REVIEW

HTLV-1 AND TUBERCULOSIS ASSOCIATION

• *a review of the literature* •

Normeide Pedreira dos Santos [a]
Monique Lírio [b]
Rita Elizabeth Moreira Mascarenhas [c]
Leonardo Pereira Santana [d]
Bernardo Galvão-Castro [c]
Maria Fernanda Rios Grassi [c]

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 coinfected 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

Corresponding author: Maria Fernanda Rios Grassi - grassi@bahia.fiocruz.br

a. MD, PhD student. Program in Medicine and Human Health, Bahiana School of Medicine and Human Health, Salvador (BA) Brazil.

b. MD, Resident of Infectious Diseases. Federal University of, BahiaSalvador (BA) Brazil.

c. PhD. Program in Medicine and Human Health, Bahiana School of Medicine and Human Health and Advanced Laboratory of Public Health, Research Center Gonçalo Moniz, Oswaldo Cruz Foundation-BA, Salvador (BA) Brazil.

d. Medical Student, Bahiana School of Medicine and Human Health, Salvador (BA) Brazil.

(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.[1] Two years later, HTLV- 2 was isolated from a patient with hairy cell leukemia.[2] More recently, two other retrovirus HTLV -3[3] and HTLV-4[4] 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.[5] The endemic areas are Southeast Japan, where about 20% of the population is infected, Equatorial Africa, Central America and South America.[6] Brazil may represent one of the countries with the highest absolute number of infected people,[5] 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.[7] 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.[8]

HTLV-1 is the etiologic agent of Adult T-cell leukemia-lymphoma – ATLL,[9] HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)[10] and HTLV-associated uveitis.[11] However, only 5-10 % of infected individuals will develop one of these diseases.[12,13] Furthermore, the virus is associated with other diseases such as arthritis,[14] polymyositis,[15] lymphocytic interstitial pneumonia,[16] infective dermatitis[17] and other immune-mediated processes such as dry syndrome.[18]

A growing body of evidence suggests that HTLV-1 may cause some degree of immunosuppression,[19] leading to a higher frequency of other infection diseases such as disseminated strongyloidiasis[20] and crusted scabies.[21,22] 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.[23-27] However, contradictory results are reported in other studies.[28,29]

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 *Mycobaterium* 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[23-26,31-33] or higher frequency of previous TB diagnosis in HTLV-1 patients,[34] compared to uninfected controls. The prevalence of HTLV-1/TB co-infection ranged from 1.49 % in Goiania, Brazil[31] to 11.4 % in patients in Peru.[34] In three studies conducted in USA,[35] Senegal[28] and Guinea –Bissau[29] no association between TB and HTLV-1 was observed. However, in the study of Murphy et al.,[35] 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. [29]

Two out of five studies found a higher mortality of patients with HTLV-1/TB co-infection compared to patients with TB alone.[25,26] 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[36] (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[37-39] 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. [40] In Brazil, Mascarenhas et al[41] demonstrated a reduction in the in vitro response to PPD in asymptomatic patients infected with HTLV - 1, compared with controls. A reduction of TNF - α in patients infected with HTLV - 1 in response to PPD was also described in vitro.[30]

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-I / 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 at 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)
Norrgren 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
Tachibana et al, 1988 (38)	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
Welles et al, 1994(39)	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)
Hisada et al, 1999 (37)	Miyazaki / Japão	Case-control	60 HTLV-1 + and 68 uninfected controls exposed to *M. tuberculosis* or BCG vaccinated	Tuberculin skin test (PPD)	Lower PPD response in HTLV-1, unrelated to gender. Among controls, lower reactivity in men.
Suzuki et al, 1999 (40)	Miyazaki / Japão	Cross-sectional	59 BCG-vaccinated individuals (30 HTLV-1 +, 29HTLV-1 -)	*In vitro* response to PPD	No restoration of the response to PPD in vitro in the presence of rIL-I 12 and IL-4 in HTLV + with PPD -, compared to HTLV - PPD - group
Mascarenhas et al, 2006 (41)	Salvador/ Brazil	Case-control	58 HTLV-1 + asymptomatic individuals, 10 uninfected controls	*In vitro* response to PPD in subjects with and without spontaneous lymphoproliferation	Reduced response to PPD in HTLV +, compared to controls
Bastos et al, 2012 (30)	Salvador/ Brazil	Case-control	13 HTLV-1+/TB+ and 25 controls HTLV-1-/TB+	*In vitro* response to PPD	Similar production of IFN-γ and lower of TNF-α 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 coinfected 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.[38] 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,[30] *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.[41]

In Brazil, one of the first studies in the 1990s in Salvador, the city with the highest prevalence of HTLV-1 in this country[8] found that 11% of patients hospitalized with TB were infected with HTLV-1.[33] 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.[24] 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.[23] In Peru, the prevalence HTLV-1 among hospitalized[26] and outpatients[27] 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.[34] 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.[29] Higher mortality and significant increase in CD4+ T-cell counts was observed in patients hospitalized with pulmonary TB, which were coinfected with HIV/HTLV-1 compared with individuals who only had HIV.[36] 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.[28] 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.[42,43] The infection induces an increase of pro-inflammatory cytokines[44] which leads to the spontaneous proliferation of T-lymphocytes.[43,45] 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 finding 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.[41]

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).

References

1. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci USA. 1980 Dec;77(12):7415-9.
2. Kalyanaraman VS, Sarngadharan MG, Robert-Guroff M, Miyoshi I, Golde D, Gallo RC. A new subtype of human T-cell leukemia virus (HTLV-II) associated with a T-cell variant of hairy cell leukemia. Science. 1982 Nov 5;218(4572):571-3.
3. Calattini S, Chevalier SA, Duprez R, Bassot S, Froment A, Mahieux R, et al. Discovery of a new human T-cell lymphotropic virus (HTLV-3) in Central Africa. Retrovirology. 2005;2:30.
4. Wolfe ND, Heneine W, Carr JK, Garcia AD, Shanmugam V, Tamoufe U, et al. Emergence of unique primate T-lymphotropic viruses among central African bushmeat hunters. Proc Natl Acad Sci USA. 2005 May 31;102(22):7994-9.
5. Gessain A, Cassar O. Epidemiological Aspects and World Distribution of HTLV-1 Infection. Front Microbiol. 2012;3:388.
6. Mueller N. The epidemiology of HTLV-I infection. Cancer Causes Control. 1991 Jan;2(1):37-52.
7. Galvao-Castro B, Loures L, Rodriques LG, Sereno A, Ferreira Junior OC, Franco LG et al. Distribution of human T-lymphotropic virus type I among blood donors: a nationwide Brazilian study. Transfusion. 1997 Feb;37(2):242-3.
8. Dourado I, Alcantara LC, Barreto ML, da Gloria TM, Galvao-Castro B. HTLV-I in the general population of Salvador, Brazil: a city with African ethnic and sociodemographic characteristics. J Acquir Immune Defic Syndr. 2003 Dec 15;34(5):527-31.
9. Seiki M, Eddy R, Shows TB, Yoshida M. Nonspecific integration of the HTLV provirus genome into adult T-cell leukaemia cells. Nature. 1984 Jun 14;309(5969):640-2.
10. Gessain A, Barin F, Vernant JC, Gout O, Maurs L, Calender A et al. Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. Lancet. 1985 Aug 24;2(8452):407-10.
11. Mochizuki M, Yamaguchi K, Takatsuki K, Watanabe T, Mori S, Tajima K. HTLV-I and uveitis. Lancet. 1992 May 2;339(8801):1110.
12. Hollsberg P, Hafler DA. Seminars in medicine of the Beth Israel Hospital, Boston. Pathogenesis of diseases induced by human lymphotropic virus type I infection. N Engl J Med. 1993 Apr 22;328(16):1173-82.
13. Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H. Adult T-cell leukemia: clinical and hematologic features of 16 cases. Blood. 1977 Sep;50(3):481-92.
14. Kitajima I, Maruyama I, Maruyama Y, Ijichi S, Eiraku N, Mimura Y, et al. Polyarthritis in human T lymphotropic virus type I-associated myelopathy. Arthritis Rheum. 1989 Oct;32(10):1342-4.
15. Morgan OS, Rodgers-Johnson P, Mora C, Char G. HTLV-1 and polymyositis in Jamaica. Lancet. 1989 Nov 18;2(8673):1184-7.
16. Setoguchi Y, Takahashi S, Nukiwa T, Kira S. Detection of human T-cell lymphotropic virus

type I-related antibodies in patients with lymphocytic interstitial pneumonia. Am Rev Respir Dis. 1991 Dec;144(6):1361-5.

17. LaGrenade L, Hanchard B, Fletcher V, Cranston B, Blattner W. Infective dermatitis of Jamaican children: a marker for HTLV-I infection. Lancet. 1990 Dec 1;336(8727):1345-7.

18. Carneiro-Proietti AB, Ribas JG, Catalan-Soares BC, Martins ML, Brito-Melo GE, Martins-Filho OA, et al. [Infection and disease caused by the human T cell lymphotropic viruses type I and II in Brazil]. Rev Soc Bras Med Trop. 2002 Sep;35(5):499-508.

19. Goon PK, Igakura T, Hanon E, Mosley AJ, Barfield A, Barnard AL, et al. Human T cell lymphotropic virus type I (HTLV-I)-specific CD4+ T cells: immunodominance hierarchy and preferential infection with HTLV-I. J Immunol. 2004 Feb 1;172(3):1735-43.

20. Porto MA, Muniz A, Oliveira JJ, Carvalho EM. [Clinical and immunological consequences of the association between HTLV-1 and strongyloidiasis]. Rev Soc Bras Med Trop. 2002 Nov;35(6):641-9.

21. Takeshita T, Takeshita H. Crusted (Norwegian) scabies in a patient with smoldering adult T-cell leukemia. J Dermatol. 2000 Oct;27(10):677-9.

22. Brites C, Weyll M, Pedroso C, Badaro R. Severe and Norwegian scabies are strongly associated with retroviral (HIV-1/HTLV-1) infection in Bahia, Brazil. AIDS. 2002 Jun 14;16(9):1292-3.

23. de Lourdes BM, Osterbauer B, Mesquita DL, Carrera CA, Albuquerque MJ, Silva L, et al. Prevalence of human T-cell lymphotropic virus type 1 infection in hospitalized patients with tuberculosis. Int J Tuberc Lung Dis. 2009 Dec;13(12):1519-23.

24. Marinho J, Galvao-Castro B, Rodrigues LC, Barreto ML. Increased risk of tuberculosis with human T-lymphotropic virus-1 infection: a case-control study. J Acquir Immune Defic Syndr. 2005 Dec 15;40(5):625-8.

25. Pedral-Sampaio DB, Martins NE, Pedrosa C, Brites C, Duarte M, Harrington W, Jr. Co-Infection of Tuberculosis and HIV/HTLV Retroviruses: Frequency and Prognosis Among Patients Admitted in a Brazilian Hospital. Braz J Infect Dis. 1997 Mar;1(1):31-5.

26. Verdonck Bosteels K, Henriquez Camacho C, Echevarria Zarate J, Huayanay Falconi L, Agapito Panta J, Cairampona Mendez R, et al. Asociación entre infección por el virus linfotrópico humano de células T Tipo I (HTLV-I) y mortalidad en pacientes hospitalizados con tuberculosis. Rev. méd. hered. 15[4], 197-202. 2004.

27. Verdonck K, Gonzalez E, Henostroza G, Nabeta P, Llanos F, Cornejo H, et al. HTLV-1 infection is frequent among out-patients with pulmonary tuberculosis in northern Lima, Peru. Int J Tuberc Lung Dis. 2007 Oct;11(10):1066-72.

28. Kaplan JE, Camara T, Hanne A, Green D, Khabbaz R, LeGuenno B. Low prevalence of human T-lymphotropic virus type I among patients with tuberculosis in Senegal. J Acquir Immune Defic Syndr. 1994 Apr;7(4):418-20.

29. Norrgren HR, Bamba S, Larsen O, Da SZ, Aaby P, Koivula T, et al. Increased prevalence of HTLV-1 in patients with pulmonary tuberculosis coinfected with HIV, but not in HIV-negative patients with tuberculosis. J Acquir Immune Defic Syndr. 2008 Aug 15;48(5):607-10.

30. Bastos ML, Santos SB, Souza A, Finkmoore B, Bispo O, Barreto T, et al. Influence of HTLV-1 on the clinical, microbiologic and immunologic presentation of tuberculosis. BMC Infect Dis. 2012;12:199.

31. Kozlowski AG, Carneiro MA, de Matos MA, Teles SA, Araujo JA, Otsuki K, et al. Prevalence and genetic characterisation of HTLV-1 and 2 dual infections in patients with pulmonary tuberculosis in Central-West Brazil. Mem Inst Oswaldo Cruz. 2014 Feb;109(1):118-21.

32. Matsuzaki T, Otose H, Hashimoto K, Shibata Y, Arimura K, Osame M. Diseases among men living in human T-lymphotropic virus type I endemic areas in Japan. Intern Med. 1993 Aug;32(8):623-8.

33. Moreira ED, Jr., Ribeiro TT, Swanson P, Sampaio FC, Melo A, Brites C, et al. Seroepidemiology of human T-cell lymphotropic virus type I/II in northeastern Brazil. J Acquir Immune Defic Syndr. 1993 Aug;6(8):959-63.

34. Verdonck K, Gonzalez E, Schrooten W, Vanham G, Gotuzzo E. HTLV-1 infection is associated with a history of active tuberculosis among family

members of HTLV-1-infected patients in Peru. Epidemiol Infect. 2008 Aug;136(8):1076-83.

35. Murphy EL, Fridey J, Smith JW, Engstrom J, Sacher RA, Miller K, et al. HTLV-associated myelopathy in a cohort of HTLV-I and HTLV-II-infected blood donors. The REDS investigators. Neurology. 1997 Feb;48(2):315-20.

36. Norrgren H, Bamba S, da Silva ZJ, Koivula T, Andersson S. Higher mortality in HIV-2/HTLV-1 co-infected patients with pulmonary tuberculosis in Guinea-Bissau, West Africa, compared to HIV-2-positive HTLV-1-negative patients. Int J Infect Dis. 2010 Sep;14 Suppl 3:e142-e147.

37. Hisada M, Stuver SO, Okayama A, Mueller NE. Gender difference in skin reactivity to purified protein derivative among carriers of HTLV-I in Japan. J Acquir Immune Defic Syndr. 1999 Nov 1;22(3):302-7.

38. Tachibana N, Okayama A, Ishizaki J, Yokota T, Shishime E, Murai K, et al. Suppression of tuberculin skin reaction in healthy HTLV-I carriers from Japan. Int J Cancer. 1988 Dec 15;42(6):829-31.

39. Welles SL, Tachibana N, Okayama A, Shioiri S, Ishihara S, Murai K, et al. Decreased reactivity to PPD among HTLV-I carriers in relation to virus and hematologic status. Int J Cancer. 1994 Feb 1;56(3):337-40.

40. Suzuki M, Dezzutti CS, Okayama A, Tachibana N, Tsubouchi H, Mueller N, et al. Modulation of T-cell responses to a recall antigen in human T-cell leukemia virus type 1-infected individuals. Clin Diagn Lab Immunol. 1999 Sep;6(5):713-7.

41. Mascarenhas RE, Brodskyn C, Barbosa G, Clarencio J, Andrade-Filho AS, Figueiroa F, et al. Peripheral blood mononuclear cells from individuals infected with human T-cell lymphotropic virus type 1 have a reduced capacity to respond to recall antigens. Clin Vaccine Immunol. 2006 May;13(5):547-52.

42. Macatonia SE, Cruickshank JK, Rudge P, Knight SC. Dendritic cells from patients with tropical spastic paraparesis are infected with HTLV-1 and stimulate autologous lymphocyte proliferation. AIDS Res Hum Retroviruses. 1992 Sep;8(9):1699-706.

43. Popovic M, Flomenberg N, Volkman DJ, Mann D, Fauci AS, Dupont B, et al. Alteration of T-cell functions by infection with HTLV-I or HTLV-II. Science. 1984 Oct 26;226(4673):459-62.

44. Nakamura T, Nishiura Y, Ichinose K, Shirabe S, Tsujino A, Goto H, et al. Spontaneous proliferation of and cytokine production by T cells adherent to human endothelial cells in patients with human T-lymphotropic virus type I-associated myelopathy. Intern Med 1996 Mar;35(3):195-9.

45. Carvalho EM, Bacellar O, Porto AF, Braga S, Galvao-Castro B, Neva F. Cytokine profile and immunomodulation in asymptomatic human T-lymphotropic virus type 1-infected blood donors. J Acquir Immune Defic Syndr. 2001 May 1;27(1):1-6.