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

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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.
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(9). 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(9) 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.

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.

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

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. <sup>a</sup>Open-label, not blinded, not all properly randomized or analyzed by intention to treat; <sup>b</sup>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; <sup>c</sup>Despite applying the GRADE approach, it was not possible to identify the studies and check the performed quality assessment; <sup>d</sup>As these studies have not been identified, we cannot affirm that finding; <sup>e</sup>Large confidence interval; <sup>f</sup>Studies were open-label, not blinded, and not all were properly randomized or analyzed by intention to treat; <sup>g</sup>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 [rifampicin + 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.
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 of 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>
<thead>
<tr>
<th>Locality, year</th>
<th>Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO, 2011(^{(4)})</td>
<td>Adults and adolescents with HIV in resource-limited settings</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>Children with HIV in resource-limited settings</td>
<td>Isoniazid (10 mg/kg/day) for 6 months for children aged &gt; 12 years unexposed of TB. In children aged &lt; 12 years, the regimen is only indicated if they are exposed to TB cases.</td>
</tr>
<tr>
<td>UK, 2011(^{(16)})</td>
<td>Adults with HIV in an area of low TB prevalence</td>
<td>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</td>
</tr>
<tr>
<td>UK, 2011(^{(17)})</td>
<td>With HIV: any age and TT ≥ 6mm without BCG or TT ≥ 15mm with BCG</td>
<td>Isoniazid for 6 months or Rifampicin for 6 months, if up to 35 years of age and contact with isoniazid-resistant TB case</td>
</tr>
<tr>
<td></td>
<td>No HIV: up to 35 years and ≥ 6mm without BCG or TT ≥ 15 mm with BCG</td>
<td>Isoniazid for 6 months or Rifampicin + isoniazid for 3 months</td>
</tr>
<tr>
<td>CDC, 2012(^{(13)})</td>
<td>Age &gt; 12 years, with or without HIV, healthy and without ART</td>
<td>Rifapetine + isoniazid (maximum 900mg each) once a week for 3 months under DOT</td>
</tr>
<tr>
<td>Australia, 2012(^{(18)})</td>
<td>With and without HIV, any age and pregnant</td>
<td>Isoniazid (300 mg/day) for 9 months (first line and pregnant women) Rifampicin for 4 months (alternative) Rifapetine without registration in Australia</td>
</tr>
<tr>
<td>USA, 2012(^{a})(^{(14)})</td>
<td>Adults with HIV, testing positive for LTBI and adults with HIV exposed to TB cases regardless of the outcome for LTBI</td>
<td>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</td>
</tr>
<tr>
<td>USA, 2012(^{b})(^{(15)})</td>
<td>Children 2-11 years with HIV, exposed to TB cases with positive TT</td>
<td>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 &lt; 2</td>
</tr>
</tbody>
</table>

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).
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 characteristic may contribute to a reduction in the efficacy of protease inhibitors in HIV-positive patients, especially those under antiretroviral therapy(60). 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.


