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INTEGRATIVE REVIEW ARTICLE

LATENT TUBERCULOSIS AMONG PEOPLE WITH HIV/AIDS

TUBERCULOSE LATENTE ENTRE PESSOAS COM HIV/AIDS

TUBERCULOSIS LATENTE ENTRE PERSONAS CON VIH / SIDA

Josiane Maria Oliveira de Souza[1], Michelle Zampieri Ipolito[2], Tayse Tâmara Paixão Duarte[3], Sandra Renata Nakashoji[4], Márcia Cristina da Silva Magro[5]

ABSTRACT

Objective: to search for evidence on the use of isoniazid preventive therapy in reducing the risk of active tuberculosis among people living with HIV / AIDS through the results of interferon-gamma (IGRA) release trials. ***Method:*** a descriptive, descriptive, integrative review type, with search of articles in the databases published from 2010 to 2017. The descriptors used were HIV, AIDS, isoniazid preventive therapy, treatment of latent tuberculosis infection, interferon-gamma, of interferon-gamma release. ***Results:*** three articles were selected, with 1815 PLHA and tuberculosis development in only one case, after 24 months of preventive therapy with isoniazid. High rates of reversal and conversion during follow-up. ***Conclusion:*** studies addressing the benefits of preventive therapy with isoniazid from the IGRA result are scarce, with an incipient suggestion of limiting the serial test for the follow-up of the therapy response among PLHA. In addition, there is a need to invest in more studies that explore the issue and overcome the limitations already encountered in view of the high relevance of investing in new strategies that impact the control of TB / HIV co-infection. ***Descriptors:*** Latent Tuberculosis; Tuberculin Test; Interferon-gamma; HIV; Nursing; Prevention of Diseases.

RESUMO

Objetivo: buscar evidências sobre o uso da terapia preventiva com isoniazida na redução do risco da tuberculose ativa entre as pessoas vivendo com HIV/Aids mediante os resultados dos ensaios de liberação do *interferon-gama* (IGRA). ***Método:*** trata-se de estudo bibliográfico, descritivo, tipo revisão integrativa, com busca de artigos nas bases de dados publicados de 2010 a 2017. Os descritores utilizados foram HIV, AIDS, terapia preventiva com isoniazida, tratamento da infecção latente da tuberculose, interferon-gama, ensaios de liberação do interferon-gama. ***Resultados:*** selecionaram-se três artigos, com 1815 PVHA e desenvolvimento de tuberculose em apenas um caso, após 24 meses de terapia preventiva com isoniazida. Altas taxas de reversão e conversão durante o seguimento. ***Conclusão:*** consideraram-se os estudos abordando os benefícios da terapia preventiva com isoniazida a partir do resultado do IGRA apresentam-se escassos, com incipiente sugestão da limitação do teste seriado para o seguimento da resposta da terapia entre as PVHA. Além disso, destaca-se a necessidade de se investir em mais estudos que explorem a temática e superem as limitações já encontradas tendo em vista a alta relevância de se investir em novas estratégias que impactem o controle da coinfecção TB/HIV. ***Descritores*****:** Tuberculose Latente; Teste Tuberculínico; Interferon-gama; HIV; Enfermagem; Prevenção de Doenças.

RESUMEN

Objetivo: buscar evidencias sobre el uso de la terapia preventiva con isoniazida en la reducción del riesgo de la tuberculosis activa entre las personas que viven con el VIH / SIDA, a través de los resultados de los ensayos de liberación del interferón gamma (IGRA). ***Método:*** estudio bibliográfico, descriptivo, tipo revisión integrativa, con búsqueda de artículos en las bases de datos publicados de 2010 a 2017. Los descriptores utilizados fueron: VIH, SIDA, terapia preventiva con isoniazida, tratamiento de la infección latente de la tuberculosis, interferón-gamma, ensayos de liberación del interferón-gamma. *0* se seleccionaron tres artículos, con 1815 PVHA y desarrollo de tuberculosis en apenas un caso, después de 24 meses de terapia preventiva con isoniazida. Altas tasas de reversión y conversión durante el seguimiento. ***Conclusión:*** los estudios abordando los beneficios de la terapia preventiva con isoniazida a partir del resultado del IGRA se presentan escasos, con incipiente sugerencia de la limitación de la prueba seriada para el seguimiento de la respuesta de la terapia, entre las PVHA. Además, se destaca la necesidad de invertir en más estudios que puedan explorar la temática y supere las limitaciones ya encontradas, visto la alta relevancia de invertir en nuevas estrategias que impacten en el control de la coinfección TB / VIH. ***Descritores*****:** Tuberculosis Latente, Prueba de Tuberculina, Interferón Gamma; VIH, Enfermería; Prevención de Enfermedades.

[1]PhD, FCE / UnB. Brasília (DF), Brazil. E-mail: josianemaria@unb.br ORCID iD: https://orcid.org/0000-0002-8400-2948; [2]PhD, FCE / UnB. Brasília (DF), Brazil. E-mail: michellezampieri@yahoo.com.br ORCID iD: https://orcid.org/0000-0001-5017-8286; [3]Master, FCE / UnB. Brasília (DF), Brazil. E-mail: taysepaixao@unb.br ORCID iD: https://orcid.org/0000-0003-1608-618X; [4]Masters student, PPGENF / UnB. Brasília (DF), Brazil. E-mail: srnakashoji@gmail.com ORCID iD: https://orcid.org/0000-0002-4116-3928; [5]PhD, FCE / UnB. Brasília (DF), Brazil. E-mail: marciamagro@unb.br ORCID iD: https://orcid.org/0000-0002-4566-3217

INTRODUCTION

Tuberculosis (TB) stands out as the most frequent opportunistic infection among people living with HIV / AIDS (PLWHA) and the leading cause of death in this group, despite the use of antiretroviral therapy (ART). [1] It is estimated that, in 2015, 1.4 million deaths were caused by TB, with 0.4 million deaths among seropositive people.[2] Brazil is among the 22 high-burden countries prioritized by the World Health Organization (WHO), concentrating 80 % of TB cases in the world. It occupies the 16th position in absolute number of cases. In addition, TB represents the first cause of death due to infectious diseases among AIDS patients in the country.[3]

Strategies for combating TB / HIV co-infection worldwide have been discussed. Since 1998, the World Health Organization (WHO) and the Joint United Nations Program on HIV / AIDS (UNAIDS) recommend treatment of latent tuberculosis infection (LTBI) among people living with HIV / AIDS (PLWHA). In 2008, this recommendation was improved by the guidance of the Three I's Strategy, which includes: i) intensification of the detection of TB cases; ii) isoniazid preventive therapy (IPT); and iii) LTBI control. These recommendations were strengthened by evidence that IPT reduces the risk of TB development from 33 to 67% among HIV-positive people.[4] Recently, WHO released new challenging goals, termed TB End-of-Life Strategies between 2016 and 2035, with 90% reduction in deaths and a decrease of 80% in the incidence of TB by 2030, considering the data for 2015.[2] The Ministry of Health, in order to achieve these goals, established among the federative units the establishment of integrated actions among the TB and HIV, with prioritization of HIV testing for all people with tuberculosis; tuberculosis screening in all PLWHA; timely antiretroviral treatment for all HIV/TB co-infected patients; promotion of adherence to the treatment of both diseases; and diagnosis and treatment of latent tuberculosis infection.[3]

The identification of LTBI is carried out through the tuberculin skin test (TST), which has numerous limitações.[5] are evident in recent studies, the benefits of IPT in reducing the incidence of TB in PLWHA with positive TST, but not with TST negativa.[6] Because of the limitations of TST new immunological tests that evaluate the gamma interferon production by T cells in response to specific antigens of Mycobacterium tuberculosis, called interferon-gamma release assays (IGRA), there have desenvolvido[4] enabling the diagnosis of LTBI in association or not with TST.[7-10] However, the benefits and the protective ability of IPT, based on IGRA results directly, are not present clear.[11]

Thus, in view of the need for advances in TB prevention strategies among PLWHA and considering the role of nurses as the main responsible for the diagnosis of LTBI through TST, it is necessary to search for scientific evidences in the sense of instrumentalize the decision-making of professionals and managers on the adoption and use of new inputs, enabling greater qualification of care, patient safety and cost-effectiveness to services and users.[12] In addition, there are already results that indicate the use of IGRA as a diagnostic strategy of LTBI among PLWHA in the national scenario. [13-4]

OBJECTIVE

- To search for evidence on the use of isoniazid preventive therapy in reducing the risk of active tuberculosis among people living with HIV / AIDS through the results of the IGRA.

METHOD

This is a bibliographic, descriptive study, type Integrative Review of Literature (RIL), which, in an organized way, aims to gather and synthesize the results found in relevant research through a guiding question that guides the study, with the purpose of deepening the knowledge of the theme proposed from previous studies and seek to reduce the gap between the scientific advances and the practice of care, a method used for the construction of evidence-based practice.[15-6]

In order for the methodology to be implemented, six stages of RIL were followed: to elaborate and establish the guiding question; search for sampling; data collect; evaluation of the selected studies, discussion of the results and synthesis of the knowledge acquired.[17] The guidelines of the items of preferential reports for systematic analysis and meta-analyzes - Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA), according to figure 1.

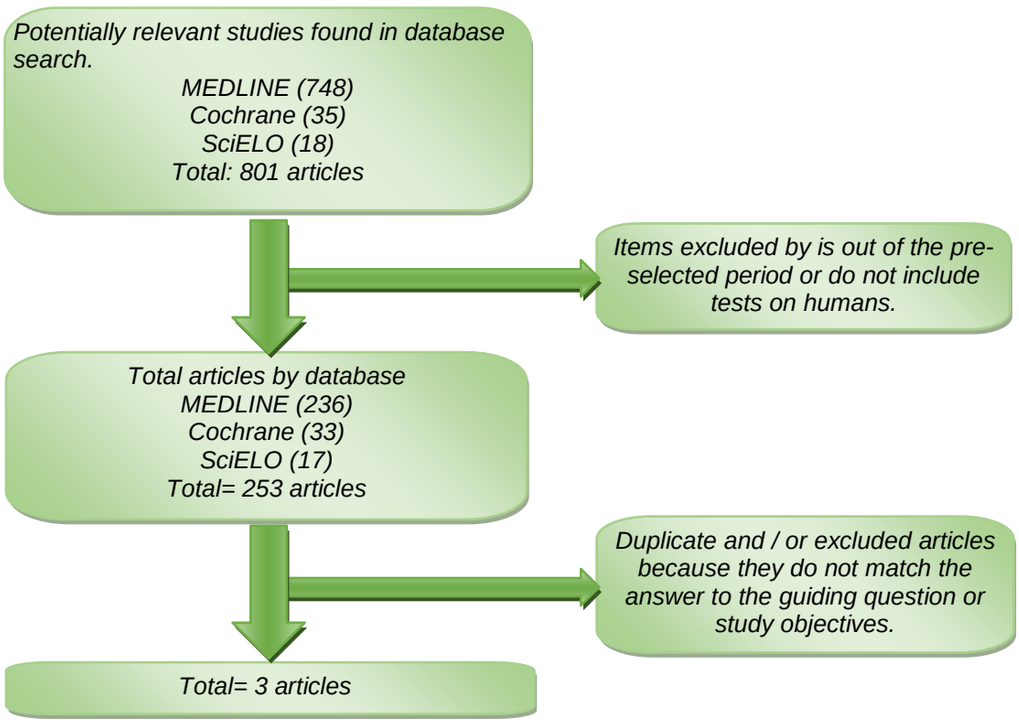

Figure 1. Flow of survey of bibliographic material in databases - 2010 to 2017. Brasília (DF), Brazil, 2018.

In this sense, evidence-based practice suggests that the guiding question be constructed based on the PICO strategy, ie Problem or Patient (Problem), Intervention, Comparison and Outcome. The PICO strategy adopted for this study is outlined in figure 2.

P	I	C	O
People living with HIV/Aids	The use of isoniazid preventive therapy from the result of the IGRA	The use of isoniazid preventive therapy from the result of the TST	Reducing the risk of active tuberculosis

Figure 2. Guiding criteria for inclusion of studies in the integrative review. Brasília (DF), Brazil, 2018.

The use of preventive therapy with isoniazid, based on the results of the interferon-gamma release assays, reduces the risk of active tuberculosis among people living with HIV / AIDS?

The search was performed in the Medical Literature Analysis (MEDLINE), consulted by PubMed, Cochrane Library and Scielo, from October to February 2016. The following descriptors were used in Portuguese and English: HIV OR AIDS OR isoniazid preventive therapy OR IPT OR treatment of latent tuberculosis infection OR LTBI AND interferon-gamma release assays (IGRA), as similarly search strategy on all bases referred.

The articles were selected from the following inclusion criteria: original articles, published between the years 2010 and February 2017, available in full and with tests made in humans. The following exclusion criteria were used: non-use of IGRA as a diagnostic method for latent tuberculosis infection in patients with HIV / AIDS and non-use of isoniazid in the treatment of latent tuberculosis. The selection of articles was by means of peer reading. The researchers in situations of divergences in the selection of the article, were based on the adopted criteria and on the standard instrument of data collection elaborated by the researchers.

An instrument was then constructed for data analysis considering the guiding question and analyzing aspects such as title, periodical of publication, objectives, sample, methodology, level of evidence and results achieved in the study. The following levels of evidence (NE) were adopted in this study: Level 1 - evidence resulting from the meta-analysis of multiple randomized controlled trials; - Level 2 - evidence obtained in individual studies with experimental design; - Level 3 - evidence from quasi-experimental studies; - Level 4 - evidence from descriptive studies (non-experimental) or qualitative approach; Level 5 - evidence from case or experience reports; - Level 6 -evidence based on expert opinions.[15]

Using the cross-referencing of the descriptors, a sample of 801 articles was obtained. After applying the filters (articles published between the years 2010 to 2016 and human testing), this number was reduced to

286 articles. Of these, 283 were excluded after duplication analysis and response to the guiding question and objectives of the study, according to figure 2.

The final sample of this review consisted of three scientific articles, selected from the inclusion and exclusion criteria previously determined and were classified and organized according to the level of evidence and year of publication.

Throughout the research, the authorship of the concepts, discussions and ideas presented by the authors in their articles was respected.

RESULTS

The description of the articles (authors / year, title, publication period, objectives, sample, method, level of evidence and results) was organized to better observe and understand the data in Figure 2.

The longitudinal study was highlighted among the articles. The clinical trial, a "gold standard" method, was presented in one of the three articles selected. Two studies have been conducted in low-burden regions of tuberculosis (USA and UK) and only one has used the IGRA T-SPOT-TB. In all studies, people with HIV did not present severe immunosuppression and the follow-up period ranged from 12 to 35 months. The total sample of studies corresponded to 1815 PLWHA and of these 246 (13.5%) received isoniazid preventive therapy. On the one hand, only one article described the development of a case (0.4%) of pulmonary tuberculosis after 24 months of IPT, on the other hand, high rates of IGRA reversal and conversion were demonstrated in all articles, during follow-up.

Authors/Year/Journal	Title of the article	Objective (s)	Sample	Method/ Level of evidence (LE)	Results
DanelC,Kabran M, Inwoley A, Badje A, Herrmann JL, Moh R *et al.*,(Costa do Marfim,2014)/ Plos one.	Quantiferon-TB Gold: Performance for Ruling out Active Tuberculosis in HIV-Infected Adults with High CD4 Countin Côte d'Ivoire, West Africa.	To evaluate the performance of IGRA in HIV-positive patients and their variation over time in treatment with early antiretroviral therapy (ART) and / or IPT.	975 initial HIV + patients and 444 were reevaluated after 12 months.	Randomized clinical trial /LE 2.	Negative QTF-GIT can rule out the occurrence of active TB in non-severely immunodepressed HIV + adults in a high TB burden region, given its high negative predictive value. There were high reversion and conversion rates at the retest after 12 months. However, there was no association between IPT use and reversion after 5 months of therapy.
Pullar ND, Steinum H, Brunn NJ, Dyrhol-Riise AM. (EUA, 2014)/ BMC Infectious Deseases	HIV patients with latent tuberculosis living in alow-endemic country do not develop active disease during a 2 year follow-up; a Norwegian prospective multicenter study	To compare the progression of LTBI to active TB of patients receiving or not preventive therapy	298 HIV-positive patients	Prospective cohort /LE 3	During 2 years, no patient developed active TB, using IPT (61%) or not (39%). There were reversals and conversions of the QTF-GIT results during follow-up indicating that it was unreliable in monitoring the efficacy of LTBI treatment in a population with low TB burden, high CD4 count, and use of antiretroviral therapy
Kall MM, Coyne KM, Garrett NJ, Boyd AE, Ashcroft AT, Reeves I, Anderson J *et al.*, (Reino Unido, 2012)/ BMC Infetious Diseases.	Latent and subclinical tuberculosis in HIV infected patients: a cross-sectional study	To assess the use of IGRA in HIV-positive patients to determine completion of preventive treatment in positive tests.	542 HIV-positive patients	Prospective cohort / LE 3	In a low-burden area TB screening using T-SPOT-TB increased the detection and treatment of TB and LTBI cases. And after an average follow-up of 35 months, no patient with a negative result (452) developed active TB and only 1/40 with a positive result developed isoniazid-resistant pulmonary TB after 24 months of IPT completion.

Figure 3. Distribution of selected scientific articles, according to authors / year, title, periodical, objectives, sample, method, level of evidence and results. Brasília (DF), Brazil, 2018

DISCUSSION

It was sought to investigate in this study and to compile the existing evidence, in the period of 2010 to mid-2017, on the use of isoniazid preventive therapy among PLWHA to reduce the risk of tuberculosis disease, based on the results of the interferon-gamma release assays. It was observed that there are still few articles that investigate the relation of protection of IPT through the results of the IGRA among people with HIV in the world, and in Brazil, they are still non-existent. However, in the three studies considered, the development of active tuberculosis was verified in only 0.4% of the study population.

It is therefore suggested that there was a degree of protection of the isoniazid preventive therapy, even in the face of the limitations of the findings, as presented in other studies with different TB loads, such as the one carried out in Ethiopia, where a reduction of the risk of 96.3% in the development of tuberculosis among the PLWHA who received IPT compared to those who did not receive it during a five-year follow-up.[18] In Brazil, Rio de Janeiro, from TST result, a reduction in the risk of active TB, 83% in a seven-year follow-up study, but in the first two years post-therapy, there was a significant increase in the incidence of TB among the TST positive who did not start the IPT compared to those who received it.[19] Another study using a mathematical model estimated that IPT can cure Mycobacterium tuberculosis latent infection in approximately one-third of people with HIV using ART and the protection is extrapolated to the treatment period.[20]

In previous studies, the durability of IPT protection in high-burden regions has been questioned.[21-2] However, given the divergences in the results of recent studies, it is argued that the rates of infection and reinfection with M. tuberculosis results in a greater individual bacillary load of latent tuberculosis in areas of high burden, which results in greater difficulty for elimination and predisposition to reinfection. Even in the face of such divergences, WHO, since 2011, has stated that isoniazid reduces the overall risk of TB development among PLWHAs, and is more significant among TST positive patients (about 64%), with a reduction in risk by up to five years.[23] In a recent review, there was strong and consistent evidence that IPT is associated with a reduction in the risk of progression to tuberculosis in people with positive TST, however, with no evidence among people with positive IGRA.[24] It was pointed out, in another relevant review study that IPT in QTF-GIT positive individuals may provide at least the same benefit of positive TST.[11]

Has been shown in several studies that the failure to treat latent tuberculosis is associated with a greater risk for progression of the disease, in the face of a positive IGRA result.[25-7] And even if there are disagreements between TST and IGRA, a positive result in any of the tests relates to the increased risk of subsequent disease (TB) development. In this scenario, both tests also show poor predictive accuracy to identify individuals who will (or may not) develop tuberculosis.[24] Such finding may be associated with the fact that the tests are susceptible to positivity in all phases of the disease. LTBI and the low rates of disease progression (HIV negative population of five to 10% during life and in HIV positive 10% per year).[32]

The results are shown with high conversion rates and reversion between the results of the IGRA and in agreement with some studies.[28-21] The sources of variability in the tests have several causes. Production problems, variations in pre-analytical and analytical processing, and immunomodulation may be highlighted, making it difficult to use a single cut-off value to define the conversion and reversion in individuals submitted to serial tests. Standardization by manufacturers and users of testing can minimize systematic variability, however, random sources of variability are inevitable and should be accounted for when interpreting the results. Once the total variability of the IGRA responses has been determined, appropriate cuts and boundary zones are defined to interpret the results of the series tests.[32] In this sense, in a recent review, it was concluded that IGRA series tests for the diagnosis of ILTB in people with HIV presents challenges, since spontaneous variability in test results has been common. Therefore, it is recommended that, in order to perform series tests in the diagnosis of ILTB, TST is preferable to IGRA until more data are available.[24]

In view of the results of this review, it is necessary to develop more studies, with a longer follow-up period, in order to identify the HIV patients who would benefit most from the treatment of latent tuberculosis, through IGRA results.[29,33] Such evidence could benefit a greater number of people, since there are still many gaps and uncertainties about the benefits of these tests in the screening and follow-up of PLWHA in different areas and burden of disease.

It is possible to carry out studies of this nature, to obtain a clearer and more rational view of the evidence for nurses' professional practice, so as to provide a safe use and indication of new inputs, with consequent legitimacy and affirmation of the profession as science. In particular, in this topic that presents with great national epidemiological relevance considering the high mortality in the scenario of TB / HIV co-infection, and social and individual relevance.

CONCLUSION

There were few studies addressing the benefits of isoniazid preventive therapy from the IGRA outcome. It was observed an incipient suggestion of the limitation of the serial test for the follow-up of the therapy response among the PLWHA, however, it is noteworthy that the results point to the need to invest in more studies that explore the issue and overcome the limitations found in view of the high relevance of investing in new strategies that impact the control of TB / HIV co-infection, with consequent repercussions on morbidity and mortality rates in this population.

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Corresponding Address

Tayse Tâmara da Paixão Duarte
Faculdade de Ceilândia – Universidade de Brasília
Departamento de Enfermagem
Centro Metropolitano, conjunto A, lote 01
CEP: 72220-900 – Brasília (DF), Brazil