not serious	not serious	none	27/514 (5.3%)	27/512 (5.3%)	**RR 1.04** (0.64 to 1.70)	**2 more per 1,000** (from 19 fewer to 37 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hepatotoxicity												
2 [2,3]	randomised trials	serious [a]	not serious	not serious	not serious	none	3/347 (0.9%)	4/339 (1.2%)	**RR 0.73** (0.18 to 2.95)	**3 fewer per 1,000** (from 10 fewer to 23 more)	⊕⊕⊕◯ MODERATE	CRITICAL

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

Explanations

a. Possible selection bias.

References

1. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. *Am Rev Respir Dis*; 1992.

2. Jimenez-Fuentes M, de Souza-Galvao M, Mila Auge C, et al. Rifampicin plus isoniazid for the prevention of tuberculosis in an immigrant population. *Int J Tuberc Lung Dis*; 2013.

3. Geijo, MP. Short-course isoniazid and rifampin compared with isoniazid for latent tuberculosis infection: a randomized clinical trial. *Enferm Infecc Microbiol Clin*; 2007.

Question: Should 3 months of isoniazid plus rifampin compared to 9 months of isoniazid be used in HIV-uninfected adults?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**3 months of isoniazid plus rifampin**	**9 months of isoniazid**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	1/98 (1.0%)	0/98 (0.0%)	**RR 3.00** (0.12 to 72.80)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
Hepatotoxicity												
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	6/98 (6.1%)	8/98 (8.2%)	**RR 0.75** (0.27 to 2.08)	**20 fewer per 1,000** (from 60 fewer to 88 more)	⨁⨁◯◯ LOW	CRITICAL

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

Explanations

a. Possible performance, attrition, and detection bias.

b. Very wide 95% CI with small sample size.

References

1. Martinez AE, Solera J, Serna E, et al. Compliance, tolerance and effectiveness of a short chemoprophylaxis regimen for the treatment of tuberculosis. *Med Clin (Barc)*; 1998.

Question: Should 4 months of rifampin compared to 6 months of isoniazid be used in HIV-uninfected children?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**4 months of rifampin**	**6 months of isoniazid**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
1 [1]	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	0/50 (0.0%)	0/50 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. Possible selection, performance, detection, attrition, and reporting bias.

b. Small sample size.

References

1. Magdorf K, Arizzi-Ruche AF, Geither LJ, et al. Compliance and tolerance of new antitubercular short-term chemopreventive regimens in childhood--a pilot project. *Pneumologie*; 1994.

Question: 4 months of rifampin compared to 9 months of isoniazid for HIV-uninfected children

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**4 months of rifampin**	**9 months of isoniazid**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious [b]	none	0/422 (0.0%)	2/407 (0.5%)	**RR 0.19** (0.01 to 4.01)	**4 fewer per 1,000** (from 5 fewer to 15 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Hepatotoxicity												
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	0/422 (0.0%)	0/407 (0.0%)	not estimable		⨁⨁⨁◯ MODERATE	CRITICAL

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

Explanations

a. Possible selection and performance bias

b. Although the 95% CI is wide, the pre-determined non-inferiority margin was met.

References

1. Diallo T, Adjobimey M, Ruslami R, et al. Safety and side effects of rifampin versus isoniazid in children. *N Engl J Med*; 2018.

Question: Should 4 months of rifampin compared to 9 months of isoniazid be used in HIV-uninfected adults?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**4 months of rifampin**	**9 months of isoniazid**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious [b]	none	8/3443 (0.2%)	9/3416 (0.3%)	**RR 0.88** (0.34 to 2.28)	**0 fewer per 1,000** (from 2 fewer to 3 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Hepatotoxicity												
1 [2,3]	randomised trials	serious [a]	not serious	not serious	not serious	strong association	11/3499 (0.3%)	60/3469 (1.7%)	**RR 0.19** (0.10 to 0.36)	**14 fewer per 1,000** (from 11 fewer to 16 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

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

Explanations

a. Possible selection and performance bias.

b. Although there is a wide 95% CI, the pre-set non-inferiority margin was met.

References

1. Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med*; 2018.

2. Menzies D, Dion MJ, Rabinovitch B, et al. 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.

3. Menzies D, Long R, Trajman A, 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.

Question: Should 3 months of isoniazid plus rifampin compared to placebo or no treatment be used HIV-infected adults?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**3 months of isoniazid plus rifampin**	**placebo or no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
2 [1,2,3]	randomised trials	serious [a]	not serious	not serious	not serious	strong association	25/638 (3.9%)	46/541 (8.5%)	**RR 0.46** (0.29 to 0.74)	**46 fewer per 1,000** (from 22 fewer to 60 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Hepatotoxicity												
1 [3]	randomised trials	serious [b]	not serious	not serious	serious [c]	none	1/82 (1.2%)	0/77 (0.0%)	**RR 2.82** (0.12 to 68.20)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL

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

Explanations

a. Possible performance, detection, and attribution bias.

b. Possible performance, detection, attribution, and reporting bias.

c. Very wide 95% CI with small sample size.

References

1. Whalen CC, Johnson JL, Okwera A, Hom DL, Huebner R, Mugyenyi P, et al.. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. *N Engl J Med*; 1997.

2. Johnson JL, Okwera A, Hom DL, Mayanja H, Mutuluuza KC, Nsubuga P, et al. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. *AIDS*; 2001.

3. Rivero A, Lopez-Cortes L, Castillo R, et al. [Ransomized trial of three regimens to prevent tuberculosis in HIV-infected patients with anergy]. *Enferm Infecc Microbiol Clin*; 2003.

Question: Should 3 months of isoniazid plus rifampin compared to 6 months of isoniazid be used in HIV-infected adults?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**3 months of isoniazid plus rifampin**	**6 months of isoniazid**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
4 [1,2,3,4,5]	randomised trials	serious [a]	not serious	not serious	not serious	none	54/1067 (5.1%)	63/1053 (6.0%)	**RR 0.85** (0.59 to 1.21)	**9 fewer per 1,000** (from 13 more to 25 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Hepatoxicity												
4 [1,2,3,4,5]	randomised trials	serious [a]	not serious	not serious	not serious	none	23/1067 (2.2%)	28/1053 (2.7%)	**RR 0.85** (0.51 to 1.48)	**4 fewer per 1,000** (from 13 fewer to 13 more)	⊕⊕⊕◯ MODERATE	CRITICAL

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

Explanations

a. Possible selection, performance, and detection bias.

References

1. Martinson NA, Barnes GL, Moulton LH, et al.. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*; 2011.

2. Rivero A, López-Cortés L,Castillo R,Verdejo J,García MA,Martínez-Marcos FJ,et al. [Randomized clinical trial investigating three chemoprophylaxis regimens for latent tuberculosis infection in HIV-infected patients]. *Enferm Infecc Microbiol Clin*; 2007.

3. Rivero A, Lopez-Cortes L, Castillo R, et al. [Ransomized trial of three regimens to prevent tuberculosis in HIV-infected patients with anergy]. *Enferm Infecc Microbiol Clin*; 2003.

4. Johnson JL, Okwera A, Hom DL, Mayanja H, Mutuluuza KC, Nsubuga P, et al. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. *AIDS*; 2001.

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Question: Should 3 months of isoniazid plus rifapentine compared to 9 months of isoniazid be used in HIV-uninfected children?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**3 months of isoniazid plus rifapentine**	**9 months of isoniazid**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	0/471 (0.0%)	3/434 (0.7%)	**RR 0.31** (0.01 to 7.52)	**5 fewer per 1,000** (from 7 fewer to 45 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hepatotoxicity												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	3/539 (0.6%)	1/493 (0.2%)	**RR 2.74** (0.29 to 26.30)	**4 more per 1,000** (from 1 fewer to 51 more)	⊕⊕⊕◯ MODERATE	CRITICAL

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

Explanations

a. Wide 95% CI with few events reported.

References

1. Villarino ME, Scott NA,Weis,SE,et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. *JAMA Pediatr*; 2015.

Question: Should 3 months of isoniazid plus rifapentine compared to 9 months of isoniazid be used in HIV uninfected adults and children?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**3 months of isoniazid plus rifapentine**	**9 months of isoniazid**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	7/3986 (0.2%)	15/3745 (0.4%)	**RR 0.44** (0.18 to 1.07)	**2 fewer per 1,000** (from 0 fewer to 3 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Hepatotoxicity												
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	strong association	18/3986 (0.5%)	103/3745 (2.8%)	**RR 0.16** (0.10 to 0.27)	**23 fewer per 1,000** (from 20 fewer to 25 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

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

Explanations

a. Possible performance and detection bias due to participants, personnel, and outcome assessment not being blinded.

References

1. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*; 2011.

Question: Should 3 months of isoniazid plus rifapentine compared to 6 month of isoniazid be used in HIV-infected adults?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**3 months of isoniazid plus rifapentine**	**6 month of isoniazid**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	24/328 (7.3%)	22/327 (6.7%)	**RR 1.09** (0.62 to 1.90)	**6 more per 1,000** (from 26 fewer to 61 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hepatotoxicity												
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	17/328 (5.2%)	17/327 (5.2%)	**RR 1.00** (0.52 to 1.92)	**0 fewer per 1,000** (from 25 fewer to 48 more)	⊕⊕⊕◯ MODERATE	CRITICAL

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

Explanations

a. Possible performance and detection bias.

References

1. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*; 2011.

Question: Should 3 months of isonaizid plus rifapentine compared to 9 months of isoniazid be used in HIV-infected adults?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**3 months of isonaizid plus rifapentine**	**9 months of isoniazid**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	2/206 (1.0%)	6/193 (3.1%)	**RR 0.31** (0.06 to 1.53)	**21 fewer per 1,000** (from 16 more to 29 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Hepatotoxicity												
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	2/206 (1.0%)	8/193 (4.1%)	**RR 0.23** (0.05 to 1.09)	**32 fewer per 1,000** (from 4 more to 39 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

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

Explanations

a. Possible selection, performance, and reporting bias.

References

1. Sterling TR, Scott NA, Miro JM, et al. Three months of weekly rifapentine and isoniazid for treatment of Mycobacterium tuberculosis infection in HIV-coinfected persons. *AIDS*; 2016.

Question: Should 3 months of isoniazid plus rifapentine compared to continuous use of isoniazid (up to 6 years) be used in HIV-infected adults?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**3 months of isoniazid plus rifapentine**	**continuous use of isoniazid (up to 6 years)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Tuberculosis Disease												
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	24/328 (7.3%)	8/164 (4.9%)	**RR 1.50** (0.69 to 3.27)	**24 more per 1,000** (from 15 fewer to 111 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hepatotoxicity												
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	strong association	17/328 (5.2%)	35/164 (21.3%)	**RR 0.24** (0.14 to 0.42)	**162 fewer per 1,000** (from 124 fewer to 184 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

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

Explanations

a. Possible performance and detection bias.

References

1. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*; 2011.