

## Sensorial changes in individuals with HTLV-1: systematic review

### Alterações sensoriais em indivíduos com HTLV-1: revisão sistemática

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**RESUMO | INTRODUÇÃO:** A função sensorial é reconhecida como precursora da recuperação do movimento, sendo assim, os sintomas apresentados por pessoas com HTLV-1 podem trazer prejuízo na realização de atividades funcionais. **OBJETIVO:** Sistematizar o conhecimento sobre alterações sensoriais em pacientes com HTLV-1. **Metodologia:** Trata-se de uma revisão sistemática, com a busca primária dos artigos realizada nas bases de dados Medline, via biblioteca virtual Pubmed, sendo incluídos estudos observacionais que abordaram a alteração sensorial em indivíduos com HTLV-1. A estratégia de busca foi conduzida de forma independente por dois pesquisadores e as divergências resolvidas por consenso. **RESULTADOS:** Foram encontrados 44 estudos na busca primária, e destes foram incluídos quatro estudos que abordaram a alteração sensorial em indivíduos com HTLV-1, com um total de 240 participantes. Todos os artigos foram classificados como baixo risco de viés no que diz respeito à descrição da questão do estudo, resultados e discussão. **CONCLUSÃO:** identificou-se uma alta prevalência de dor e alteração na sensibilidade vibratória em relação às outras disfunções sensoriais, no entanto, a escassez de trabalhos publicados acerca deste tema sugere que novas abordagens sejam feitas mostrando uma grande lacuna de conhecimento a ser explorada.

**PALAVRAS-CHAVE:** Privação sensorial. Sensação. Vírus linfotrópico da célula humana 1 (HTLV-1). Paraparesia espástica tropical.

**ABSTRACT | BACKGROUND:** Sensory function is recognized as a precursor of the movement recovery. Therefore, the symptoms presented by people with HTLV-1 can result in impairment in the performance of functional activities. **AIM:** To systematize knowledge about sensory alterations in patients with HTLV-1. **Methods:** This is a systematic review, with the primary search of the articles carried out in the Medline databases, via the Pubmed virtual library, including observational studies that addressed the sensory alteration in individuals with HTLV-1. The search strategy was conducted independently by two researchers and the divergences resolved by consensus. **RESULTS:** A total of 44 studies were found in the primary search, including four studies addressing sensory impairment in individuals with HTLV-1, with a total of 240 participants. All articles were classified as low risk of bias regarding the description of the study question, results and discussion. **CONCLUSION:** We identified a high prevalence of pain and altered vibratory sensitivity in relation to other sensory disorders, however, shortage of published works on this topic suggests new approaches are made showing a large knowledge gap to be explored.

**KEYWORDS:** Sensory deprivation. Sensation. Human T-Lymphotropic Virus 1. Paraparesis tropical spastic.

## Introduction

Human T-cell leukemia virus 1<sup>1</sup> (HTLV-1) is a retrovirus that infects millions of people worldwide<sup>2</sup> and is associated with causes of neurological disorders<sup>3</sup>. In these outbreaks, HTLV-1 seroprevalence in adults is estimated to be at least 1-2%, but may also reach 20-40% in people older than 50 years in some specific groups<sup>4</sup>.

It estimates that 15-20 million people live with the infection worldwide and high prevalence rates are found in tropical areas<sup>5</sup>, such as the Caribbean, West and Central Africa, South America and Japan<sup>6</sup>. Brazil, which potentially hosts 800,000 people with HTLV-1, is the largest number of patients on the American continent<sup>6</sup>. Salvador in Bahia is a great city in the northeastern part of the country, with the majority of inhabitants of African descent. It is envisaged the Brazilian city with the highest overall prevalence of HTLV-1<sup>4</sup>.

About 0.25-3.8% of infected individuals develop HTLV-associated myelopathy/tropical spastic paraparesis (HAM / TSP), in which individuals may present neurogenic bladder, sexual dysfunction, sensory dysfunctions and gait alteration<sup>7</sup>. Sensory alterations include low back pain in the lower limbs, with 51.7% being neuropathic, paraesthesia, alteration in vibratory sensitivity (hypoesthesia or apesthesia) and hyperreflexia in the lower limbs, often with clonus and presence and signal of Babinski<sup>7</sup>. It also occurs, less frequently, loss of segmental notion of inferior limbs<sup>8</sup>.

The sensorial symptoms presented by people with HTLV-1 bring impairment in the performance of functional activities<sup>9</sup>. Sensory deficit in the lower limb, including pain<sup>10</sup>, may compromise gait, with decreased balance phase, velocity and symmetry of step<sup>11</sup>, increasing disability<sup>10</sup>. Sensory function is recognized as a precursor to the recovery of movement and functional activity, so it is necessary to gather information about the sensory changes and their possible repercussions in this population. In this context, the objective of this study was to systematize knowledge about sensory alterations in patients with HTLV-1.

## Methodology

This is a systematic review based on the methodology proposed by the Cochrane Collaboration. The research was carried out at a pre-determined protocol, with the elaboration of the project. The primary search of the articles was carried out in the Medline databases, via the Pubmed virtual library, using the following descriptors (DECS): Sensory deprivation, sensation, human t-lymphotropic virus 1, tropical spastic paraparesis, through combinations of Boolean operators and OR), without delimitation of time and language. The search strategy was conducted independently by two researchers and the divergences resolved by consensus.

After the initial survey, critical selection of titles, analysis of abstracts and exclusion of duplicates, bibliographic references of selected articles were consulted and the criteria for the development of the systematic review were re applied, arriving at the final selection.

## Eligibility criteria

The criteria for inclusion in studies in the review were those that addressed the sensory alteration in individuals with HTLV-1. We excluded studies that addressed other clinical manifestations, as well as when associated with other pathology, studies with drug action, protocol of treatment, besides the exclusion of duplicates

## Analysis of methodological quality

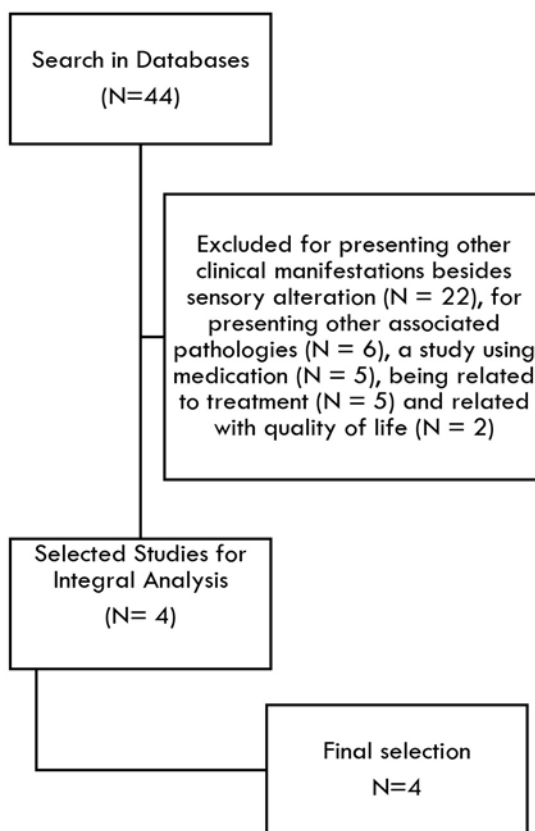
For the evaluation of methodological quality and risk of bias, the Agency for Health Care Research and Quality (AHRQ) scale was modified and adapted by West et al<sup>12</sup>, in which the following components are analyzed: Study questions, population, comparability of topics for observational studies, exposure, measurement of outcomes, statistical analysis, results, discussion, financial support. The

studies were assigned to each item of these as “low risk” when clearly described, “high risk” when not described and “unclear” if they were not clearly described in the text.

## Results

There were 44 studies, of which four were selected from the analysis of the titles and abstract and 40 were excluded, 22 for other clinical manifestations besides sensory alteration, six for other diseases besides HAM / TSP, five for being clinical trials using drugs, five because they are related to treatment and finally two articles by addressing quality of life (Figure1). Thus, four studies were added to methodological evaluation (Table 1). The total population included in the studies resulted in 240 participants. It is to be noted that the four articles refer to the year 2009<sup>10</sup>, 1999<sup>13</sup>, 1996<sup>14</sup> and 1992<sup>15</sup>, described in English.

Figure 1. Data Collection and Extraction Flowchart



**Chart 1.** Evaluation of the methodological quality of observational studies by the Agency for Healthcare Research and Quality (AHRQ) scale. 2018

Author / Year	Castro-Costa et al / 2009	Castillo et al / 1999	Moritoyo et al / 1996	Kakigi et al / 1992
Study Questions	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Population	Uncertain risk of bias	Uncertain risk of bias	Uncertain risk of bias	Uncertain risk of bias
Comparability of Topics for Observational Studies	Uncertain risk of bias	Low risk of bias	Uncertain risk of bias	Low risk of bias
Exposure or intervention	High risk of bias	High risk of bias	Low risk of bias	High risk of bias
Measurement of Outcomes	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias
Statistical analysis	High risk of bias	Low risk of bias	High risk of bias	High risk of bias
Results	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Discussion	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Financial Support	High risk of bias	High risk of bias	High risk of bias	Low risk of bias

## Discussion

It has been observed that HTLV-1 can compromise the sensory pathways of infected individuals due to involvement of ascending spinal cord and spinal cord tract fibers. In the evaluation of the methodological quality of the included studies, all articles were considered to be low risk of bias regarding the description of the study question, results and discussion. In other items of the AHRQ, there was a variation in this classification among the studies.

In all the studies systematized in this review<sup>10,13-15</sup>, the authors report sensorial alterations in individuals diagnosed with HTLV-1, with emphasis on reduction of vibration, thermal and touch sensitivity, and presence of pain. In other studies, the presence of numbness and tingling<sup>16</sup> and sensation of burning in the lower limbs was observed<sup>17</sup>. Neuropathic pain has been frequent, and the cause of this pain may be related to dysfunction of the nervous system, as a result of the altered activation of the nociceptive pathway<sup>11</sup>. The sensation of pain can generate functional limitations, worsens the quality of life and also causes other sensorial alterations such as loss of light touch, vibration and thermoalgesic sensation<sup>13</sup>.

Articles<sup>13-15</sup> corroborate the findings on the decrease in vibration sensitivity, showing that in half of the sample of individuals with HTLV-1<sup>14,15</sup>, in addition to tactile hypoesthesia<sup>13,14</sup> dysesthesia<sup>14</sup>, hypoesthesia in needling and paresthesia<sup>13</sup>. The discrepancy in the results found may be based on the quality of the

samples, since all the studies presented an uncertain risk regarding the population, not quantifying the quantity to be evaluated. Besides the variation of the time of the disease.

The authors report the presence of subclinical alterations in people with HAM / TSP<sup>15,18</sup>, due to lesions in ascending spinal pathways and in the spinothalamic tract<sup>13-15</sup>. In this way, people infected with HTLV-1 can present sensorial changes of central origin, medullary and encephalic, as saw in studies that verified reduction of sensorial conduction at the thoracic level<sup>13-15</sup>. A positive correlation was observed between this spinal cord involvement and the higher level of functional disability<sup>14</sup>, confirming that the sensory alteration has a direct impact on the functionality of people infected with the virus.

Increasing the importance of the early investigation of these sensory alterations, it was verified that individuals diagnosed with MS, a disease that is also demyelinating<sup>19</sup>, have the most common initial sensory symptoms, commonly seen as paraesthesia and altered vibratory perception<sup>20</sup>. The sensorial clinical manifestations of the mentioned diseases are probably similar owing to the involvement of the same pathways in the central nervous system.

In contrast to the study that identified that this sensorial alteration was due only to central impairment in individuals with HTLV-1<sup>13</sup>, some studies show that there is also a reduction in nerve conduction time of peripheral sensory nerves<sup>14</sup>, with the presence of

peripheral neuropathy<sup>18</sup>. This disagreement may be due to the methodological difference of evaluation between the studies.

The following study had the advantage of being able to systematize information about the sensory alterations resulting from HTLV-1, even in the subclinical environment. Besides the evaluation of the methodological quality of the articles that allows a greater reliability of the same. As a disadvantage, the lack of studies focused on sensory dysfunction in individuals with HTLV-1, making it difficult to deepen the subject studied.

### Final considerations

The present study identified that people with HTLV-1 have sensory dysfunctions, mainly pain and alteration in vibratory sensitivity. It is to be noted that changes in sensory pathways may be present even with the absence of symptoms. However, there is a methodological divergence between the included studies, which found it difficult to analyze them in a homogeneous way. Due to the scarcity of published work on this subject. It is suggested that new approaches be made to better understand the sensorial disorders in this population, with a view to their prevention.

### Authors' contributions

All authors participated in the study conception and design, collection and analysis of the data, interpretation of the results and in the writing of the scientific article.

### Competing interests

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

### References

1. Gallo RC, Willems L, Tagaya Y. Time to Go Back to the Original Name. *Front Microbiol.* 2017;8:1800. doi: [10.3389/fmicb.2017.01800](https://doi.org/10.3389/fmicb.2017.01800)
2. Santos DN, Santos KOB, Paixão AB, Andrade RCP, Costa DT, S-Martim DL et al. Factors associated with pain in individuals infected by human T-cell lymphotropic virus type 1 (HTLV-1). *Braz J Infect Dis.* 2017;21(2):133-139. doi: [10.1016/j.bjid.2016.11.008](https://doi.org/10.1016/j.bjid.2016.11.008)
3. Sá KN, Macêdo MC, Andrade RP, Mendes SD, Martins JV, Baptista AF. Physiotherapy for human T-lymphotropic virus 1-associated myelopathy: review of the literature and future perspectives. *J Multidiscip Healthc.* 2015;8:117-125. doi: [10.2147/JMDH.S71978](https://doi.org/10.2147/JMDH.S71978)
4. Gessain A, Cassar O. Epidemiological Aspects and World Distribution of HTLV-1 Infection. *Front Microbiol.* 2012;3:388. doi: [10.3389/fmicb.2012.00388](https://doi.org/10.3389/fmicb.2012.00388)
5. Caskey MF, Morgan DJ, Porto AF, Giozza SP, Muniz AL, Orge GO et al. Clinical Manifestations Associated with HTLV Type I Infection: A Cross-Sectional Study. *AIDS Res Hum Retroviruses.* 2007;23(3):365-371. doi: [10.1089/aid.2006.0140](https://doi.org/10.1089/aid.2006.0140)
6. Nunes D, Boa-Sorte N, Grassi MFR, Taylor GP, Teixeira MG, Barreto ML et al. HTLV-1 is predominantly sexually transmitted in Salvador, the city with the highest HTLV-1 prevalence in Brazil. *PLoS ONE.* 2017;12(2):e0171303. doi: [10.1371/journal.pone.0171303](https://doi.org/10.1371/journal.pone.0171303)
7. Yamano Y, Sato T. Clinical pathophysiology of human T-lymphotropic virus-type 1-associated myelopathy/tropical spastic paraparesis. *Front Microbiol.* 2012;3:389. doi: [10.3389/fmicb.2012.00389](https://doi.org/10.3389/fmicb.2012.00389)
8. Ribas JGR, Melo GCN. Mielopatia associada ao vírus linfotrópico humano de células T do tipo 1 (HTLV-1). *Revista da Sociedade Brasileira de Medicina Tropical.* 2002;35(4):377-384.
9. Coutinho IJ, Galvão-Castro B, Lima J, Castello C, Eiter D, Grassi MFR. Impacto da mielopatia associada ao HTLV/paraparesia espástica tropical (TSP/HAM) nas atividades de vida diária (AVD) em pacientes infectados pelo HTLV-1. *Acta Fisiatr.* 2011;18(1):6-10. doi: [10.5935/0104-7795.20110001](https://doi.org/10.5935/0104-7795.20110001)
10. Castro-Costa CM, Araujo AQC, Camara CC, Ferreira AS, Santos TJT, Castro-Costa SB et al. Pain in Tropical Spastic Paraparesis/HTLV-I Associated Myelopathy Patients. *Arq Neuropsiquiatr.* 2009;67(3b):866-70. doi: [10.1590/S0004-282X2009000500016](https://doi.org/10.1590/S0004-282X2009000500016)

11. Lima DHF, Queiroz PA, Salvo G, Yoneyama SM, Oberg TD, Lima NMFV. Brazilian version of the nottingham sensory assessment: validity, agreement and reliability. *Rev Bras Fisioter.* 2010;14(2):166-74.
12. West S, King V, Carey TS, Lohr KN, McKoy N, Sutton SF et al. Systems to rate the strength of scientific evidence. Evidence Report/ Technology Assessment No. 47. AHRQ publication no. 02- E016. Rockville, MD: Agency for healthcare research and quality [periódico on-line]. 2002.
13. Castillo JL, Cea JG, Verdugo RJ, Cartier L. Sensory Dysfunction in HTLV-I-Associated Myelopathy/Tropical Spastic Paraparesis: A Comprehensive Neurophysiological Study. *Eur Neurol.* 1999;42(1):17-22. doi: [10.1159/000008063](https://doi.org/10.1159/000008063)
14. Moritoyo H, Arimura K, Arimura Y, Tokimura Y, Rosales R, Osame M. Study of lower limb somatosensory evoked potentials in 96 cases of HTLV-I-associated myelopathy/ tropical spastic paraparesis. *J Neurol Sci.* 1996;138(1-2):78-81.
15. Kakigi R, Kuroda Y, Takashima H, Endo C, Neshige R, Shibasaki H. Physiological functions of the ascending spinal tracts in HTLV-I-associated Myelopathy (HAM). *Electroencephalogr Clin Neurophysiol.* 1992;84(2):110-114.
16. Tanajura D, Castro N, Oliveira P, Neto A, Muniz A, Carvalho NB et al. Neurological manifestations in human T-cell lymphotropic virus type 1 (HTLV-1)-infected individuals without HTLV-1-associated myelopathy/tropical spastic paraparesis: a longitudinal cohort study. *Clin Infect Dis.* 2015;61(1):49-56. doi: [10.1093/cid/civ229](https://doi.org/10.1093/cid/civ229)
17. Araujo AQC, Silva MTT. The HTLV-1 neurological complex. *Lancet Neurol.* 2006;5(12):1068-76. doi: [10.1016/S1474-4422\(06\)70628-7](https://doi.org/10.1016/S1474-4422(06)70628-7)
18. Leite AC, Silva MT, Alamy AH, Afonso CR, Lima MA, Andrada-Serpa MJ et al. Peripheral neuropathy in HTLV-I infected individuals without tropical spastic paraparesis/ HTLV-I-associated myelopathy. *J Neurol.* 2004;251(7):877-881. doi: [10.1007/s00415-004-0455-7](https://doi.org/10.1007/s00415-004-0455-7)
19. Learmonth YC, Paul L, McFadyen AK, Mattison P, Miller L. Reliability and clinical significance of mobility and balance assessments in multiple sclerosis. *Int J Rehabil Res.* 2012; 35(1):69-74. doi: [10.1097/MRR.0b013e328350b65f](https://doi.org/10.1097/MRR.0b013e328350b65f)
20. Beiske AG, Pedersen ED, Czujko B, Myhr KM. Pain and sensory complaints in multiple sclerosis. *Eur J Neurol.* 2004;11(7):479-482. doi: [10.1111/j.1468-1331.2004.00815.x](https://doi.org/10.1111/j.1468-1331.2004.00815.x)