

Implementation of the cascade of care for latent *Mycobacterium tuberculosis* infection in people living with HIV/Aids

Implementação da cascata de cuidados da infecção latente por
Mycobacterium tuberculosis em pessoas vivendo com HIV/Aids
Implementación de la cascada de atención a la infección latente por
Mycobacterium tuberculosis en personas que viven con HIV/Aids

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ABSTRACT

Objective: To describe the outcome indicators of implementing a cascade of care for latent *Mycobacterium tuberculosis* infection in people living with the human immunodeficiency virus.

Method: Cross-sectional study, carried out with people living with HIV, from 2022 to 2024, in a reference service in Campo Grande, Mato Grosso do Sul. It occurred after the implementation of the following work process: Identification of people at risk for investigation of Latent Tuberculosis Infection (LTBI); Test for LTBI; Exclusion of active TB cases; Treatment for LTBI; Adherence to treatment; and Completion of treatment. Data were analyzed using descriptive statistics, Chi-square test and Fisher's exact test.

Results: 735 people were monitored, of which 29.6% were indicated to start treatment for latent infection, and 32.5% started it. Treatment completion was higher in those who used the shortened regimen (90.2% versus 71.8%; p -value < 0.05, 7.8% with isoniazid and 2% with rifampin). There was one (0.9%) serious adverse reaction.

Conclusion: The implementation of the cascade of care demonstrated that 1/3 of participants had an indication for treatment and expanded access to recommended treatment. The conclusion was greater with the shortened scheme. Adverse reactions were infrequent.

Descriptors: Latent tuberculosis. *Mycobacterium tuberculosis* infection. Tuberculin.

RESUMO

Objetivo: Descrever os indicadores de resultado da implementação de uma cascata de cuidados da infecção latente por *Mycobacterium tuberculosis* em pessoas vivendo com o vírus da imunodeficiência humana.

Método: Estudo transversal realizado com pessoas vivendo com HIV no período de 2022 a 2024 em serviço de referência de Campo Grande, Mato Grosso do Sul. Foi feito após a implementação do seguinte processo de trabalho: Identificação de pessoas em risco para investigação de Infecção Latente da Tuberculose (ILT); Teste para ILTB; Exclusão de casos de TB ativa; Tratamento para ILTB; Adesão ao tratamento; e Conclusão do tratamento. Os dados foram analisados por estatística descritiva, teste Qui-quadrado e teste exato de Fisher.

Resultados: Foram acompanhadas 735 pessoas. Desse total, 29,6% tinham indicação de iniciar o tratamento de infecção latente, das quais 32,5% iniciaram. A taxa de conclusão do tratamento foi maior no grupo que usou o esquema encurtado (90,2% versus 71,8%; p -value < 0,05, 7,8% com Isoniazida e 2% com Rifampicina). Houve uma (0,9%) reação adversa grave.

Conclusão: A implementação da cascata de cuidados demonstrou que um terço dos pacientes tinha indicação de tratamento e ampliou o acesso ao tratamento preconizado. A taxa de conclusão do tratamento foi maior com o esquema encurtado. As reações adversas foram infrequentes.

Descritores: Tuberculose latente. Infecção por *Mycobacterium tuberculosis*. Tuberculina.

RESUMEN

Objetivo: Describir los indicadores de resultados de la implementación de una cascada de atención para la infección latente por *Mycobacterium tuberculosis* en personas que viven con el virus de la inmunodeficiencia humana.

Método: Estudio transversal, realizado con personas que viven con VIH, de 2022 a 2024, en un servicio de referencia en Campo Grande, Mato Grosso do Sul. Ocurrió después de la implementación del siguiente proceso de trabajo: Identificación de personas en riesgo de contraer VIH; investigación de la Infección Tuberculosis Latente (LTBI); Prueba de LTBI; Exclusión de casos de tuberculosis activa; Tratamiento para la LTBI; Adherencia al tratamiento; y Finalización del tratamiento. Los datos fueron analizados mediante estadística descriptiva, prueba de Chi-cuadrado y prueba exacta de Fisher.

Resultados: Se monitorearon 735 personas, de las cuales al 29,6% se les indicó iniciar tratamiento por infección latente y al 32,5% lo iniciaron. La finalización del tratamiento fue mayor en aquellos que utilizaron el régimen acortado (90,2% versus 71,8%; valor de p < 0,05, 7,8% con isoniazida y 2% con rifampicina). Hubo una reacción adversa grave (0,9%).

Conclusión: La implementación de la cascada de atención demostró que 1/3 de los participantes tenía una indicación de tratamiento y un acceso ampliado al tratamiento recomendado. La conclusión fue mayor con el esquema acortado. Las reacciones adversas fueron poco frecuentes.

Descriptores: Tuberculosis latente. Infección por *Mycobacterium tuberculosis*. Tuberculina.

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■ INTRODUCTION

Tuberculosis (TB) is a preventable and generally curable disease of social determinants. However, it is estimated that a quarter of the world's population is infected with *Mycobacterium tuberculosis* (MTb) and that approximately 5% to 10% of these people will develop active TB⁽¹⁾. In 2023, 80,012 new cases of TB were diagnosed in Brazil, corresponding to an incidence rate of 37.0 cases per 100,000 inhabitants. The probability of developing active TB is higher among People Living with HIV/AIDS (PLWHA). TB-HIV co-infection went from 8.6% in 2022 to 9.3% in 2023^(2,3).

The diagnosis of Latent Tuberculosis Infection (LTBI) can be made using the Tuberculin Skin Test (TT) or the Interferon-Gamma Release Assay (IGRA-TB) detection assay, as long as active TB is adequately ruled out⁽⁴⁾. According to the World Health Organization (WHO) and the Center for Disease Control and Prevention (CDC), both tests can be used to diagnose LTBI⁽²⁻⁴⁾. Access to and expansion of treatment for people with LTBI are considered important preventive strategies for controlling LTBI, as they reduce the number of people who will develop the active form of the disease⁽²⁻⁴⁾.

The implementation of the HIV/AIDS continuous cascade of care is one of the clinical monitoring strategies that portrays the trajectory of PLWHA in health services, as it refers to the sequence of stages that PLWHA need to go through in care, from diagnosis to viral load suppression^(5,6). MTb-HIV co-infection poses unique challenges in the clinical management and control of TB. Thus, the cascade of care plays an important role in identifying access gaps, and generating tactical information to improve care for these patients⁽⁵⁾.

In the management of LTBI in PLWHA, the continuous care cascade observes the following steps: 1) Identification of people at risk for LTBI investigation; 2) Testing for LTBI; 3) Exclusion of active TB cases; 4) Treatment for LTBI; 5) Adherence to treatment; and 6) Completion of treatment. Among the strategies adopted by Brazil to achieve the goal are the inclusion of the IGRA-TB test for diagnosis and the provision, in the Unified Health System (SUS), of short-course LTBI treatment regimens, such as therapy with Rifapentine and Isoniazid⁽⁷⁾. Four therapeutic regimens are currently recommended for Preventive Treatment for Tuberculosis (TPT) in Brazil: Isoniazid for six or nine months (6H or 9H), Rifampicin for four months (4R) or Rifapentine associated with Isoniazid for three months (3HP)⁽⁴⁾.

The assessment of the stages of the continuous care cascade and the monitoring of the different treatment regimens for MTb infection are axes that, together with the assessment of the risk of treatment discontinuation, generate strategic information to support the expansion and sustainability of

TPT⁽⁵⁾. Thus, the present study aimed to describe the outcome indicators of the implementation of a cascade of care for PLWHA for LTBI screening.

■ METHOD

Cross-sectional observational epidemiological study carried out at the Day Hospital – Esterina Corsini, in Mato Grosso do Sul, which had an HIV/AIDS and Tuberculosis outpatient clinic and was a public reference service for the care of PLWHA. The population included in the study consisted of patients followed at the reference service, regardless of the time elapsed since HIV/AIDS diagnosis. Data from the period from May 2022 to February 2024 were used.

The inclusion criteria established were: a) having received care at least once at the study site; b) having HIV/AIDS; c) being over 18 years old. The exclusion criteria were: a) having been diagnosed with active TB; b) be under 18 years old.

The work process implemented in the reference service observed the following steps: 1) Identification of people at risk for investigation of LTBI and invitation made to the patient at the time of the viral load test for HIV/AIDS monitoring – the individuals were being monitored at the reference service; Testing for LTBI and assessment of the patient's last CD4+ cell count within the last six months; 3) Exclusion of active TB cases; 4) Treatment for LTBI – indication of TPT for those with TT > 5 mm or positive IGRA-TB and for all with LT-CD4+ count ≤ 350 cells/mm³, regardless of the TT or IGRA-TB result, provided that active TB is ruled out by clinical evaluation, imaging tests and/or laboratory tests; 5) Adherence to treatment; and 6) Completion of treatment.

The study variables were prospectively recorded in a nursing care record book. Variables related to the indication of LTBI treatment, such as TT, IGRA-TB and LT-CD4+ count, were obtained from the Logistics Information System (SIL) of the reference service, the Infectious and Parasitic Diseases Research Laboratory (LABDIP) and the Medication Logistics Control System (SICLOM), respectively.

The demographic variables gender and age were analyzed; the variables related to the indication for LTBI treatment previously described; the treatment regimen; the type of treatment, whether self-administered (SAT) or directly observed (DOT); and the outcome variables: adherence to treatment, occurrence of adverse reactions and completion of treatment.

Analyzes of association between types of treatment and treatment completion outcome were carried out using the Chi-square test and Fisher's exact test, when the expected value was less than 5.

This study was approved by the Research Ethics Committee of the Federal University of Mato Grosso do Sul under Certificate of Presentation for Ethical Appreciation no. 11903819.5.0000.0021.

■ RESULTS

The results are presented in the sequence of the implemented steps of the continuous care cascade.

1st step of the cascade – Identification

The first step of the cascade was the identification of people treated at the reference service for LTBI treatment screening. Patients were identified at the outpatient clinic on weekdays when blood collection was performed for LT-CD4+ cell count and viral load. All individuals were instructed and invited to read and sign the FICF.

A total of 735 PLWHA were included, most of whom were men (62% men; 38% women), with a mean age of 47 years and a mean LT-CD4+ count of 642 cells/mm³.

2nd step of the cascade – Testing for LTBI

The patients were tested for LTBI using the IGRA-TB test, regardless of CD4+ TL count. Of the 704 patients tested, 117 tested positive for LTBI; 117 (16.6%) tested negative, 526 (74.7%) were undetermined 61 (8.7%). Furthermore, the TT result prior to May 2022 was used, totaling 10 (4.6%) positive cases.

Regarding the frequency of the LT-CD4+ result, it was shown that 634 patients (86.3%) had CD4+ TL > 350 cells/mm³, 101 (13.7%) had CD4+ TL ≤ 350 cells/mm³. Among those who had CD4+ TL ≤ 350 cells/mm³, 10 (9.9%) also had positive IGRA.

3rd step of the cascade – Exclusion of active TB cases

Active TB was investigated in patients with an indication to start TPT and excluded due to the absence of clinical symptoms and signs and through imaging tests and/or laboratory tests. A total of 18 (2.4%) patients met the exclusion criteria for active TB: 67% were undergoing treatment for active TB and 33% had a history of previous treatment.

4th step of the cascade – Treatment for LTBI

TPT depends on the diagnosis of LTBI (positive result in TST or IGRA-TB) and the patient's clinical indication. Therefore,

218 (29.6%) patients were indicated for treatment: 117 (53.7%) because they had a positive IGRA-TB, 10 (4.6%) because they had a previous positive TT, and 91 (41.7%) because they had CD4+ TL + ≤ 350 cells/mm³.

Of the 218 patients eligible to start treatment, 71 (32.5%) received this prescription. This study did not evaluate the reasons why treatment was not prescribed to some of the eligible patients.

Regarding indication, 53 (74.6%) patients started treatment due to positive IGRA-TB, 10 (14.1%) due to previous positive TT, and 8 (11.3%) due to CD4+ TL + ≤ 350 cells/mm³.

The treatment initiation schemes available in the service were: 1) Isoniazid 300 mg 1 tablet (cp) per day for 9 months; 2) Rifapentine 150 mg 6 tablets associated with Isoniazid 300 mg 3 tablets once a week for 12 weeks; and 3) Rifampicin 300 mg 2 tablets orally once a day for 4 months. All medications were routinely available at the Specialized Care Service (SAE) Pharmacy.

Regarding the frequency of TPT initiation by regimen, 59 (83.1%) initiated 3HP, 11 (15.5%) commenced 9H and 1 (1.4%) initiated 4R. Furthermore, 3HP was performed in Directly Observed Treatment (DOT) and Self-Administered Treatment (SAT), in the following proportion: 43 (72.9%) performed DOT, and 16 (27.1%) performed SAT.

5th step of the cascade – Adherence to treatment

There were 4 (5.6%) treatment discontinuations, 2 (50%) using 3HP and 2 (50%) using 9H. Of the total number of patients using 3HP, 4 (9.3%) patients switched from 3HP in DOT to 3HP in SAT. Of the patients with positive IGRA, one (0.9%) did not want to start treatment.

6th step of the cascade – Completion of treatment

Of the patients who started treatment, 51 (71.8%) completed treatment and 20 (28.2%) did not.

Patients treated with the 3HP regimen completed treatment more frequently than those treated with other regimens (p-value < 0.05), as shown in Table 1. There was no association between the treatment completion rate among users who performed the DOT and those who performed the SAT (p-value > 0.05), according to Table 2.

The total reasons why patients did not complete treatment were treatment interruption (20%), lack of medication (5%), and serious adverse reaction (5%). Also, one (0.1%) patient discontinued TPT to start treatment for active TB.

Table 1 – Completion of preventive treatment for tuberculosis using the three-month regimen of Rifapentine plus Isoniazid and another regimen, in a reference service, 2022-2024

	Completion of treatment (yes)	Completion of treatment (no)	Total	p-value
3HP* regimen	46 (78.00%)	13 (22.00%)	59 (100%)	0.01
Another scheme	5 (41.70%)	7 (58.30%)	12 (100%)	
Total	51 (71.83%)	20 (28.17%)	71 (100%)	

Source: Hospital Day – Esterina Corsini, Campo Grande, Mato Grosso do Sul.

* 3HP: three months of Rifapentine with Isoniazid; Another scheme: 9H: nine months of Isoniazid, and 4R: four months of Rifampicin.

Table 2 – Completion of preventive treatment for tuberculosis using the three-month regimen of Rifapentine plus Isoniazid in a directly observed treatment and self-administered treatment, in a reference service, 2022-2024

	Completion of treatment (yes)	Completion of treatment (no)	Total	p-value
3HP DOT*	36 (83.70%)	7 (16.30%)	43 (100%)	0.08
3HP regimen SAT*	10 (62.50%)	6 (37.50%)	16 (100%)	
Total	46 (78.00%)	13 (22.00%)	59(100%)	

Source: Hospital Day – Esterina Corsini, Campo Grande, Mato Grosso do Sul.

*3HP DOT: three months of Rifapentine plus Isoniazid performed in Directly Observed Treatment;

3HP SAT: three months of Rifapentine plus Isoniazid performed in Self-Administered Treatment.

There were 2 (1.7%) patients with Adverse Drug Reactions (ADR) associated with interruption and change of treatment regimen, one (0.9%) mild reaction, and one (0.9%) severe reaction. Mild reactions, such as nausea and vomiting, were not the focus of the study. However, one (0.9%) patient had to change the regimen from 3HP to 9H due to a mild adverse reaction. Furthermore, one (0.9%) patient discontinued 3HP treatment due to a serious adverse reaction (hepatotoxicity).

DISCUSSION

In the implementation of a work process in the reference service, all stages of the care cascade were evaluated: Identification of people at risk for investigation of LTBI; Test for LTBI; Exclusion of active TB cases; Treatment for LTBI;

Adherence to treatment; and Completion of treatment. The cascade of care takes on even greater importance in LTBI in PLWHA due to the possibility of reducing the number of new cases of active TB.

Of the number of HIV cases reported in Sinan, by gender and sex ratio, by year of diagnosis in Brazil from 2007 to 2023, 345,069 (70.5%) were men and 144,364 (29.5%) were women⁽⁸⁾. Therefore, in the reference service, the proportion reflected the national frequency. Regarding age groups, in the 2007-2023 period, new HIV infections in men occurred predominantly in the 20-24 age group, and in women, the predominance was in the 25-29 age group⁽⁸⁾. The study sample had an average age of 47 years, but it should be noted that the study was carried out with PLWHA whose HIV diagnosis occurred in a previous period.

The test most used in the screening process was IGRA-TB, which was incorporated into the SUS in 2020 for screening LTBI in certain groups, including PLWHA with a CD4+ T-lymphocyte (CD4+) count >350 cells/mm³(9). There was a special focus on PLWHA because these people are at greater risk of developing the active form of the disease, due to the less effective immune response and the low sensitivity of routinely used diagnostic tests⁽⁴⁾.

An average CD4+ T lymphocytes count of 642 cells/mm³ was observed in the study. However, it should be noted that the patients monitored were using Antiretroviral Therapy (ART) and it is known that when patients use ART, a CD4+ TL count higher than 500 cells/mm³(10) is achieved. Monitoring of CD4+ TL is used as a laboratory parameter predictive of the prognosis of HIV disease, and regular use of ART is an effective strategy to increase the level of CD4+ TL, which reduces the incidence of active TB. Values are regarded as abnormal when serial counts are below 500 cells/mm³(11).

Screening for LTBI in newly diagnosed PLWHA and adherence to LTBI treatment protocols are low in health services, especially due to the weaknesses of TT⁽¹²⁾. In the study, screening was performed mainly through the IGRA-TB test, which has advantages compared to TT^(6,13,14), but, regardless of the TT or IGRA result, patients with CD4+TL ≤ 350 cells/mm³(4) were eligible to start treatment. However, although the universal indication for treatment is made according to the CD4+ TL level, the treatment rate was higher when laboratory evidence of testing for LTBI was available, corroborating the low adherence to the protocol of the Ministry of Health.

The first step in screening for LTBI to start treatment is to exclude the possibility of active TB and to rule out a history of treated TB⁽⁴⁾. The diagnosis of the active form of the disease in this reference service is facilitated by access to X-rays and CT scans that can be performed on the same day the patient returns, ensuring longitudinal care and easy access for the user, which explains why this step is completed for all patients.

The annual risk of progression to the active form of TB in PLWHA with LTBI is 5-10%(15). The study found 18 (2.4%) patients with exclusion criteria for active TB, a number lower than that found in a study carried out in 2021 in the same reference service, which showed that among patients with a positive TT, 10.25% (8/78) were diagnosed with active TB⁽⁵⁾. Treatment of LTBI, when followed correctly, helps prevent TB disease development⁽⁹⁻¹⁶⁾.

For 58.25% of patients, the indication was based on positive IGRA-TB and previous positive TT, and for 41.7% it was based on CD4+TL ≤ 350 cells/mm³. At the beginning of treatment, indication was predominantly based on positive IGRA (74.6%). Treatment was prescribed for 32.5% of patients, despite the recommendation of treatment for all PLWHA

diagnosed with LTBI⁽⁴⁾. The rate of adherence to the treatment protocol was low, both among patients with CD4+TL > 350 cells/mm³, which can reach 50%, and among those with CD4+TL < 350 cells/mm³ (treatment independent of screening), which is only 1.8%⁽¹²⁾.

Furthermore, there is a predominance at the beginning of treatment when there was laboratory evidence, of positive IGRA-TB and/or a previous positive TST. Also, in a study with PLWHA, in an HIV/AIDS reference service, in 2021, the indication of TPT was made for 62.85% of patients with positive TST, while only 0.9% started treatment with LT-CD4+ < 350 cells/mm³(5).

Social vulnerability increases susceptibility to the disease and the chance of delayed diagnosis, as well as reducing treatment adherence⁽¹⁷⁾. The low indication of TPT may be related to several factors, including the lack of human resources, barriers to access to outpatient follow-up care, and the Covid-19 pandemic. Despite studies that indicate the use of Isoniazid in reducing illness by 60% to 90%, with the duration and adherence to treatment depending on the professionals' concern with the risk of hepatotoxicity and resistance, the low indication of the drug persists⁽⁹⁻¹⁶⁾.

Thus, in the implementation of the cascade of care, strategies were formed, including monitoring the results of tests performed with an active search for patients with indication for treatment and support with DOT for patients who wished to receive monitoring from the nursing team. Strategies related to social care and educational strategies are described in the literature as capable of reducing the vulnerability of individuals with HIV/AIDS and those susceptible to developing TB⁽¹⁵⁻¹⁷⁾.

In the service, instead of using the 6H schedule, the 9H schedule was indicated because the 270-dose schedule is more effective compared to the 180-dose schedule⁽⁴⁾. Regarding the choice of 3HP or 9H, it is known that the 3HP regimen is more efficient, more cost-effective, and has the important advantage of a shorter treatment time⁽⁷⁾. The choice of the 3HP scheme depends on the possibility of patients going to the service once a week, as this directly observed modality has better treatment adherence and greater connection between patients and the health team⁽⁴⁻⁷⁾.

Furthermore, the use of 4R is indicated for cases of toxicity before the use of Isoniazid, considered one of the main concerns of medical professionals when prescribing this treatment⁽⁴⁻⁷⁾. In a TPT implementation study conducted in Indonesia with children and adults with LTBI in 2011-2017, it was found that the completion rate of 4R treatment was significantly higher than that of 9H treatment (78.7% versus 65.5%)(18).

The most recommended regimen for starting treatment was 3HP (83.1%), which was performed in DOT (72.9%) and

in SAT (27.1%), because the patient had the possibility of choosing the treatment most appropriate to their needs. DOT is strongly recommended for patients using 3HP⁽⁹⁾, and it is worth highlighting the role of nursing in welcoming and monitoring initiatives⁽¹¹⁾. However, although DOT promoted greater adherence to the treatment regimen, there was no evidence of its superiority over SAT (p-value > 0.05) in our study.

Adherence to treatment is related to the completion of drug treatment, and factors such as access to medication and medical consultations and organization of the health service directly affect adherence rates. The adherence rate was high in our study, as 94.3% of patients completed treatment. Factors that positively impacted adherence may be related to the adoption of strategies such as integrated work by the multidisciplinary team, with longitudinal access (care, laboratory and imaging tests) performed on the same day of care, and care provided by nurses.

Analysis of TPT completion in a study carried out in Indonesia, from 2020 to 2022 with household contacts of people with bacteriologically confirmed TB, revealed that the use of 3HP has high TPT completion rates (91.5%), because care is person-centered and regimens are shorter⁽¹⁹⁾.

The TPT completion rate was higher (71.8%) than other national studies. In a study with PLWHA carried out in an HIV/AIDS reference service in Campo Grande-MS in 2021, the treatment completion rate was 67.44% (n=43), and, in a study carried out in a service in Paraná with PLWHA in 2019 and 2020, the treatment completion rate was 61.4% (n=386)⁽⁵⁻¹⁷⁾.

Treatment was discontinued due to hepatotoxicity. An analysis of LTBI care cascade carried out at a reference hospital in São Paulo with candidates and/or recipients of solid organs or hematopoietic pluripotent cells transplants from 2009 to 2022 revealed that only 3.1% (n=194) of candidates had treatment suspended due to toxicity⁽²⁰⁾. Therefore, in immunosuppressed populations, adverse drug reactions (ADRs) are generally low and well tolerated^(5,8,13).

In order to increase the treatment completion rate, the sixth stage of the continuous care cascade, the adoption of specific strategies is recommended: introduction of short regimens, which have higher treatment completion rates, and adherence support, such as reminders and patient education⁽⁵⁾. The use of 3HP provides a higher rate of treatment completion for individuals with LTBI and has proven to be a safe alternative^(7,9).

The study had some limitations such as non-probabilistic sampling of people who were already being monitored for viral load and who entered the study, a reduced number of patients using Isoniazid and 80% of patients using the 3HP

regimen, which may have caused a selection and sampling bias. However, the study was carried out in a health service during the implementation of the cascade of care, faithfully reflecting what was happening in that service.

■ CONCLUSION

The outcome indicators, after the implementation of the continuous care cascade for LTBI in PLWHA in a specialized service, required a change in the work process of the health team. The use of a shortened regimen (3HP) was associated with a better treatment completion rate compared to other therapeutic regimens and a reduced number of serious adverse events.

Thus, the present study contributes to the description of the implementation of each stage of the care cascade, with identification, active search for treatment and follow-up of individuals with indication for LTBI treatment, in order to reduce morbidity and mortality due to TB among PLWHA.

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