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ORIGINAL ARTICLE

Evaluation of latent tuberculosis infection in adolescents and young adults living with human immunodeficiency virus in a reference clinic in Brazil

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Abstract

To avoid the occurrence of tuberculosis reactivation in people living with HIV (PLHIV) who have latent tuberculosis infection (LTBI), the therapeutical indications to this population were expanded in Brazil in 2018, with the recommendation of treatment for those with CD4 T lymphocyte count less than or equal to 350 cells/mm3, regardless of the result of the tuberculin test (TT). To evaluate the practical application of this recommendation, we decided to determine the prevalence of LTBI in PLHIV followed in our outpatient clinic. Ninety-nine adolescents and young adults living with HIV accompanied in a Reference Service were evaluated for the occurrence of LTBI with TT and TCD4 cell count application. The prevalence of LTBI was estimated at 7.1% considering the result of TT, and 18% when considering patients with CD4 lymphocyte count less than or equal to 350 cells/mm3. This difference reinforces the idea that the detection of patients with TCD4 lymphocytes less than or equal to 350 cells/mm3 effectively expands the indication for treatment of LTBI. However, only 4 (22.2%) of 18 patients with TCD4 less than or equal to 350 cells/mm3 adhered to the therapeutic proposal. The rebellious aspect inherent to this population, the failure to attend consultations and the refusal to use another drug were some of the reasons for the low adherence to treatment.

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INTRODUCTION

Diagnosis and treatment of latent tuberculosis infection (LTBI) in people living with HIV (PLHIV) are essential to minimize the risk of active infection in this population. Recent reports have shown that PLHIV are 21 times more likely to develop active tuberculosis than those without the virus infection[1] have 48% lower chance of cure, 50% more chance of abandoning treatment and 94% more chance of dying from tuberculosis compared to those without coinfection[2].

In 2015, the World Health Organization (WHO) published the End TB Strategy, whose goal is to eliminate the disease as a public health problem by the year 2035[3]. As part of tuberculosis control in Brazil, the Ministry of Health launched the National Plan to End Tuberculosis as a Public Health Problem, considering it essential to increase screening, diagnosis and treatment of latent infection by Mycobacterium tuberculosis[4].

Early detection and treatment of LTBI in immunocompromised patients can reduce the development of active tuberculosis by 62% and mortality by 26%.[5] The tuberculin skin test (TT) is the most used method in Brazil for diagnosing LTBI and when ≥ 5 mm indicates the start of treatment with isoniazid.[6] In June 2018, the Ministry of Health released a technical note expanding the recommendation to treat latent tuberculosis infection with isoniazid for PLHIV, also recommending treatment for those with T-CD4+ lymphocyte counts less than or equal to at 350 cells/mm^3, regardless of the tuberculin skin test, except for patients diagnosed with active tuberculosis or who have already received adequate treatment for LTBI in the past[7].

METHODS

The objective of the present study was to analyze the practical aspects of complying with the new therapeutic recommendations. Adolescents and young adults living with HIV were evaluated, followed at a reference outpatient clinic in the city of São Paulo from July 2018 to December 2019. The prevalence of LTBI was evaluated through TST and TCD4 lymphocyte count. CD4 T lymphocytes ≤ 350 cells/mm^3 and/or TT ≥ 5 mm should be treated, describing the aspects involved in the follow-up of these patients.

Data collected were age, sex, clinical and immunological classification, drugs used in antiretroviral therapy (ART), number of TCD4 lymphocytes, HIV viral load, previous treatment for TB or LTBI. To rule out active tuberculosis, clinical criteria, chest X-ray and AFB search in sputum or rapid molecular test (Xpert MTB/RIF) were used, when necessary.

An individual with TT ≥5 mm was considered to have LTBI, as long as active TB was properly ruled out. All PLHIV with T-CD4+ lymphocyte count ≤350 cells/mm^3 also received an indication for treatment for LTBI, regardless of the tuberculin skin test, except for patients with LTBI diagnosis of active tuberculosis or who had already received adequate treatment for LTBI in the past. The proposed treatment for LTBI was isoniazid, 5-10 mg/kg, up to a maximum dose of 300mg/day, with a total of 180 doses scheduled, taken every six to nine months, or 270 doses taken every nine to twelve months.

Patient compliance was subjectively evaluated during outpatient consultations and recorded in the medical records, through questioning the patient during medical care. In this, the patient himself verbally informed how he characterized his compliance to his treatment and his difficulties. Their absences from scheduled appointments were also observed and recorded in the agenda.

RESULTS

Ninety-nine patients were included in the study, with ages ranging from 10 to 28 years (mean = 20.8 years); 47 (47.5%) were male and 52 (52.5%) were female.

Table 1 shows the clinical and immunological classification, the therapeutic schemes performed (ART), the HIV viral load, the TCD4 lymphocyte count, the PPD result and the indication for LTBI treatment.

The analysis of the clinical and laboratory characteristics of the patients living with HIV followed up at the clinic showed that most of them live with many difficulties, as most of them have already presented moderate to severe symptoms (51.5% belong to clinical category B and 33.3% to category C), are submitted to complex treatment schemes (with more than three drugs) and have difficulties in controlling their own HIV infection (detectable viral load) (Table 1).

HIV viral load ranged from <40 to 3,685,315 copies/mm3 (mean: 62,518 copies). TCD4 cell count ranged from 6 to 2027 cells/mm^3 (mean = 646).

As for the PPD, only 56 of the 99 patients underwent the test. Six out of 56 patients had TT results ≥5 mm, but 2 were excluded because they had previously treated TB or LTBI. Thus, in the present study, a prevalence of LTBI with indication for treatment of 7.1% (4/56) was obtained.

DISCUSSION

Similar to other studies, we found difficulties both in the diagnosis and in the treatment of latent tuberculosis infection in HIV-infected individuals. It was not possible to determine the prevalence of LTBI through the tuberculin skin test in all patients included. Although the test was requested for all 99 patients, only 56 of them underwent the test, for reasons that ranged from difficulty in paying for transportation (need for 2 visits, one for application, another for reading) to lack of commitment to the clinical follow-up, a difficulty commonly found in the follow-up of adolescents.

In a recent study carried out in Indonesia, with a larger sample (112 individuals), the prevalence of LTBI in PLHIV defined through TT was 19%[8].

The prevalence of PLHIV with TCD4+ lymphocyte count ≤350 cells/mm^3 was 26.2% (26/99); however, eight of them had already undergone previous treatment for LTBI or TB, totaling 18 patients with indication for treatment (18%). Of these 26 patients,

Table 1. Clinical and laboratory characteristics of the 99 patients evaluated.

Clinical classification (CDC 1994)	**N**	
N or A	15	
B or C	84	
Immune classification (CDC 1994)	**N**	
1 or 2	85	
3	14	
Antiretroviral treatment (ARVT)	**%**	
TDF + 3TC + RTV + ATZ	36	
AZT + 3TC + RTV + ATZ	8	
TDF + 3TC + DRV + RTV	6	
TDF + 3TC + DGT	5	
None	4	
Other	41	
CD4 count	**N**	**%**
≤350 cells/mm³	26/99	26,2
<200 cells/mm³	14/99	14,1
Viral load	**N**	**%**
Undetectable	61/99	61,7
Detectable	38/99	38,3
PPD	**N**	**%**
Done	56/99	56,5
Reactor (≥5mm)	6/56	10,7
Non-reactor (<5mm)	50/56	89,3
Not done	43/99	89,3
Treatment indication for ILTBN	**N**	**%**
PPD	4/56	7,14
CD4 ≤350	18/99	18

Legend: Clinical and immunological classification: N: asymptomatic; A: mild symptoms; B: moderate symptoms; C: severe symptoms. Immunological categories: 1: no evidence of immunosuppression; 2: moderate immunosuppression; 3: severe immunosuppression. TARV: TDF: tenofovir; 3TC: lamivudine; RTV: ritonavir; AZT: zidovudine; ATV: atazanavir; DRV: darunavir; DGT: dolutegravir; PPD: tuberculin test.

15 (57.6%) underwent TT, 14 (93%) of whom were non-reactors. If the LTBI treatment indication were based only on the tuberculin skin test, many patients would not have a treatment recommendation.

Considering the prevalence of LTBI identified by the TT (7.1%), the identification of patients with CD4 T-cell count ≤350/mm³ (18%) actually increases the indication of treatment with isoniazid for these patients, enabling the supply of LTBI treatment to a larger number of patients. However, of the 18 patients who should have been treated, only 4 (22.2%) actually started it. Low compliance has been identified as one of the main reasons for LTBI treatment failure in these patients. The reasons for low compliance ranged from non-attendance to consultations, either due to lack of financial conditions, difficulty in getting around due to distant housing, to refusal to use another drug in addition to ART, evidencing the lack of understanding the need for prophylaxis. Other studies report similar situations[9-11]. In a study carried out in Italy in 2001[11], of 83 PLHIV who were supposed to receive prophylaxis, only 40 agreed to start it and only 29 completed the treatment.

Other factors implicated in low compliance to LTBI treatment are prolonged duration of medication, possible side effects of associated medications and low cultural level[12]. Compliance to antiretroviral therapy alone is already difficult. We found a significant number of patients with detectable HIV viral load (69.2% of patients with CD4 T ≤ 350/mm³), which suggests low compliance to regular treatment of HIV infection.

One of the limitations of this study was the failure to assess compliance to treatment in an objective and systematic way, as this was not our initial objective. However, problems with compliance took on such an important role, due to their reflection in the results, that it became evident that if the resolution of these factors is not addressed, there will hardly be success in the treatment of LTBI.

In clinical practice, the recommendation to administer one more medication to treat LTBI in young people living with HIV with CD4+ T lymphocyte count ≤ 350/mm³ proved to be very difficult to implement. Added to the aforementioned factors are the characteristics inherent to adolescence and HIV infection itself, such as questioning and rebelliousness, non-acceptance of seropositivity, compromised self-esteem, and the incurability of the disease. The economic difficulties that usually occur in this population further worsen compliance. When dealing with PLHIV with latent tuberculosis infection, educational, emotional and social support needs to be offered. Healthcare professionals need to use all their efforts to clarify the importance of using isoniazid, so that the targets for reducing the incidence and mortality from tuberculosis are achieved by 2035.

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