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## THE RELEVANCE OF SITUATIONAL STRATEGIC PLANNING AND COMBAT HUMAN T-CELL LYMPHOTROPIC VIRUS ASSOCIATED WITH PERIODONTAL DISORDERS

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**Abstract:** This literature review evaluates the relationship between periodontal disease (PD) and human T-cell lymphotropic virus type 1 (HTLV-1) and whether this interaction occurs in symptomatic and asymptomatic patients. We investigated whether periodontal problems are triggered by the exacerbated immune response caused by HTLV-1 infection or by complex treatments related to the clinical manifestations of this deltaretrovirus. Currently, worldwide, HTLV-1 affects 20 million people, a number that may be underreported. Brazil occupies 1st place in the world ranking, apparently, with 2.5 million patients. Late diagnosis and the lack of effective treatment generate systemic changes, but also oral changes that contribute to the development and/or worsening of periodontal disease, which is why dentists must be prepared to face a probable hyperendemia. Recent studies have shown that many professionals are unaware of the existence of the virus. Addressing the issue must adopt a situational strategic planning proposal instead of deterministic planning models, which are more concerned with the economic aspect than with identifying and attacking the problems and threats of social reality, a mistaken trend in public management that, however, is still adopted and has generated social setbacks for Public Health.

**Keywords:** Dentistry; Human T-cell lymphotropic virus type 1; Periodontal disease.

## INTRODUCTION

Human T-cell lymphotropic virus type 1 (HTLV-1), a member of the *retroviridae* family, was the first human retrovirus in infected lymphocytes from a patient with cutaneous T-cell lymphoma observed in the laboratory. Between 1981 and 2005 four different types of HTLV were identified: HTLV-1, HTLV-2, HTLV-3 and HTLV-4. The HTLV-1 endemic

in South America, subtype A (cosmopolitan), is associated with several systemic and oral clinical manifestations, being capable of attacking various organs of the human body, generating co-infections and genetic changes (Schierhout et al., 2020).

HTLV-1 is associated with the neurodegenerative worsening of HTLV-associated myelopathy (MAH), which is the most frequent clinical manifestation, causing serious damage to the central nervous system (CNS). Cases involving hematological disorders of Adult T-Cell Leukemia (ALL), with degeneration of CD4+ T Lymphocytes and other cells (macrophages, dendritic cells) due to the viral synapse and the action of TAX and HBZ proteins, have also been shown to be relevant. (Proietti, 2015; Vale, 2017).

Since the emergence of AIDS, HTLV has been and continues to be globally neglected by health authorities, public managers, health professionals, delaying public policies and the development of financing programs aimed at research and innovation, even though its vertical transmissibility has already been widely observed and capable of affecting several human generations (Garcia & Hennington, 2019).

Thanks to the reduced volume of research, HTLV was not even able to meet the criteria for inclusion in the list of Neglected Tropical Diseases of the World Health Organization (WHO) or even in the National List of Compulsory Notification of Diseases, Conditions and Public Health Events, created by Ordinance no. 204, of February 17, 2016, from the Brazilian Ministry of Health, the country where the largest number of cases of the disease are concentrated (Brazil, 2022; Carneiro-Proietti et al., 2002).

The majority of patients diagnosed with HTLV are found in highly endemic regions and among vulnerable populations – due to biological, psychosocial, behavioral, religious,

political, marketing and corporate factors – which contributes to information asymmetries, greater difficulties in accessing health services health, worsening social situation and greater exposure and susceptibility to risks (Rosadas, 2018).

In Brazil, HTLV-1 predominates in the states of Pará, Maranhão, Roraima, Acre and Amazonas, but it also appears in Bahia, Pernambuco, Mato Grosso do Sul, Alagoas, Goiás, Piauí, Rio Grande do Norte, Sergipe, Goiás, Rio de Janeiro, São Paulo, Minas Gerais, Paraná and Santa Catarina (Eusebio-Ponce, Candel & Anguita, 2019).

In these communities, the diagnosis is made by Enzyme Immunosorbent Assay (ELISA) screening in the first phase and, subsequently, by serological confirmation, by Western-Blot, when the existence of antibodies against HTLV-1/2 will be defined or not, and can be differentiated by using the polymerase chain reaction (PCR) (Gallo et al, 1993).

HTLV-1 is the etiological agent of MAH and ALL and also increases the patient's risk of developing other clinical manifestations, such as oral changes in soft tissues, salivary glands and periodontium. HTLV-2, in turn, has a lower incidence and is less pathogenic, having been linked to random cases of neurological disorders (Plemons, Al-hashimi & Marek, 2014).

To reduce the impact of HTLV on global public health, appropriate strategies and planning are necessary. The expansive use of science and technology without efficiency, without cost control, without the formalization of adequate planning that is capable of considering the particularities and circumstances of each of the social actors at stake is not enough.

## THEORETICAL FRAMEWORK

We used as a theoretical reference, to examine the premises raised in this work, the Situational Strategic Planning (P.E.S.) by Carlos Matus, a theoretical-methodological proposal that seeks to examine the causes and consequences of problems and threats within a circumstantial perspective, considering the reality of social games, always non-deterministic (Carrazato, 2000).

## THEORETICAL FOUNDATION

Carlos Matus was a prominent Chilean economist who, at the end of the 1960s, worked at the Economic Commission for Latin America (ECLAC - UN) and joined Salvador Allende's government (1970-73) as minister (Carrazato, 2000).

Matus' Situational Strategic Plan opened a severe criticism of the traditional planning models adopted in Latin America, which focused on modeling deterministic solutions without considering reality as it is. Matus supports his convictions on the idea that reality is not the same for everyone. Each person (actor) finds themselves in a subjectively different reality from the other actors, each with their own values, traditions, information and sensibilities (Carrazato, 2000).

The P.E.S. (Situational Strategic Planning) was designed to be applied at different levels (global, regional or institutional), being a method aimed at identifying problems (deficiencies detected during the observation of reality, the social game and the interaction of social actors, which must be addressed through reactive acts), threats (potential dangers to be attacked through proactive acts) and opportunities (where and how it is possible to act). Even though problems and threats may never be definitively resolved, intervention using the P.E.S. (Situational Strategic Planning) contributes to gradual changes, as Matus' planning constitutes a

continuous process of learning, correction and adaptation (Carrazato, 2000).

## PREVIOUS INVESTIGATION

The HTLV virus was discovered in the early 1980s in the United States and Japan. The first studies evaluated the profile of patients, the transmissibility pathways and the affinity of HTLV with host cells (Nishijima et al., 2019; Rosadas, 2019; Shimizu et al., 2019).

It is currently estimated that in endemic regions, HTLV-1 contagion has already reached 15 to 20 million people and that HTLV-2 may have already affected 50 thousand people. These numbers, however, are most likely underreported (Romanelli, 2010).

Brazil is the country with the highest number of confirmed cases of HTLV-1 and HTLV-2, whose transmission normally occurs via hematogenous, vertical and sexual routes. Hematogenically, the virus is inoculated through blood transfusions, sharing contaminated sharps or skin scarification and self-harm in religious ceremonies. There is the possibility of vertical contagion, from mother to child, through breastfeeding, cross-nursing or vaginal birth. Sexually, contagion occurs in unprotected sexual relations, with this happening six times more likely from man to woman than from woman to man (Carneiro-Proietti et al., 2002; Pereira, 2021; Romanelli, 2010; Rosadas, 2021).

It is estimated that there are two and a half million seroprevalent people in Brazil, preferably from vulnerable population groups, of both sexes, regardless of whether they are adults, adolescents or children and whether they live in urban areas or not. Some articles reveal a more worrying scenario in the Amazon region, between the States of Pará, Maranhão and Amazonas (Braço et al., 2019; Paiva, 2015; Rosada, 2021; Tobouti, 2017; Vallinoto, 2019).

Brazilian data on the presence of HTLV, as in the rest of the world, may be underreported, as diagnostic findings still depend on just two protocols:

- i) Blood collection in blood centers, since 1993 (Brazil, 1993, 2016);
- ii) Assisted reproduction, since 2011 (Brazil, 2011).

## PATHOGENESIS

HTLV can manifest itself multisystemically through a) HTLV-1-associated myelopathy, considered the most frequent clinical manifestation; b) adult T-cell leukemia, a neoplasm that affects 3 to 5% of people with HTLV-1; c) inflammatory and infectious diseases; d) severe neuropsychomotor problems and e) oral changes associated with multiple factors that destabilize the homeostasis of the oral cavity (Watt, 2019).

Research indicates that the HTLV viral protein, in contact with the membrane surface of CD4+ and CD8+ T cells, activates the receptor channels of the transport proteins (GLUT-1, NRP1 and HSPGs) to penetrate the cell. Inside the cell, viral RNA is transmuted into viral DNA and incorporated into the cells' DNA. Infected T cells become HTLV reservoirs with long periods of viral latency, at which time most patients remain asymptomatic. Viral particles expelled by the T cell membrane infect, through viral synapses, other cells not yet infected by the virus, as TAX proteins spontaneously activate infected cells, promote cellular genetic instability and decrease the activity of the immune system (Bangham & Matsuoka, 2017; Nakamura et al, 2019).

When CD4+ and CD8+ T cells are infected by HTLV-1, there is the possibility of worsening periodontal disease, with respective tissue destruction as a result of the release of pro-inflammatory cytokines and worsening of HTLV-1 infection (Brito-Melo,

2007; Garlet et al., 2010).

Early diagnosis helps reduce costs and increases opportunities for patients, with preventive control being more appropriate than drug control, given the possibility of multiple adverse reactions, with negative effects on patients' oral health (Plemons, Al-Hashimi & Marek, 2014).

The literature indicates that treatments against HTLV 1 can cause Sjögren's Syndrome, xerostomia, hyposalivation, fissured and depapillated tongue, herpetic lesions, candida infections and worsening of periodontal disease, *verbi gratia*: the administration of antibiotics (Ciclosporin, Fosfomycin, Nitrofurantoin and Norfloxacin) can generate xerostomia or gingival hypertrophy; the administration of hormones (Dexamethasone, Methylprednisolone and Prednisone) can create herpetic lesions; the use of antidepressants (Amitriptyline, Citalopram, Fluoxetine Hydrochloride, Sertraline Hydrochloride, Venlafaxine Hydrochloride, Imipramine and Nortriptyline) and anxiolytics (Diazepam) can cause xerostomia accompanied by a burning sensation, gum problems and potentiation of vasoconstrictor effects during infiltrative anesthesia; the administration of immunomodulators (Ciclosporin and Interferon-alpha) promotes a sensation of dry mouth, stomatitis and gingival hyperplasia; finally, antiretrovirals (Zalcitabine and Zidovudine) cause oral ulcerations (Cerqueira, 2011; Garlet et al., 2010; Giozza, 2006, Lins et al., 2012; Martins et al., 2010).

Some specific studies have specifically highlighted the relationship between HTLV and the worsening or development of periodontal disease, namely:

a) in 2006, it was possible to find an association between periodontal disease and HTLV-1 infection, however it was not possible to relate pro-inflammatory

cytokines with salivary flow. In patients infected with HTLV, plaque-induced gingivitis and chronic periodontitis were found, with more intense inflammation and greater bone loss (Giozza, 2006);

b) in 2007, a cross-sectional study highlighted the presence of gingivitis and periodontitis as a result of the immune response to HTLV infection. Furthermore, it was confirmed that the link between HTLV-1 and periodontal disease alters the levels of cytokines that determine the elevation of Tumor Necrosis Factor (TNF) and Interferon (IFN- $\gamma$ ). TNF is a pro-inflammatory cytokine synthesized in response to inflammation that activates endothelial cells and facilitates the migration of leukocytes. IFN- $\gamma$  is a cytokine produced by T lymphocytes to protect cells against viral infections that activates NK cells and macrophages (Caskey et al., 2007; Garlet et al., 2010).

c) in 2010, viral RNA was identified in periodontal tissue in patients with HTLV-1 and, simultaneously, with chronic periodontitis. These individuals also had higher levels of IL-1 $\beta$  and IFN- $\gamma$ . IL-1 $\beta$  is a molecule secreted by dendritic cells, monocytes and macrophages and IFN- $\gamma$  is a pro-inflammatory cytokine produced by T lymphocytes to protect cells against viral infections. Lower expression of Foxp3 and IL-10 was also confirmed. Foxp3 is a transcriptional factor that acts mainly on regulatory T cells, modulating the immune response and altering the development and progression of diseases. IL-10 is an anti-inflammatory cytokine produced by T lymphocytes that inhibits pro-inflammatory cytokines, prevents the synthesis of IFN- $\gamma$  by natural killers (NK) and increases the presence of mast cells. The authors identified that periodontal disease can worsen in HTLV-1 seropositive



patients due to an imbalance in the expression of cytokines and an exacerbated host response to periodontal bacteria. During the research, it was concluded that patients with periodontal disease, when seropositive for HTLV-1, present greater bleeding on probing, greater depth of pockets and greater loss of attachment in relation to patients who only have periodontal disease (Garlet et al., 2010);

d) in 2012, another study associated the proviral load present in saliva with oral manifestations (periodontitis, gingivitis and probing depth), examining viral variations in peripheral blood mononuclear cells and salivary cells (Lins et al., 2012);

e) in 2013, a study evaluated the stages (severity) of periodontitis and the relationship of this oral pathology with the expression of cytokines and the proviral load. THE RELEVANCE OF SITUATIONAL STRATEGIC PLANNING AND COMBAT HUMAN T-CELL LYMPHOTROPIC VIRUS ASSOCIATED WITH PERIODONTAL DISORDERS. Siral load of patients infected by HTLV-1, with and without MAH. It was concluded that HTLV-1 infection may contribute more to the severity of periodontal disease than the expression of cytokines and proviral load in peripheral blood mononuclear cells (Alves, 2013);

f) in 2019, in Japan, it was demonstrated that elderly patients with alterations in the hematopoietic system (decrease in reticulocyte count) and who live with states of chronic inflammation stimulated by the HTLV TAX protein can develop atherosclerosis (a condition that favors the relationship between the virus and advanced periodontitis) and endothelial changes. Faced with microvascular changes, there is a decrease in nutrient

transport, cell migration and diffusion of antibodies that are extremely important for fighting microorganisms, neutralizing bacterial adherence and inactivating toxins. (Nishijima et al., 2019; Shimizu et al., 2019).

g) Although the majority of HTLV-1 seropositive individuals are asymptomatic, HTLV-1 infection aggravates chronic periodontitis associated with the virus, whether symptomatic or asymptomatic patients. Therefore, in vulnerable populations, research reveals that the strategic control plan must focus on the largest and most silent route of spread of HTLV, which occurs vertically from mother to child, especially during breastfeeding. By stopping breastfeeding or reducing long-term breastfeeding, the risk of HTLV1/2 transmissibility and the entire list of consequences is reduced (Cook et al., 2019).

h) Ordinance GM/MS no. 715/2022 opened the possibility of expanding the identification of HTLV contagion by establishing mandatory testing, diagnosis, treatment and monitoring of the virus in the Maternal and Child Care Network of the Brazilian Unified Health System (SUS). However, on January 13, 2023, Ordinance GM/MS n. 13 suppressed the maternal-infant protocol created by the previous act. This situation indicates a serious social setback, demonstrating the lack of concern of the Brazilian Public Administration with the maintenance of Public Health policies aimed at prevention (Brazil, 2022, 2023).

The public manager is obliged to plan and meet established goals (article 174 of the 1988 Constitution<sup>1</sup>), Administrative decisions that alter or invalidate current rules without indicating the practical, legal and administrative consequences are not

1. Article 174. As a normative agent and regulator of economic activity, the State will exercise, in accordance with the law, the functions of inspection, incentive and planning, which is decisive for the public sector and indicative for the private sector.

admissible in Brazil, according to articles: 20<sup>2</sup> and 21<sup>3</sup> of the Law of Introduction to the Norms of Brazilian Law (Decree-law:4.657/1942, with wording given by Law 13,655/2018) (Brazil, 2002).

In addition to the legal gap, the revocation of the maternal and child protocol demonstrates the Brazilian government's intention to move away from dialogue with society and the search for cooperative arrangements with a view to reducing inequality of access to control and treatment of diseases caused by HTLV. There is no doubt that the health authority's decision deviated from the situational reality, from the concrete examination of the causes and consequences, which will lead to an unacceptable deficit in diagnoses and safeguarding practices for the most vulnerable communities (Brazil, 2022, 2023).

## **MULTIDISCIPLINARITY IN THE MANAGEMENT OF HTLV**

Given the fact that vertical transmission is the main cause of HTLV infection in vulnerable communities, health professionals must, regardless of the Ministry of Health's stance, contraindicate breastfeeding of babies by mothers diagnosed with HTLV, encouraging the replacement of breastfeeding or cross-breastfeeding with milk formulas (Ishak, 2020; Machado et al., 2021; Morais, 2017).

HTLV-1 requires multidisciplinary attention. Its clinical manifestations cause psycho-emotional shocks and motor incapacity, with harm to daily activities. The association of MAH or LLTA with other diseases or opportunistic infections worsens the patient's condition, which can lead to death (Paiva, 2015; Ribeiro, 2018; Righolt et al, 2015; Shimizu et al., 2019;).

2. Article 20. In the administrative, controlling and judicial spheres, decisions will not be made based on abstract legal values without considering the practical consequences of the decision.

3. Article 21. The decision that, at the administrative, controlling or judicial levels, decrees the invalidation of an act, contract, adjustment, process or administrative rule must expressly indicate its legal and administrative consequences.

Many dentists who practice outside endemic areas are unaware of the existence of HTLV. Others are unaware of the forms of transmission or the effects of the infection in the oral cavity, with some even confusing HTLV with HIV. In the country with the highest number of cases, such misinformation brutally compromises the possibility of diagnosis and control, a fact that points to the lack of effective situational planning (Cerqueira et al., 2011; Tobouti, 2017).

## **CONCLUSION**

This work demonstrated the need for governments and international organizations, together with society, to establish a cooperative dialogue in search of situational strategic planning capable of guiding actions to combat the human T-cell lymphotropic virus and its variants. Controlling this problem is of interest to all nations, as around 20 million people across the globe are already infected by HTLV and the possibility of a dramatic increase in numbers is quite likely due to the ease of transmission and contagion of the virus (Carazzato, 2000; Romanelli, 2010).

In Brazil (and around the world) actions are needed to map the infection and establish the epidemiological profile. Strangely, Brazil preferred the path of social and legal regression by issuing Ordinance GM/MS No. 13/2023 of the Ministry of Health, which excluded the mandatory testing of maternal and child health by public health services. This attitude is worrying as there will be an increase in the vertical transmissibility of HTLV, with inter and intrafamilial diffusion of the virus and neurodegenerative clinical manifestations that will develop from early childhood (Araújo, 2012).

Brazil, the country with the highest number

of cases, in 2022 became a global example of combating the HTLV virus, by implementing the maternal and child protection protocol. Inexplicably, without worrying about the causes of the problem and without examining the practical consequences of its recent decision, it unilaterally removed the mandatory testing by women and children's care services (Brazil, 2023).

By the way, the World Health Organization (W.H.O.) could have already developed a

global situational strategic plan seeking to guide actions to combat HTLV and its variants, in order to identify seropositive people (symptomatic and asymptomatic) and the regions of greatest endemicity and transmissibility, with the creation of prevention and treatment routines, cooperating with countries to encourage them to offer professional updating and mandatory testing programs.

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