

# Latent tuberculosis among people living with HIV and contacts in a hyperendemic state

Tuberculose latente entre pessoas vivendo com HIV e contatos num estado hiperendêmico  
Tuberculosis latente entre personas que viven con el VIH y contactos en un estado hiperendémico

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## Abstract

**Objective:** To assess latent tuberculosis among people living with HIV and contacts of people with tuberculosis.

**Methods:** This is a cross-sectional, quantitative study, carried out in the state of Pará, based on cases of latent tuberculosis infection reported between 2019 and 2020. Data were extracted from the Latent Tuberculosis Infection Information System, at the State Department of Public Health, from November to December 2021. For analysis, descriptive statistics, chi-square test and G test were used, in addition to prevalence ratio, in Bioestat 5.3, with a significance level of 5%.

**Results:** A total of 1,116 cases of latent tuberculosis were studied: 653 in 2019 and 463 in 2020. The outcome indicated a low proportion of complete treatments (n=734). Among the records, 371 were of people living with HIV and 416 were of contacts of tuberculosis cases. An association was observed between latent infection in people living with HIV and contacts with the variables sex, age, origin and termination situation (p<0.0001).

**Conclusion:** Latent tuberculosis in people living with HIV and contacts presents different patterns when associated with the sociodemographic profile, making it necessary to prioritize the identification of these groups in order to adopt strategic actions that impact disease management.

## Resumo

**Objetivo:** Avaliar a tuberculose latente entre pessoas vivendo com HIV e contatos de pessoas com tuberculose.

**Métodos:** Estudo transversal, quantitativo, realizado no estado do Pará, a partir dos casos de infecção tuberculosa latente notificados entre os anos 2019 e 2020. Os dados foram extraídos do Sistema de Informação de Infecção Latente por Tuberculose, na Secretaria de Estado de Saúde Pública, no período de novembro a dezembro de 2021. Para análise, utilizaram-se a estatística descritiva, o teste qui-quadrado e o teste G, além da razão de prevalência, no *Bioestat* 5.3, com nível de significância de 5%.

**Resultados:** Foram estudados 1.116 casos de tuberculose latente, sendo 653 em 2019 e 463 em 2020. O desfecho indicou baixa proporção de tratamentos completos (n=734). Entre os registros, 371 eram de pessoas vivendo com HIV e 416 contatos de casos de tuberculose. Observou-se associação da infecção latente em pessoas vivendo com HIV e contatos com as variáveis sexo, idade, procedência e situação de encerramento (p<0,0001).

**Conclusão:** A tuberculose latente em pessoas vivendo com HIV e contatos apresenta diferentes padrões quando associada ao perfil sociodemográfico, sendo necessário priorizar a identificação desses grupos para a adoção de ações estratégicas que impactem no controle da doença.

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**Conflicts of interest:** nothing to declare.

## Resumen

**Objetivo:** Evaluar la tuberculosis latente entre personas que viven con el VIH y los contactos de personas con tuberculosis.

**Métodos:** Estudio transversal, cuantitativo, realizado en el estado de Pará, a partir de casos de infección por tuberculosis latente notificados entre los años 2019 y 2020. Los datos se extrajeron del Sistema de Información de Infección por Tuberculosis Latente, de la Secretaría de Salud Pública del Estado de Pará, en noviembre y diciembre de 2021. Para el análisis se utilizó la estadística descriptiva, la prueba ji cuadrado y la prueba G, además de la razón de prevalencia, en *Bioestat* 5.3, con nivel de significación de 5 %.

**Resultados:** Se estudiaron 1.116 casos de tuberculosis latente, de los cuales 653 fueron en 2019 y 463 en 2020. El resultado indicó baja proporción de tratamiento completo ( $n=734$ ). Entre los registros, 371 eran de personas que viven con el VIH y 416 contactos de casos de tuberculosis. Se observó relación entre la infección latente en personas que viven con el VIH y los contactos, con las variables sexo, edad, procedencia y situación de cierre ( $p<0,0001$ ).

**Conclusión:** La tuberculosis latente en personas que viven con el VIH y contactos presenta diferentes patrones al relacionarla con el perfil sociodemográfico, por lo que es necesario priorizar la identificación de estos grupos para adoptar acciones estratégicas que impacten en el control de la enfermedad.

## Introduction

It is estimated that a quarter of the world's population is infected by *Mycobacterium tuberculosis* without active disease. Infected people remain healthy for many years, without transmitting the bacillus and with partial immunity to the disease. The most important action for diagnosing latent tuberculosis infection (LTBI) is the tuberculin skin test; however, there is no indication for indiscriminate investigation in the general population. This research is only recommended in populations that will potentially benefit from the recommended treatment for the infection.<sup>(1)</sup>

The identification of groups considered most vulnerable and the implementation of treatment for confirmed cases of LTBI have become two of the priorities for tuberculosis management. In Brazil, although latent infection treatment is included in the recommendations to be followed by health teams, it is still carried out incipiently. In Pará, there is low identification of LTBI in all services that carry out the exam.<sup>(2)</sup>

Among the priority groups for tuberculosis infection, contacts of people with pulmonary tuberculosis stand out, as they exhibit a high risk of becoming infected and developing the disease due to household contact with *M. tuberculosis*, making it essential to screen for, assess and treat prophylactically. Another group, equally a priority, are people living with HIV, due to compromised immune systems, making them more susceptible to infection, who are not always tested.<sup>(3)</sup>

In the world, in 2021, around 10.6 million people fell ill from tuberculosis. There were 1.4 million

deaths due to the disease, which is the second cause of death due to a single infectious agent. It affects, proportionally, young males in low-income countries, confirming the association with socioeconomic factors.<sup>(4)</sup> In Brazil, in 2022, 78 thousand new cases were diagnosed with an incidence coefficient of 36.3 cases/100 thousand inhabitants. The state of Pará reported, in the same year, 4,344 new cases, and the incidence coefficient was 49.4/100 thousand inhabitants, with 253 deaths in 2021.<sup>(2)</sup>

To combat tuberculosis, in 2017, Brazil presented a national plan with the objective of eliminating the disease as a public health concern by 2035, with the goals of reducing the incidence rate to less than ten cases/100 thousand inhabitants and the mortality rate to less than one death/100 thousand inhabitants. It is based on three pillars: prevention and integrated patient-centered care; bold policies; and support system and research and innovation intensification.

Among the innovations, we highlighted the Ministry of Health's recommendation for reporting LTBI cases in all Federated Units, grouping data by year, from 2015 onwards, informing the number of people undergoing treatment, sex, age, age group, treatment recommendation and termination. In 2018, the LTBI protocol was launched to better guide health teams in case management and assist in implementing the Latent Tuberculosis Infection Information System (IL-TB) to consolidate specific data.<sup>(5)</sup>

The IL-TB implementation initiative was recognized as fundamental for gathering data related to latent infection in Brazil and, therefore, generating information for calculating indicators

for monitoring and assessing LTBI surveillance actions. Such indicators made it possible to build the epidemiological overview in the territories, monitor assistance to people undergoing treatment and generate information to support decision-making. IL-TB implementation was considered a milestone in the perspective of achieving important results in reducing the burden of tuberculosis in Brazil.<sup>(5)</sup>

The imperative of identifying and treating LTBI as tuberculosis prevention actions is recognized, especially in the most vulnerable groups. These actions can prevent illness, reducing the number of infected people who will fall ill early throughout their lives. In this regard, based on the overview presented, this study aimed to assess latent tuberculosis among people living with HIV and contacts of people with tuberculosis.

## Methods

This is a cross-sectional study, with a quantitative approach, carried out with IL-TB data, obtained from November to December 2021 from the State Department of Public Health of Pará (SESPA - *Secretaria de Estado de Saúde Pública do Pará*). The study followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) recommendations for cross-sectional studies.

It was carried out in the state of Pará, located in northern Brazil, with an area of 1,245,955 km<sup>2</sup> and a demographic density of 6.07 inhabitants/km<sup>2</sup>. All cases of LTBI, reported in 2019 and 2020 to IL-TB, were included, totaling 1,116 records, with no data exclusion. The period was defined because the system was implemented in the state in 2019 and the study was completed in 2022, when only data up to 2020 were available.

Demographic and epidemiological data were collected, such as type of entry, sex, age, race, HIV test, origin and termination status. Subsequently, the data were stored in a digital spreadsheet, using Excel version 2016. Demographic and epidemiological data were analyzed descriptively, and cate-

gorical variables were described in frequencies and percentages and numerical variables in mean and standard deviation. To assess the relationship between categorical variables, chi-square test and G test were used. G test allowed exploring the relationship between variables that presented frequencies lower than five. Statistical analyzes were carried out using the Bioestat 5.3 program, and the significance level adopted was 5%.

This study is part of a multicenter study entitled “Pattern of latent tuberculous infection in undergraduate nursing students at public universities and educational technology construction and validity” and was approved by a Research Ethics Committee, under Opinion 1.084.210 (Certificate of Presentation for Ethical Consideration (*Certificado de Apresentação para Apreciação Ética*) 19308719.7.0000.5170).

## Results

A total of 1,116 cases of LTBI were included in this study, with 58.5% (n=653) reported in 2019 and 41.5% (n=463) in 2020. According to Table 1, 99.4% (n =1,109) were new cases, 51.7% (n=577) were female, 40.9% (n=456) were between 31 and 50 years old, 79.3% (n=885) were brown, and 58.7% (n=655) were tested for HIV. Regarding origin, 52.6% (n=587) were from Metropolitan Region I, 16% (n=179) from *Carajás* and 9.9% (n=110) from *Rio Caetés*. The regions of Marajó I, Marajó II, *Araguaia* and *Xingú* presented records below 1% each.

Table 2 showed that 29.2% (n=326) of records relating to treatment recommendation corresponded to “Adult and child contacts, regardless of previous vaccination with BCG”, 33.1% (n=370) should the sum of the groups of people living with HIV and 15.1% (n=169) to “Individuals using tumor necrosis factor-alpha inhibitors or corticosteroids”. It was also observed that in 9.4% (n=105) of records there was no indication of the reasons that led to LTBI treatment.

Regarding the treatment outcome, 73.4% (n=479) and 55.1% (n=255) of cases completed

**Table 1.** Clinical and epidemiological variables of reported cases of latent tuberculosis in the Latent Tuberculosis Infection Information System

Variables	n(%)
Type of entry	
New case	1109(99.4)
Reentry after schema change	1(0.1)
Reexposure	1(0.1)
Reentry after abandonment	5(0.4)
Sex	
Female	577(51.7)
Male	539(48.3)
Age*	
<10	88(7.9)
11-30	259(23.2)
31-50	456(40.9)
>51	313(28)
Race	
Yellow	5(0.4)
White	105(9.4)
Indigenous	6(0.5)
Brown	885(79.3)
Black	80(7.2)
Ignored	35(3.1)
HIV	
Performed	655(58.7)
In progress	20(1.8)
Nor performed	441(39.5)
Origin	
Araguaia	1(0.1)
Lower Amazon	44(3.9)
Carajás	179(16.0)
Lago de Tucuruí	46(4.1)
Marajó I	5(0.4)
Marajó II	2(0.2)
Metropolitan Region I	587(52.6)
Metropolitan Region II	13(1.2)
Metropolitan Region III	87(7.8)
Rio Caetés	110(9.9)
Tapajós	18(1.6)
Tocantins	17(1.5)
Xingu	7(0.6)

\*Age: 39.0 ± 19.9 (mean ± standard deviation)

the recommended treatment for LTBI in 2019 and 2020, respectively, totaling 65.8% (n=734) of the cases studied. However, 15.2% (n=170) and 1.4% (n=16) were suspended due to an adverse reaction; 0.6% (n=7) had active tuberculosis; 0.4% (n=5) died; 0.2% (n=3) were suspended due to a tuberculin skin test < 5mm in primary chemoprophylaxis; 0.2% (n=3) were transferred to another country; 0.1% (n=1) had suspension due to clinical conditions unfavorable to treatment; and 15.8% (n=177) had no information about termination. Table 3 shows that, in the group of people

**Table 2.** Treatment recommendation stratified by group of cases reported in the Latent Tuberculosis Infection Information System

Groups	n(%)
Adult and child contacts, regardless of prior BCG vaccination	326(29.2)
People living with HIV with a CD4+ cell count less than or equal to 350 cells/μL	298(26.7)
People using tumor necrosis factor alpha inhibitors or corticosteroids (>15 mg of prednisone for more than 1 month)	169(15.1)
Other (not reported)	105(9.4)
Contacts of people with tuberculosis confirmed by laboratory criteria	90(8.1)
People living with HIV with CD4+ > 350 cells/μL	40(3.6)
People living with HIV laboratory-confirmed pulmonary tuberculosis contacts	16(1.4)
People living with HIV with documented record of having had PT ≥ 5mm or positive IFN-γ and not undergoing LTBI treatment at the time	16(1.4)
Healthcare professionals	13(1.2)
People with isolated calcification (without fibrosis) on x-ray	11(1)
Other indications	32(2.8)

BCG - bacillus Calmette and Guérin; IFN-γ - interferon-gamma

living with HIV, there was a higher prevalence of LTBI in males, with 65.5% (n=243), whereas in females there was a higher prevalence in the group of contacts, with 57.2% (n=238) (p<0.0001). Regarding age, both in the group of people living with HIV and in the group of contacts, there was a higher incidence of LTBI in the age group from 31 to 50 years old, with 52% (n=193) and 33.2% (n=138), respectively. As for origin, the group of people living with HIV appears most frequently in *Carajás*, with 32.3% (n=120), following Metropolitan Region I, with 27.5% (n=102), and *Rio Caetés*, with 24.8% (n=92), whereas in the contact group the highest frequency occurred in the Metropolitan Region I, with 64.9% (n= 270), in Lower Amazonas, with 7.7 (n=32), and in *Lago Tucuruí*, with 7% (n=29). Concerning termination, in both groups assessed, the highest percentage was complete treatment, 65.5% (n=243), among people living with HIV, and 69% (n=287), among contacts.

Considering the prevalence ratio, people aged between 31 and 50 years are more likely to have LTBI (prevalence ratio of 1.45). Among the sexes, females stood out (prevalence ratio of 1.07) and, among the races identified, browns reached the highest proportion (prevalence ratio of 3.8). Regarding place of residence, being a resident of Metropolitan Region I implies a higher probability of LTBI when compared to other health regions (prevalence ratio of 1.10).

**Table 3.** Association of Latent Tuberculosis Infection between people living with HIV and contacts and sex, age, origin and termination status

Variables	PLWHIV n(%)	Contact n(%)	p-value
Sex			<0.0001†
Female	128(34.5)	238(57.2)	
Male	243(65.5)	178(42.8)	
Age			<0.0001‡
≤10	4(1.1)	68(16.3)	
11-30	82(22.1)	137(32.9)	
31-50	193(52.0)	138(33.2)	
≥51	92(24.8)	73(17.5)	
Regions			<0.0001‡
Lower Amazon	4(1.1)	32(7.7)	
Carajás	120(32.3)	27(6.5)	
Lago Tucuruí	10(2.7)	29(7.0)	
Metropolitan Region I	102(27.5)	270(64.9)	
Metropolitan Region II	0(0)	5(1.2)	
Metropolitan Region III	41(11.1)	20(4.8)	
Rio Caetés	92(24.8)	10(2.4)	
Tapajós	1(0.3)	16(3.8)	
Tocantins	1(0.3)	5(1.2)	
Xingú	0(0)	2(0.5)	
Termination			0.0693
Complete treatment	243(65.5)	287(69)	
Abandonment	65(17.5)	60(14.4)	
Active tuberculosis	5(1.3)	2(0.5)	
Others	11(3)	4(1.0)	
Ignored*	47(12.7)	63(15.1)	

\*Was not included in statistical calculation; † chi-square test; ‡ G test; PLWHIV - people living with HIV.

## Discussion

LTBI has been affecting people, regardless of sex, color and age. In this study, people aged between 31 and 50 years old, living in Metropolitan Region I of the state of Pará, were more likely to be infected. It was found that people living with HIV and tuberculosis contacts constitute the groups most affected by the infection, with each one having a peculiar geographic distribution in the territory of Pará. In people living with HIV, the highest frequencies were identified in *Carajás*, Metropolitan Region I and *Rio Caetés*, whereas among contacts, the highest proportions were in Metropolitan Region I, Lower Amazon and *Lago Tucuruí*.

The heterogeneity in infection behavior between the two groups may be related to the marked differences in the regions. The *Carajás* region faced a large migratory movement due to the implementation of hydroelectric plants, mining industries and livestock farming activities, resulting in disorderly

population growth. A study carried out in the state of Pará identified two spatial risk regions for HIV: the southwestern mesoregion, which includes the *Carajás* region, and the municipality of Belém.<sup>(6)</sup>

In relation to tuberculosis contacts, the study supported a high percentage of infection in the Metropolitan Region I group, attributing it to the high coefficients of active disease associated with the population profile and the presence of economically deprived areas and with incipient and poorly resolving healthcare services.<sup>(7,8)</sup> Furthermore, the Ministry of Health recognizes, in Pará, seven priority municipalities for tuberculosis management, including Belém and Ananindeua, which are part of Metropolitan Region I.<sup>(9)</sup>

According to IL-TB, from 2019 to 2020, there was a significant reduction in cases with treatment terminated and an increase in cases without information, which compromises the more qualified analysis of the epidemiology of LTBI, a fact attributable to the occurrence of the coronavirus disease 2019 (COVID-19) pandemic, which caused compromise the fight against *M. tuberculosis*.<sup>(3)</sup> Among the terminations, there is significant abandonment of therapeutic regimen, indicating weakness in monitoring cases in the service network, compromising disease surveillance.

The age profile of LTBI supports a higher proportion among adults (31 to 50 years old), similar to the findings of a study carried out at a global level, which concluded that LTBI was progressive, with increasing age of individuals.<sup>(10)</sup> These findings indicate that as social contact increases, the risk of infection increases, especially where the rate of illness is high.

However, cases were recorded at all ages, including children under 10 years. Considering that the social groups attended by children are smaller than by adults, intra-household infection is admitted, confirming the need to implement tests for all tuberculosis contacts, given the imminent risk.

A study carried out in three Colombian cities, which assessed the risk of tuberculosis in a cohort of 1,400 contacts of adults with laboratory confirmation, identified 43.7% with a reactive tuberculin skin test, with 65.7% being under 10 years, which



demonstrates the need for differentiated attention in all age groups, especially when it comes to contact.<sup>(11)</sup>

People who live with a bacteriologically confirmed case of tuberculosis are highly exposed to *M. tuberculosis* and may develop LTBI as well as active infection of the disease.<sup>(12,13)</sup> Hence, a study carried out in Spain, which monitored contacts of cases of pulmonary tuberculosis, identified approximately one third of LTBI, of which 60.7% were children up to 5 years. It also highlighted that not everyone underwent preventive treatment and, among those who started and did not complete it, 89% developed tuberculosis.<sup>(3)</sup>

Contact assessment is one of the essential activities in the search for early diagnosis and identification of cases of latent infection, which may exhibit weaknesses in a state with a large territorial extension, such as Pará. This geographic aspect was referred to in a study carried out in the United Kingdom, which highlighted challenging implications providing care for people with LTBI, which could compromise diagnosis, therapy and even work practice.<sup>(14)</sup>

There is no doubt about the imperativeness of strategies and actions for effective LTBI screening aiming at greater identification and treatment of latent infection as a nursing activity, considered a priority in line of care for monitoring people undergoing treatment for TB.<sup>(5)</sup>

Another group that gained prominence in the highest proportion of LTBI data are people living with HIV, which has been recognized internationally and boosted the proposition of priority actions, given the vulnerability of these people's immune systems, which can lead to the development of active tuberculosis.<sup>(15)</sup> A study carried out in Brazil, which investigated the presence of LTBI among people living with HIV, confirmed 9.6% among those tested.<sup>(16)</sup> In Ethiopia, a similar study identified a prevalence of LTBI among people living with HIV of 44.2%.<sup>(17)</sup>

Therefore, it is possible to state that these two groups, contacts of cases with active tuberculosis and people living with HIV, are considered essential for LTBI screening, as they are more prone to in-

fection: contacts, due to close and long-term coexistence with a case of tuberculosis, becoming more exposed to the bacillus, and people living with HIV because they have immunosuppression resulting from the characteristics of the AIDS virus.<sup>(18,19)</sup>

LTBI surveillance actions must also consider the heterogeneous disposition of cases in the territory of Pará. The predominance of tuberculosis in Metropolitan Region I is related to the fact that this is the region with the highest incidence of cases, suggesting a greater number of contacts. In this regard, a study carried out in Australia showed that large urban centers concentrated a greater number of people with LTBI.<sup>(20)</sup> In addition to demographic density, geographic aspects that hinder access to healthcare services and compromise management actions stand out.<sup>(20)</sup>

Pará has an extensive and diverse geographic area, with a concentration of cases in the Metropolitan I region, which should be valued when defining strategies to manage LTBI. It is important to recognize the existence of regions with difficult access to healthcare services, which require journeys that can take several hours or even days by river, which even compromises professional retention, interfering with continuity of program activities.

From this perspective, a study carried out in Portugal, which mapped the geographic pattern of tuberculosis cases with the aim of identifying areas at risk for infection, indicated that the highest risk of infection with *M. tuberculosis* is found in Metropolitan Regions.<sup>(21)</sup>

In this regard, nurses are considered to be the leading actors for assessing contacts of tuberculosis cases and people living with HIV, as one of their duties is to perform a tuberculin skin test, screen the population at increased risk for LTBI, follow up people undergoing treatment, notify people to start treatment, discuss the epidemiological situation with other Primary Health Care professionals and participate in the formulation of strategies aimed at managing tuberculosis. Therefore, this study can be explored by nurses when carrying out their duties.<sup>(5)</sup> The limitations of this study concern the use of data from a secondary source and, therefore, subject to inconsistencies due to human action when feeding IL-TB.

## Conclusion

The proportion of cases of LTBI is higher in people living with HIV and contacts of people with tuberculosis. When association of LTBI in people living with HIV and tuberculosis contacts with sociodemographic variables is made, different patterns of infection are evident between the two groups. Therefore, the identification of people with LTBI is essential for tuberculosis management. Furthermore, knowing sociodemographic variables, origin and termination status of these cases allows us to direct health surveillance actions and services. Furthermore, IL-TB implementation represents an advance in data organization and systematization, contributing to more qualified epidemiological analysis, being able to offer epidemiological and spatial information to support action planning and achieve greater management of LTBI and, consequently, tuberculosis, in the social environment.

## Collaborations

Silva ALG, Sá AMM, Santos DN, Lima IB, Corrêa LRS and Nogueira LMV collaborated with study design, data analysis and interpretation, article writing, relevant critical review of intellectual content and approval of the final version to be published.

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