Revista da Sociedade Brasileira de Medicina Tropical

REFERÊNCIA

VIDAL, Júlia Souza; SILVA, Marcus Tolentino; SANCHEZ, Mauro Niskier. Rifapentine for latent tuberculosis infection treatment in the general population and human immunodeficiency virus-positive patients: summary of evidence. **Revista da Sociedade Brasileira de Medicina Tropical**, Uberaba, v. 48, n. 5, p. 507-513, set./out. 2015. Disponível em: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0037-86822015000500507&lng=en&nrm=iso>. Acesso em: 10 maio 2018. doi: http://dx.doi.org/10.1590/0037-8682-0156-2014.

Revista da Sociedade Brasileira de Medicina Tropical 48(5):507-513, Sep-Oct, 2015
http://dx.doi.org/10.1590/0037-8682-0156-2014

Review Article

Rifapentine for latent tuberculosis infection treatment in the general population and human immunodeficiency virus-positive patients: summary of evidence

Júlia Souza Vidal[1], *Marcus Tolentino Silva*[2] *and Mauro Niskier Sanchez*[1]

[1]. Departamento de Saúde Coletiva, Faculdade de Ciências da Saúde, Universidade de Brasília, Brasília, Distrito Federal, Brazil. [2]. Departamento de Saúde Coletiva, Faculdade de Medicina, Universidade Federal do Amazonas, Manaus, Amazonas, Brazil.

ABSTRACT

Latent tuberculosis infection (LTBI) and human immunodeficiency virus (HIV)-coinfection are challenges in the control of tuberculosis transmission. We aimed to assess and summarize evidence available in the literature regarding the treatment of LTBI in both the general and HIV-positive population, in order to support decision making by the Brazilian Tuberculosis Control Program for LTBI chemoprophylaxis. We searched MEDLINE, Cochrane Library, Centre for Reviews and Dissemination, Embase, LILACS, SciELO, Trip database, National Guideline Clearinghouse, and the Brazilian Theses Repository to identify systematic reviews, randomized clinical trials, clinical guidelines, evidence-based synopses, reports of health technology assessment agencies, and theses that investigated rifapentine and isoniazid combination compared to isoniazid monotherapy. We assessed the quality of evidence from randomized clinical trials using the Jadad Scale and recommendations from other evidence sources using the Grading of Recommendations, Assessment, Development, and Evaluations approach. The available evidence suggests that there are no differences between rifapentine + isoniazid short-course treatment and the standard 6-month isoniazid therapy in reducing active tuberculosis incidence or death. Adherence was better with directly observed rifapentine therapy compared to self-administered isoniazid. The quality of evidence obtained was moderate, and on the basis of this evidence, rifapentine is recommended by one guideline. Available evidence assessment considering the perspective of higher adherence rates, lower costs, and local peculiarity context might support rifapentine use for LTBI in the general or HIV-positive populations. Since novel trials are ongoing, further studies should include patients on antiretroviral therapy.

Keywords: Latent tuberculosis. Evidence-based practice. Decision making.

INTRODUCTION

Tuberculosis (TB) is a pronounced public health problem worldwide[1]. Unlike the active disease, latent tuberculosis infection (LTBI) is a manifestation wherein bacilli have low metabolic activity, and hence, affected patients do not show any obvious symptom or etiologic agent signs in sputum despite a positive tuberculin test[2]. Around one-third of the global population is currently infected by latent TB bacilli[1,3]. Bacilli dormancy and human immunodeficiency virus (HIV) coinfection are responsible for the persistence of TB as a public health problem[1]. Hence, control measures are needed to control TB transmission and LTBI development into active disease.

To control the spread of TB, the Brazilian Ministry of Health and the World Health Organization (WHO) currently recommend isoniazid monotherapy for LTBI treatment (also known as secondary chemoprophylaxis)[4,5]. In Brazil, the National Tuberculosis Control Program [Programa Nacional de Controle da Tuberculose (PNCT)] recommends isoniazid for at least 6 months for both the general population and HIV-positive adults and adolescents[3,5].

Although isoniazid monotherapy is used for LBTI treatment, the efficacy of rifamycins (e.g., rifapentine), their low cost, and concerns about adherence and isoniazid-induced hepatitis led researchers to investigate the use of rifamycins in monotherapy or combination therapy with others anti-TB drugs. Recently, a 3-month course of isoniazid-rifapentine combination therapy was reported, which was one of the shortest course regimens thus far[3,6]. However, rifapentine has not been approved for this use in Brazil[7].

Considering the emerging therapeutic alternatives to isoniazid monotherapy, the present study aimed to assess and to synthetize evidence on the effectiveness and safety of rifapentine-isoniazid combination therapy in LTBI chemoprophylaxis in the general and HIV-positive population to support national recommendations for TB control.

Corresponding author: Dr. Mauro Niskier Sanchez. Faculdade de Ciências da Saúde/Depto de Saúde Coletiva/UnB. Campus Universitário Darcy Ribeiro s/n, Asa Norte, 70910-900 Brasília, Distrito Federal, Brasil.
Phone: 55 61 3107-1952
e-mail: mauro.sanchez4@gmail.com
Received 14 April 2015
Accepted 12 June 2015

METHODS

This study is a summary of evidence that comprehends systematic literature search, studies selection, quality of evidence assessment, and data extraction of effectiveness and safety of rifapentine-isoniazid combination therapy compared to LTBI isoniazid monotherapy in the general and HIV-positive population. International recommendations for LTBI chemoprophylaxis were also evaluated. In case of missing data, the authors of the respective studies were contacted.

Literature search - in April 2014, a systematic research was conducted, including systematic reviews, randomized controlled trials (RCT), clinical guidelines, reports of health technology assessment agencies, evidence-based synopses and theses that could update the Brazilian recommendations for LTBI chemoprophylaxis published in 2011[5]. A sensible research strategy was applied using the terms *rifapentine* and *latent tuberculosis* in MEDLINE (via PubMed), Cochrane Library (via www.bvs.br), Centre for Reviews and Dissemination (CRD), Embase, LILACS, SciELO, Trip database, National Guideline Clearinghouse (NGC), and Brazilian Theses Repository. Study type filters were activated, and no restrictions were placed on languages or publication dates.

Studies selection - the search aimed to identify systematic reviews or RCT, both of which are considered high-quality methodological studies. Systematic reviews and RCT were eligible if the assessed effectiveness and safety of isoniazid and rifapentine combination were compared to those of isoniazid monotherapies in the general population with LTBI, including co-infected and diagnosed individuals with HIV. Other clinical trials designs, patients with active TB, comparisons not based on isoniazid, and pharmacokinetic studies were ineligible.

In addition to effectiveness studies, clinical guidelines, reports of health technology-assessment agencies, evidence-based synopses and theses were selected to discuss the inclusion of rifapentine in international treatment protocols. One author (JSV) selected the studies after reading the titles and abstracts. Data on the effectiveness and safety of rifapentine + isoniazid combination therapy were peer reviewed to confirm the findings.

Analysis of eligible studies - study quality was assessed using the criterion proposed by Jadad[8] for RCT and the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach for other sources of information[9]. This analysis allowed classification of information reliability and recommendation implications. Data on the effectiveness and safety of rifapentine + isoniazid combination therapy are shown below.

RESULTS

Four hundred studies were found through the literature search. In total, 10 studies were included **(Figure 1)**: 1 systematic review[10], 2 randomized controlled trials[11] [12], 1 American evidence-based synopsis[13], and 6 clinical guidelines from different settings – United States of America[14] [15], United Kingdom[16] [17], Australia[18], and WHO[4]. The results of the quality-of-evidence assessment of the systematic review, evidence-based synopsis, and 3 clinical guidelines that considered the use of rifapentine are shown in **Table 1**.

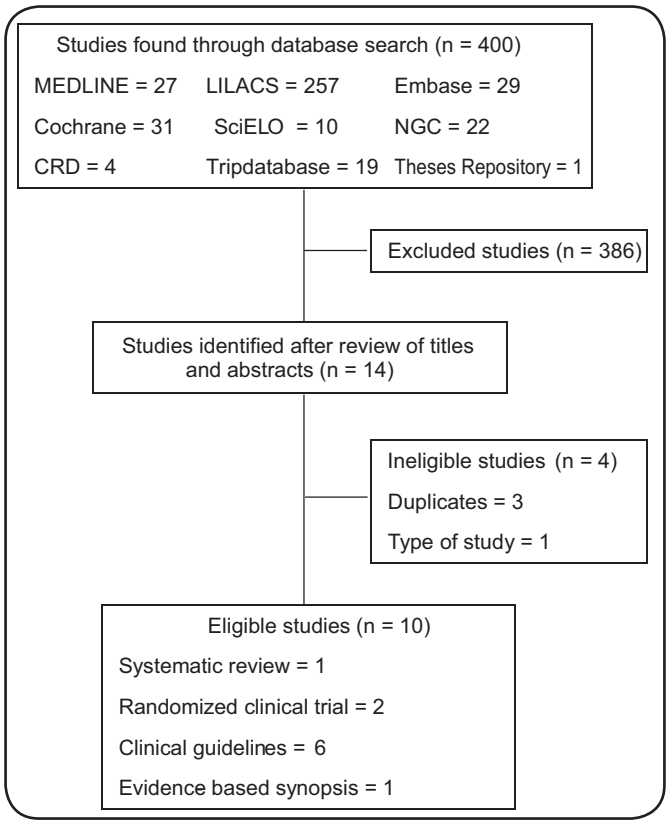

FIGURE 1 - Search results and selection of articles. LILACS: *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (Literature in the Health Sciences in Latin America and the Caribbean, in Portuguese language); **SciELO**: Scientific Electronic Library Online; **NGC:** National Guideline Clearinghouse**; CRD:** Centre for Reviews and Dissemination.

Both the RCTs included defined antiretroviral therapy as an exclusion criterion. Martinson et al.[11] designed an open-label RCT, but properly described randomization since the algorithm was computer generated. Follow-up losses were not clear; it was possible to identify how many subjects withdrew consent, but not the number of subjects who completed the follow-up time. Nevertheless, the primary endpoint statistical analysis was based on intention-to-treat analysis. When consulted, the authors confirmed that randomization concealment was maintained. Sterling et al.[12] designed an open-label non-inferiority RCT. It was a well-conducted cluster randomization, and its supplementary appendix clearly described the randomization and losses to follow-up. However, the study did not mention if there was randomization concealment. Further, it was not a blinded study, and the preference of the per-protocol analysis for efficacy endpoints instead of the intention-to-treat analysis may have presented a methodological limitation.

The systematic review by Sharma et al.[10] evaluated the effects of rifamycins (rifampin, rifabutin, and rifapentine) compared to isoniazid in HIV-negative patients at high risk of developing active TB. This study was selected as available

TABLE 1 - Quality-of-evidence assessment for rifapentine chemoprophylaxis in LTBI from a systematic review, evidence-based synopsis, and clinical guidelines, adapted from GRADE.

Author/ Locality, year	Recommendation	Evidence of support	Risk of bias	Inconsistency in results	Directness of evidence	Imprecision	Publication bias	Large magnitude of effect	All plausible confounding factors could reduce the demonstrated effect	Dose-response gradient	Quality of evidence
Sharma, 2013[10]	Experience with rifapentine is limited and the potential for adverse events should be monitored	1 RCT	Present[a]	No	No	No	No	No	No	No	Moderate
WHO, 2011[4]	Regimens with pyrazinamide, rifampin, or rifapentine are as effective as isoniazid, but with higher rates of toxicity	Not clear[b]	Present[c]	Not clear[d]	Not clear[c]	Yes[e]	Not clear[c]	No	No	No	Low
CDC, 2012[13]	Rifapentine + isoniazid (max. 900mg each) once a week for 3 months under DOT	3 RCT	Present[f]	No	No	Yes[d]	Yes[g]	No	No	No	Moderate
USA, 2012a[14]	Does not recommend rifapentine + isoniazid for 3 months: risk of interaction with ART	1 RCT	Present[e]	No	No	No	No	No	No	No	Low
USA, 2012b[15]	Does not recommend rifapentine + isoniazid for patients aged < 2 years and children on ART	3 RCT	Present[e]	No	No	Yes[d]	Yes[g]	No	No	No	Moderate

LTBI: latent tuberculosis infection**; GRADE:** Grading of Recommendations, Assessment, Development and Evaluations**; RCT:** randomized controlled trials; **WHO**: World Health Organization; **CDC**: Centers for Disease Control and Prevention; **DOT**: directly observed therapy; **USA**: United States of America; **ART**: antiretroviral therapy. [a]Open-label, not blinded, not all properly randomized or analyzed by intention to treat; [b]According to the authors, these were based on 8 studies comparing isoniazid monotherapy to other regimens (with pyrazinamide, rifampin, and rifapentine), but such studies are not specified; [c]Despite applying the GRADE approach, it was not possible to identify the studies and check the performed quality assessment; [d]As these studies have not been identified, we cannot affirm that finding; [e]Large confidence interval; [f]Studies were open-label, not blinded, and not all were properly randomized or analyzed by intention to treat; [g]The exclusive availability of small studies may indicate a high risk of publication bias.

evidence for the efficacy and safety of rifapentine in the general population. For rifapentine, specifically, the authors described the results of the RCT by Sterling et al.[12]. The characteristics and results of this systematic review and the two RCTs are shown in **Table 2**.

Effectiveness - In the study by Martinson et al.[11], the proposed regimen of 3 months of rifapentine (900mg) + isoniazid (900mg) combination administered once a week under directly observed therapy (DOT) did not reduce TB incidence or mortality in adults with LTBI and HIV compared to the actual standard regimen of 6 months of isoniazid (300mg) self-administered daily. Similar to the rifapentine + isoniazid combination, others proposed regimens for LTBI chemoprophylaxis were not superior to isoniazid 6-month monotherapy in reducing TB or death incidences [rifamycin + isoniazid for 3 months: relative ratio (RR) = 0.80, 95% confidence interval (CI): 0.50-1.29, p = 0.34 and isoniazid monotherapy for up to 6 years: RR = 0.75, 95% CI: 0.38-1.38, p = 0.34].

In the RCT by Sterling et al.[12], LTBI chemoprophylaxis with 3 months of rifapentine (900mg) + isoniazid (900mg) combination therapy administered once a week under DOT is at least non-inferior to preventive treatment with 9 month isoniazid (300mg) self-administered daily for TB activation. It is noteworthy that this finding refers to not only HIV-positive individuals, but also a population at high risk of progression to active TB.

TABLE 2 - Characteristics and results of the systematic review and both RCTs included in this summary of evidence.

Study	Characteristics	Outcomes	Results
Martinson, 2011[11]	RCT (South Africa) n = 1,150 HIV-positive adults with LTBI 33 months of follow-up ▪ Rifapentine+isoniazid DOT for 12 weeks (RPT+H) 1x/week ▪ Rifamicin+isoniazid DOT for 12 weeks (RIF+H) 2x/week ▪ Isoniazid self-administered up to 6 years (6yH) 1x/day ▪ Isoniazid self-administered for 6 months (6mH) 1x/day	TB cases	RPT+H *versus* 6mH RR = 1.05 [95% CI: 0.56–1.97]; p = 0.87
		Death cases	RPT+H *versus* 6mH RR = 0.66 [95% CI: 0.33–1.26]; p = 0.18
		TB or death cases	RPT+H *versus* 6mH RR = 0.87 [95% CI: 0.54–1.39]; p = 0.54
		Adherence	RPT+H = 95.7% 6mH = 83.8%
		Severe adverse events	RPT+H = 8.7%; 6mH = 15.4% (p > 0.05) RIF+H = 10.6%; 6mH = 15.4% (p > 0.05)
		Hepatotoxicity	RPT+H =1.5%; 6mH = 5.5% RIF+H = 2.4%; 6mH = 5.5%
Sharma, 2013[10] and Sterling, 2011[12]	Multicenter RCT (Brazil, Canada, USA and Spain) n = 8,053 People aged > 12 years at high risk of LTBI progression to active disease Non-inferiority study 33 months of follow-up ▪ Rifapentine+isoniazid DOT for 3 months (3HP) 1x/week ▪ Isoniazid self-administered for 9 months (9H) 1x/day	TB cases	Difference in rates of TB = -0.19% with noninferiority margin of 0.75% (per protocol analysis) Difference in rates of TB = -0.24% with noninferiority margin of 0.75% (modified intention-to-treat analysis) RR = 0.44 [95% CI: 0.18–1.07]
		Death cases	RR = 0.75 [95% CI: 0.47–1.19]
		Adherence	3HP = 82.1%; 9H = 69% (p < 0.001) RR = 1.19 [95% CI: 1.16–1.22]
		Hepatotoxicity	3HP = 0.4%; 9H = 2.7% (p < 0.001) RR = 0.16 [95% CI: 0.10–0.27]
		Discontinuation due to an adverse event	3HP = 4.9%; 9H = 3.7% (p = 0.009) RR = 1.32 [95% CI: 1.07–1.64]

RCT: randomized controlled trials; **HIV:** human immunodeficiency virus; **LTBI:** latent tuberculosis infection**; DOT**: directly observed therapy; **TB**: tuberculosis; **RPT+H:** rifapentine+isoniazid**; 6mH:** isoniazid for 6 months**; 6yH:** isoniazid up to 6 years**; RR**: relative risk; **CI**: confidence interval; **RIF+H:** rifamicin+isoniazid; **USA:** United States of America; **3HP:** rifapentine+isoniazid for 3 months; **9H:** isoniazid for 9 months.

Both studies showed that adherence was higher in participants who received the combination of rifapentine + isoniazid, which was administered by DOT[11] [12].

Safety - Martinson et al.[11] reported that severe adverse events were less frequent with rifamycins like rifapentine, compared to the control (6 months with isoniazid), but this difference was not significant. Similarly, no difference was observed between the rifamycins and control groups in terms of increasing the levels of liver transaminases[11].

In contrast, Sterling et al.[12] reported benefits of the rifapentine + isoniazid combination, as the incidence of hepatotoxicity was lower than that with isoniazid monotherapy for 9 months. However, the addition of rifapentine was associated with a higher rate of treatment discontinuation due to adverse events, particularly hypersensitivity. No differences were observed in mortality (p = 0.22) and grade 3 (p = 0.24) and 4 (p = 0.32) adverse events[12], as defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

International recommendations - The recommendations from the clinical guidelines and evidence-based synopsis about LTBI treatment are shown in **Table 3**. Treatments with and without rifapentine were reviewed to guide the update of the Brazilian recommendation. We found that clinical guidelines available until 2011[4] [16] [17] did not recommended the use of rifapentine for LTBI chemoprophylaxis; the year in which the results of both RCTs[11] [12] herein presented were published.

Since 2012, guidelines started to cite rifapentine for prevention. The evidence-based synopsis of the Centers for Disease Control and Prevention (CDC), United States fo America[13], recommends isoniazid + rifapentine combination for 3 months under DOT for the general population and healthy HIV-positive patients. The recommendation was based on both RCTs reviewed in this summary study[11] [12] and on a third RCT, which was excluded because it was a phase II design and its comparator was different from isoniazid[19].

Despite considering the same RCTs, the guidelines from the National Institutes of Health (NIH) of the United States

TABLE 3 - Recommendations for LTBI treatment from clinical guidelines and evidence-based synopsis that rejected the hypothesis of active tuberculosis.

Locality, year	Population	Recommendation
WHO, 2011[4]	Adults and adolescents with HIV in resource-limited settings	Isoniazid (300mg/day) for 6 months (applies to pregnant women and patients on ART) Regimens with pyrazinamide, rifampin, or rifapentine are as effective as isoniazid, but with higher rates of toxicity
	Children with HIV in resource-limited settings	Isoniazid (10 mg/kg/day) for 6 months for children aged > 12 years unexposed of TB. In children aged < 12 years, the regimen is only indicated if they are exposed to TB cases.
UK, 2011[16]	Adults with HIV in an area of low TB prevalence	Isoniazid for 6 months or Rifampicin + isoniazid (300mg/day) for 3 months or Rifampicin + isoniazid (900mg/week) for 3 months or Rifampicin for 4 months
UK, 2011[17]	With HIV: any age and TT ≥ 6mm without BCG or TT ≥ 15mm with BCG	Isoniazid for 6 months or Rifampicin for 6 months, if up to 35 years of age and contact with isoniazid-resistant TB case
	No HIV: up to 35 years and ≥ 6mm without BCG or TT ≥ 15 mm with BCG	Isoniazid for 6 months or Rifampicin + isoniazid for 3 months
CDC, 2012[13]	Age > 12 years, with or without HIV, healthy and without ART	Rifapentine + isoniazid (maximum 900mg each) once a week for 3 months under DOT
Australia, 2012[18]	With and without HIV, any age and pregnant	Isoniazid (300 mg/day) for 9 months (first line and pregnant women) Rifampicin for 4 months (alternative) Rifapentine without registration in Australia
USA, 2012a[14]	Adults with HIV, testing positive for LTBI and adults with HIV exposed to TB cases regardless of the outcome for LTBI	Isoniazid (300mg/day) for 9 months Isoniazid (900mg/2× week DOT) for 9 months. Recommend daily rifampin or rifabutin monotherapy for 4 months, but with dose adjustment if there is concomitant use of ART Not recommend rifapentine + isoniazid for 3 months: risk of interacting with ART Not recommend rifampicin + pyrazinamide for 2 months: risk of fatal hepatotoxicity
USA, 2012b[15]	Children 2-11 years with HIV, exposed to TB cases with positive TT	Isoniazid (10–15mg/kg/1× day) for 9 months or Isoniazid (20–30mg/kg/2× day) for 9 months with DOT by trained professional, if adherence cannot be guaranteed by parents or family members Rifampicin for 6 months, if exposed to TB resistant to isoniazid Rifapentine + isoniazid not recommended for patients aged < 2

LTBI: latent tuberculosis infection**; TB**: tuberculosis; **WHO**: World Health Organization; **UK**: United Kingdom; **CDC**: Centers for Disease Control and Prevention; **USA**: United States of America; **HIV:** human immunodeficiency virus; **TT:** tuberculin test; **BCG**: Bacillus Calmette-Guérin vaccine; **ART**: antiretroviral therapy; **DOT**: directly observed therapy. **Note:** USA guidelines (2012) recommend the administration of isoniazid associated with pyridoxine (25mg).

fo America[14] [15] recommend isoniazid monotherapy for LTBI chemoprophylaxis for the general population and HIV-positive patients, including adults and children.

DISCUSSION

The studies analyzed indicated that thus far, rifapentine + isoniazid combination treatment for 3 months is neither inferior nor superior to isoniazid monotherapy for 6 or 9 months, in the prevention of mortality or progression of LTBI to TB in the general population and HIV-positive patients. This result may indicate that there is some equivalence between the combination therapy and monotherapy.

The strongest evidence for this was obtained from a non-multicenter, non-blinded study[11]. Although blinding is largely known as a commandment in RCT, it does not represent an absolute absence of bias: participants' beliefs about allocation may have a role in biased results[20]. In both the selected RCTs[11] [12], the intervention arms of rifapentine + isoniazid combination involved DOT, which has benefited the adherence in these groups and indicates a successful strategy to guarantee treatment effectiveness.

The RCT that was excluded in the selection of studies was conducted in Brazil[19]. Although the sample representativeness for the Brazilian setting, the study was a phase II design study and compared rifapentine to the rifampin + pyrazinamide combination, which is not recommended by the Brazilian National Tuberculosis Control Program for LTBI control in Brazil.

Although pharmacokinetic studies were excluded to gather the findings on the efficacy, these studies highlighted that rifamycins are cytochrome P450 enzyme complex inducers, and this characteristc may contribute to a reduction in the efficacy of protease inhibitors in HIV-positive patients, especially those under antiretroviral therapy[6]. The exclusion of patients under antiretroviral therapy in both RCTs[11] [12] represents a limitation of the results, since there is a significant population outside the controlled conditions that will be exposed to this drug interaction. Thus, future studies on patients with HIV/acquired immunodeficiency virus under antiretroviral therapy are needed.

Many studies involving patients at high risk of progression of LTBI to active TB have been conducted. A systematic review investigated treatments for LTBI in HIV-positive patients, but did not explore the use of rifapentine[21]. In another database (ClinicalTrials.gov), there were registrations from two ongoing clinical studies that may provide more information about the effectiveness and safety of isoniazid + rifapentine combination. One of them (NCT00023452) was a continuation of the RCT by Sterling et al[12], and the other (NCT01404312) is still in the recruitment phase; the latter RCT is an open-label study and compares the benefits of the 4-week isoniazid + rifapentine combination therapy to the 9-month isoniazid monotherapy in HIV-infected persons.

Although a few studies on the effectiveness of rifapentine therapy have been published, it has been internationally recommended for LTBI chemoprophylaxis. The CDC recommends rifapentine + isoniazid combination for 3 months[13] based on the same evidence shown in this study.

In conclusion, the studies included to support the decision to incorporate rifapentine combination regimen for LTBI chemoprophylaxis were of moderate methodological quality and point to a probable equivalent efficacy in comparison to isoniazid monotherapy. Monitoring is recommended due to the risk and variance in hepatotoxicity findings, as well as dosage adjustment in patients on antiretroviral therapy. Besides scientific evidence, local context, rifapentine market availability, population acceptability, costs, and feasibility are other essential parameters to be considered when planning and implementing health policies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FINANCIAL SUPPORT

This project was supported by funding from the Pan American Health Organization/Ministry of Health.

REFERENCES

1. Guimarães RM, Lobo AP, Siqueira EA, Borges TF, Melo SC. Tuberculose, HIV e pobreza: tendência temporal no Brasil, Américas e mundo. J Bras Pneumol 2012; 38:511-517.
2. Biblioteca Virtual em Saúde - Consulta ao DeCS – Descritores em Ciências da Saúde (Internet). São Paulo (Brazil): Centro Latino-Americano e do Caribe de Informação em Ciências da Saúde. 2014 – (cited 2014 Feb 21). Available at: http://decs.bvs.br/homepage.htm
3. Siqueira KZ, Mendonça SA, Penedo CC. Indicação da prova tuberculínica e infecção latente da tuberculose em HIV-positivos, Município de Blumenau, Estado de Santa Catarina, Brasil, 2004-2009. Epidemiol Serv Saude 2012; 21:635-644.
4. World Health Organization (WHO), Stop TB Department, Department of HIV/AIDS. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Genebra (Switzerland): Centers for Disease Control and Prevention and United States Agency for International Development; 2011.
5. Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância Epidemiológica, Coordenação Geral do Programa Nacional de Controle da Tuberculose. Manual de recomendações para o controle da tuberculose no Brasil. Brasília (Brazil): Ministério da Saúde; 2011.
6. Vernon A. Treatment of latent tuberculosis infection. Semin Respir Crit Care Med 2013; 34:67-86.
7. Ministério da Saúde. Agência Nacional de Vigilância Sanitária. Consulta a produtos - Medicamentos (Internet). Brasília (Brazil): Agência Nacional de Vigilância Sanitária. 2003 – (cited 2014 Apr 04). Available at: http://www7.anvisa.gov.br/datavisa/Consulta_Produto/consulta_medicamento.asp
8. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17:1-12.
9. Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol 2013; 66:151-157.

10. Sharma SK, Sharma A, Kadhiravan T, Tharyan P. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. Cochrane Database Syst Rev 2013; 7: CD007545.

11. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med 2011; 365:11-20.

12. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med 2011; 365:2155-2166.

13. Centers for Disease Control and Prevention (CDC). Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection. MMWR Morb Mortal Wkly Rep 2011; 60:1650-1653.

14. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health. Atlanta (GA): CDC; 2013.

15. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. Washington (DC): Department of Health and Human Services; 2013.

16. Pozniak AL, Coyne KM, Miller RF, Lipman MC, Freedman AR, Ormerod LP, et al. British HIV Association guidelines for the treatment of TB/HIV coinfection 2011. London (UK): British HIV Association (BHIVA); 2011.

17. National Collaborating Centre for Chronic Conditions. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London (UK): National Institute for Health and Clinical Excellence (NICE). 2011.

18. Street A, McBryde E, Denholm J, Eisen D. Management of tuberculosis: a handbook for clinicians. Melbourne (Australia): Victorian Infectious Diseases Service; 2012.

19. Schechter M, Zajdenverg R, Falco G, Barnes GL, Faulhaber JC, Coberly JS, et al. Weekly rifapentine/isoniazid or daily rifampin/pyrazinamide for latent tuberculosis in household contacts. Am J Respir Crit Care Med 2006; 173:922-926.

20. Mathieu E, Herbert RD, McGeechan K, Herbert JJ, Barratt AL. A theoretical analysis showed that blinding cannot eliminate potential for bias associated with beliefs about allocation in randomized clinical trials. J Clin Epidemiol 2014; 67:667-671.

21. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev 2010; 1: CD000171.