

# HTLV-1 AND TUBERCULOSIS ASSOCIATION

• *a review of the literature* •

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## Abstract

Objective: To review and evaluate the scientific evidences on the relationship between tuberculosis (TB) and HTLV-1 infection. Methods: Searches on MEDLINE, LILACS/SciELO and Cochrane Library databases were performed using the following keywords: HTLV-1 Infection, Human T-lymphotropic virus type 1; Paraparesis Tropical Spastic; Tuberculosis. The following data were evaluated: Study design, sample size, number of controls, frequency of HTLV-1 infection in patients with TB and uninfected controls, mortality in HTLV-1/TB coinfecting individuals compared with controls group, response *in vivo* and *in vitro* to PPD, frequency of individuals with tuberculin skin test (TST) positive or negative. Results: Nineteen articles were selected: twelve investigated prevalence, four mortality, three evaluated both prevalence and mortality and six described immunological findings. The majority of the studies was conducted in South America (Brazil and Peru), and Japan. Seven out of 12 studies found an increased risk of HTLV-1 in patients with TB diagnosis. The prevalence of HTLV-1/TB co-infection ranged from 1.49 % in Brazil to 11.4 % in patients in Peru. Two out of five studies found a higher mortality of patients with HTLV-1/TB co-infection compared to patients with TB alone. Three studies conducted in Africa

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(Guinea Bissau and Senegal) found no increase in the mortality of patients co-infected with TB and HTLV-1. A decreased response to PPD *in vitro* or *in vivo* was observed in co-infected individuals compared with patients with TB alone. Conclusion: Patients with TB diagnosis have a higher prevalence of HTLV-1, compared with uninfected controls. Co-infection HTLV-1/TB increases the mortality of TB.

**Keywords:** Human T-Lymphotropic Virus-1 (HTLV-1); Tuberculosis; Prevalence; Immune response; Review.

## INTRODUCTION

The Human T-cell lymphotropic virus type 1 (HTLV-1) was the first retrovirus associated with diseases in humans, isolated in 1980 from a patient with cutaneous T-cell lymphoma.<sup>(1)</sup> Two years later, HTLV-2 was isolated from a patient with hairy cell leukemia.<sup>(2)</sup> More recently, two other retroviruses HTLV-3<sup>(3)</sup> and HTLV-4<sup>(4)</sup> were isolated, both restricted to West Africa, and until now with no proved association with diseases. The HTLV-1 is the most prevalent and has a universal distribution; it is estimated that 10 million people are infected worldwide with this virus.<sup>(5)</sup> The endemic areas are Southeast Japan, where about 20% of the population is infected, Equatorial Africa, Central America and South America.<sup>(6)</sup> Brazil may represent one of the countries with the highest absolute number of infected people,<sup>(5)</sup> with a prevalence of the infection in blood donors ranging from 0.1% in Manaus and Florianopolis, 0.33% in Recife and Rio de Janeiro to 1.35% in Salvador.<sup>(7)</sup> A population-based study conducted in Salvador determined a prevalence of 1.76% in the general population, reaching 9.3% in women above 50 years. In addition, this study found that the infection is more frequent in individuals with lower education and lower income.<sup>(8)</sup>

HTLV-1 is the etiologic agent of Adult T-cell leukemia-lymphoma – ATLL,<sup>(9)</sup> HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)<sup>(10)</sup> and HTLV-associated uveitis.<sup>(11)</sup> However, only 5-10 % of infected individuals will develop one of these diseases.<sup>(12,13)</sup> Furthermore, the

virus is associated with other diseases such as arthritis,<sup>(14)</sup> polymyositis,<sup>(15)</sup> lymphocytic interstitial pneumonia,<sup>(16)</sup> infective dermatitis<sup>(17)</sup> and other immune-mediated processes such as dry syndrome.<sup>(18)</sup>

A growing body of evidence suggests that HTLV-1 may cause some degree of immunosuppression,<sup>(19)</sup> leading to a higher frequency of other infection diseases such as disseminated strongyloidiasis<sup>(20)</sup> and crusted scabies.<sup>(21,22)</sup> It has also been reported an association between HTLV-1 and Tuberculosis (TB). An increased prevalence of the virus infection among individuals with active TB and higher mortality in co-infected individuals are described for several authors.<sup>(23-27)</sup> However, contradictory results are reported in other studies.<sup>(28,29)</sup>

The aim of this study was to review and evaluate the scientific evidences on the relationship between tuberculosis and HTLV-1 infection.

## METHODS

To the search strategy, MEDLINE, LILACS/SciELO and Cochrane Library databases were examined using the following keywords: *HTLV-1 Infection*, *Human T-lymphotropic virus type 1*; *Paraparesis Tropical Spastic*; *Tuberculosis*. MeSH terms, the U.S. National Library of Medicine's controlled vocabulary used for indexing articles for MEDLINE was used.

**Inclusion criteria:** Scientific articles on HTLV-1/TB co-infection addressing the prevalence or incidence of HTLV-1 in outpatients or hospitalized subjects with TB, mortality in HTLV-1/TB co-infection, evaluation of immunological response to *Mycobacterium* antigens *in vivo* or *in vitro*, published in Portuguese, Spanish or English, during the period from 1980 (year of isolation of HTLV) to 2014 .

**Exclusion criteria:** Studies with others mycobacteria other than *Mycobacterium tuberculosis*; review articles or case reports.

After the search for articles, the authors evaluated whether the complete articles analyzed could be included in the review. The following data were extracted: Study design, sample size, number of controls, frequency of HTLV-1 infection in patients with TB and uninfected controls, mortality in HTLV-1/Tb co-infected individuals compared with controls group, response *in vivo* and *in vitro* to PPD, frequency of individuals with tuberculin skin test (TST) positive or negative

## RESULTS

Nineteen articles: eight cross-sectional, seven cohort and four case-control studies were selected. Twelve articles investigated prevalence, four mortality, three evaluated both prevalence and mortality and six described immunological findings. The majority of the studies was conducted in South America: seven from Brazil and three from Peru. There were five studies from Japan, two from Guinea-Bissau, one from USA and one from Senegal.

Details of studies reporting prevalence of HTLV-1/TB co-infection are presented in Table 1. Seven out of 12 studies found an increased risk of HTLV-1

in patients with TB diagnosis<sup>(23-26,31-33)</sup> or higher frequency of previous TB diagnosis in HTLV-1 patients,<sup>(34)</sup> compared to uninfected controls. The prevalence of HTLV-1/TB co-infection ranged from 1.49 % in Goiania, Brazil<sup>(31)</sup> to 11.4 % in patients in Peru.<sup>(34)</sup> In three studies conducted in USA,<sup>(35)</sup> Senegal<sup>(28)</sup> and Guinea –Bissau<sup>(29)</sup> no association between TB and HTLV-1 was observed. However, in the study of Murphy et al.,<sup>(35)</sup> patients with HTLV-2 infection had an increased risk of TB compared with uninfected controls, while in the study of Guinea-Bissau, association between TB and HTLV-1 was found only when patients were infected by HIV.<sup>(29)</sup>

Two out of five studies found a higher mortality of patients with HTLV-1/TB co-infection compared to patients with TB alone.<sup>(25,26)</sup> In one study performed in Guinea-Bissau, an increased mortality was observed only in patients who, in addition to the diagnosis of HTLV-1 and TB, were co-infected with HIV-2<sup>(36)</sup> (Table 2). Regarding the immunological aspects of HTLV/TB co-infection (Table 3), four out of six studies were conducted in Japan and involved patients from the cohort of Myazaki. Three studies<sup>(37-39)</sup> evaluated the response to the PPD skin test, indicating a reduced response in patients co-infected by HTLV-1/TB, compared to uninfected controls. Another study reported a reduced response to PPD *in vitro* in individuals infected with HTLV - 1 vaccinated with BCG and TST-. The addition of IL-12 and IL-4 to cultures of cells of these individuals did not restore the response to PPD, as observed for the control group that was not infected with HTLV-1 and TST negative.<sup>(40)</sup> In Brazil, Mascarenhas et al<sup>(41)</sup> demonstrated a reduction in the *in vitro* response to PPD in asymptomatic patients infected with HTLV - 1, compared with controls. A reduction of TNF -  $\alpha$  in patients infected with HTLV - 1 in response to PPD was also described *in vitro*.<sup>(30)</sup>

**Table 1.** Prevalence of HTLV-1 in patients with Tuberculosis worldwide

(to be continued)

AUTHOR/YEAR/ REFERENCE	REGION/ COUNTRY	STUDY TYPE	SAMPLE	MAIN RESULTS
Moreira et al, 1993 (33)	Salvador / Brazil	Case-control	337 patients with several comorbidities, (90 TB) and 327 controls (healthy individuals)	Comorbidities group: 18,4% of HTLV-1+ Negative controls: 1,8% of HTLV-1+ TB group: 11.1%
Matsuzaki et al, 1993 (32)	HTLV-1 Endemic areas in Japan	Cross-sectional	2,847 men that underwent triage exams	HTLV-1 - Group: 2.88% past of TB (74/2569) HTLV-1 + Group: past of TB 6.1% (17/278) (adjusted OR 3.1 95% CI (1.1-3.3))
Kaplan et al, 1994 (28)	Senegal	Case-control	197 cases (TB + in hospital), 181 controls (patients TB - in hospital)	Cases: 1.5% of HTLV-1 Controls: 1.1% of HTLV-1
Pedral-Sampaio et al, 1997 (25)	Salvador/Brazil	Cross-sectional	378 patients hospitalizes for TB treatment	HTLV-1 +: 8.5% HTLV-1 / 2 +: 0.5% HIV-1 / HTLV-1: 2.4%
Murphy et al, 1997 (35)	United States of America	Cohort	154 HTLV-1 + 387 HTLV-2 + 799 uninfected controls;	HTLV-1 + group: 3.2% of TB (adjusted OR 3.3 (CI 99% 0.8-14.2)) HTLV-2 + Group: 4.6% of TB (adjusted OR 3.9 (CI 99% 1.3-11.6 p <0.01)) Control group: 1.4%
Verdonck et al 2004 (26)	Peru	Cross-sectional	193 patients hospitalized due to TB	7.3% infected with HTLV-1
Marinho et al, 2005 (24)	Salvador/Brazil	Case-control	375 cases (TB +) 378 controls (TB -)	Case: 4.27% HTLV-1 Controls: 1.32% of HTLV-1 in controls adjusted OR 3.01 (95% CI, 1.06 to 8.58)
Verdonck et al 2007 (27)	Peru	Cross-sectional	311 patients outpatients with TB	HTLV-1+: 5.8% HTLV-2+: 0%
Verdonck et al 2008 (34)	Peru	Cross-sectional	1233 family members of patients with HTLV-1: 394 HTLV-1 +; 839 HTLV-;	HTLV-1 + group: 11.4% of TB HTLV-1 group -: 4.3% of TB (x2 test, P <0.001).

**Table 1.** Prevalence of HTLV-1 in patients with Tuberculosis worldwide

(conclusion)

AUTHOR/YEAR/ REFERENCE	REGION/ COUNTRY	STUDY TYPE	SAMPLE	MAIN RESULTS
Norrgren et al 2008 (29)	Guinea-Bissau	Cohort	2127 population- based 280 with TB +	TB group: 11.4% HTLV-1 + (32/280) Population-based: 3.5% HTLV-1 + (OR = 1.61, 95% CI 0.95 to 2.70, P = 0.074). TB/HIV group: 22% HTLV-1+ Population-based/HIV: 12,3% HTLV-1+ (OR = 2.41, 95% CI 1.26 to 4.61, p=0.008)
De Lourdes- Bastos et al, 2009 (23)	Salvador/Brazil	Case-control	Cases: 360 hospitalized patients with a history of TB + Controls: 247 TB - hospitalized patients	Cases: 10.8% HTLV-1 +; Controls: 4.5% HTLV-1 + OR = 2.57 (95% CI, 1.22 to 5.33)
Kozlowiski et al, 2013 (31)	Goiania/Brazil	Corte transversal	402 outpatients and patients hospitalized due to TB	1.49% HTLV1/2+ This prevalence was higher than that observed in local blood donors (0.13%; 95% CI: 0.11-0.17) (AG Kozlowski, unpublished observations)

TB = Tuberculosis; HTLV-1/2 = Human T lymphotropic virus type 1/2; HIV = Human immunodeficiency virus; (-) = Negative; (+) = Positive

**Table 2.** Morbidity and / or mortality of co-infection HTLV-1 and Tuberculosis

AUTHOR/YEAR/ REFERENCE	REGION/ COUNTRY	STUDY TYPE	SAMPLE	MAIN RESULTS
Pedral-Sampaio et al, 1997 (25)	Salvador/Brasil	Cross-sectional	378 patients hospitalizes for TB treatment	Mortality: Retrovirus (-): 25/319 (8%); HTLV-1(+): 8/32 (25%); HIV-1(+): 6/18 (33%); HIV-1(+)/ HTLV-1(+): 5/9 (56%).
Verdonck et al 2004 (26)	Peru	Cross-sectional	193 patients hospitalized due to TB	Mortality: HTLV-1(+): adjusted OR 9.4 (95% CI 2.2 - 40.6)
Verdonck et al 2007 (27)	Peru	Cross-sectional	311 patients outpatients with TB	There was no higher morbidity in the HTLV-1(+) group; Sputum smear (3+): 53% in HTLV-1(+) and 21% in HTLV-1 (-) (p=0.006)
Norrgrén et al, 2010 (36)	Guinea-Bissau	Cohort	280 hospitalized patients with pulmonar TB	Mortality: HIV(-): 18.6/100 persons-years; HIV-2(+)/ HTLV-1(-): 39.5/100 persons-years HIV-2(+)/HTLV-1(+): 113.6/100 persons-years (RR 4.7, 95% CI 1.5-14.4;p <0.01).

Legenda: TB = Tuberculosis; HTLV-1 = Human T lymphotropic virus type 1; HIV-1 = Human immunodeficiency virus type 1; HIV-2 = Human immunodeficiency virus type 2; (-) = Negative; + (+) = Positive

**Table 3.** Immunological aspects involved in co-infection of HTLV-1 and Tuberculosis

REFERENCE	REGION/ COUNTRY	STUDY DESIGN	SAMPLE	TYPE OF IMUNE EVALUATION	IMMUNOLOGICAL FINDINGS
<b>Tachibana et al, 1988 (38)</b>	Miyazaki / Japão	Case- control	39 HTLV-1 + and 87 uninfected controls	Tuberculin skin test (PPD)	Reduced response to PPD in HTLV-1+, mainly those > 60 years old
<b>Welles et al, 1994(39)</b>	Miyazaki / Japão	Cross- sectional	150 HTLV-1+ (25 with flower cells, 125 with normal lymphocytes ) 378 soronegatives	Tuberculin skin test (PPD)	HTLV-1 + relative risk of 2.6 for lower response to PPD (HTLV-1 with flower cells RR 3.4)
<b>Hisada et al, 1999 (37)</b>	Miyazaki / Japão	Case- control	60 HTLV-1 + and 68 uninfected controls exposed to <i>M. tuberculosis</i> or BCG vaccinated	Tuberculin skin test (PPD)	Lower PPD response in HTLV-1, unrelated to gender. Among controls, lower reactivity in men.
<b>Suzuki et al, 1999 (40)</b>	Miyazaki / Japão	Cross- sectional	59 BCG- vaccinated individuals (30 HTLV-1 +, 29HTLV-1 -)	<i>In vitro</i> response to PPD	No restoration of the response to PPD in vitro in the presence of rIL-12 and IL-4 in HTLV + with PPD -, compared to HTLV - PPD - group
<b>Mascarenhas et al, 2006 (41)</b>	Salvador/ Brazil	Case- control	58 HTLV-1 + asymptomatic individuals, 10 uninfected controls	<i>In vitro</i> response to PPD in subjects with and without spontaneous lymphoproliferation	Reduced response to PPD in HTLV +, compared to controls
<b>Bastos et al, 2012 (30)</b>	Salvador/ Brazil	Case- control	13 HTLV-1+/TB+ and 25 controls HTLV-1-/TB+	<i>In vitro</i> response to PPD	Similar production of IFN- $\gamma$ and lower of TNF- $\alpha$ in HTLV-1 + / TB+, compared to HTLV-1-/TB +

PPD = Purified Protein Derivative; *M. tuberculosis* = Mycobacterium tuberculosis; BCG = Bacillus Calmette-Guérin; IL = Interleucin; rIL = recombinant Interleucin; IFN = Interferon; TNF = Tumor Necrosis Factor; HTLV-1 = Human T lymphotropic virus type 1; (-) = Negative; (+) = Positive

## DISCUSSION

The results obtained in this literature review indicated a higher prevalence of HTLV-1 in patients with TB and an increase in mortality in TB /HTLV-1 coinfecting patients, compared with patients with TB alone. Co-infection of TB and HTLV-1 was first described in 1988 in Japan, when Tachibana et al measured the delayed hypersensitivity to PPD in healthy adults in an endemic area for HTLV-1 in the south of the country, finding a lower frequency response, and reduction in size of induration in individuals infected with HTLV-1. Among participants with HTLV-1, only 15% had detectable induration after exposure to PPD, compared with 46% of uninfected individuals. The decreased response to PPD was more frequent among individuals aged 60 years or more. The authors concluded that there is a degree of subclinical immunosuppression in individuals infected with HTLV-1, which increases with age.<sup>(38)</sup> Although this study demonstrated lower PPD reactivity in patients infected with HTLV-1 without previous history of TB, a recent study found high positivity of this test in patients with co-infection HTLV-1/TB, similar to that observed in patients with TB without HTLV-1,<sup>(39)</sup> *in vivo* and *in vitro*. This result was also higher than that found by Mascarenhas et al in 2006, that observed 33% positivity to PPD *in vitro* in individuals infected with HTLV-1, in addition to a decreased response to other memory antigens.<sup>(41)</sup>

In Brazil, one of the first studies in the 1990s in Salvador, the city with the highest prevalence of HTLV-1 in this country<sup>(8)</sup> found that 11% of patients hospitalized with TB were infected with HTLV-1.<sup>(33)</sup> Recently, two other studies also conducted in Salvador, confirmed these results. The first, conducted with 753 outpatients with pulmonary TB and patients without TB from five health districts of Salvador, found a risk that was three times higher of being infected with HTLV-1 in TB group compared with control group.<sup>(24)</sup> The second study investigated the prevalence of HTLV-1 in 607 hospitalized patients, finding 6.4% of co-infection. Interestingly, the authors found no association between HTLV-

1/TB and HIV-1 infection in these patients.<sup>(23)</sup> In Peru, the prevalence HTLV-1 among hospitalized<sup>(26)</sup> and outpatients<sup>(27)</sup> with TB was five to seven times higher than that of Peruvian population. Moreover, it was found that the infection with HTLV-1 and the relationship to the index case were factors associated with active TB, suggesting that HTLV-1 infection may increase the susceptibility to TB.<sup>(34)</sup> In Guinea-Bissau, the infection with HTLV-1 alone was not sufficient to increase the risk of TB. However, HTLV-1 increased the risk of TB among patients infected with HIV.<sup>(29)</sup> Higher mortality and significant increase in CD4+ T-cell counts was observed in patients hospitalized with pulmonary TB, which were coinfecting with HIV/HTLV-1 compared with individuals who only had HIV.<sup>(36)</sup> These findings may suggest that HTLV-1 has an effect on the immune system for HIV seropositive patients, regardless of CD4+ T-cell counts, which makes these individuals more vulnerable to TB. In contrast, in Senegal, a country with low prevalence of HTLV-1, a study showed no association between HTLV-1 infection and the development of TB.<sup>(28)</sup> The conflicting results presented in the literature may be due to methodological differences such as origin of populations, sample or low prevalence of HTLV-1 in the country of the study, as is the case of Senegal.

HTLV-1 has a preferential tropism for CD4+ T-lymphocytes, but also infects CD8+ T-lymphocytes, macrophages, glial cells and dendritic cells.<sup>(42,43)</sup> The infection induces an increase of pro-inflammatory cytokines<sup>(44)</sup> which leads to the spontaneous proliferation of T-lymphocytes.<sup>(43,45)</sup> Subpopulations of CD4+ and CD8+ T-lymphocytes are involved, and particularly the CD4 + CD45RO +T-cell subsets, which are responsible for the response to memory antigens such as cytomegalovirus, candidin, tetanus toxoid and tuberculin. These findings could explain why individuals infected with HTLV-1 have a reduced T-cell response to memory antigens *in vitro*, including purified protein of *M. tuberculosis* – PPD.<sup>(41)</sup>



In summary, there are strong evidences that individuals with TB have a higher prevalence of HTLV-1 infection, especially in countries where both infections are endemics, as occurs in Brazil. Regarding mortality, all studies were conclusive as to the increase in co-infection HTLV-1/TB, nevertheless two studies found higher mortality only when patients were also infected with HIV. Further studies should be conducted to establish the risk factors of TB infection in HTLV-1 infected individuals.

### Acknowledgements

This study was supported by the Fundação de Amparo a Pesquisa da Bahia (FAPESB). Leonardo Pereira Santana held a grant from Institutional program for Scientific Initiation (PIBIC) of the National Council of Technological and Scientific Development (CNPq) of Oswaldo Cruz Foundation – Bahia (FIOCRUZ-BA).

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