Abstract
Infection with Human T-cell Lymphotropic Virus type 1 (HTLV-1) represents an important social problem. Clinical manifestations associated with the infection include the HTLV-1 associated myelopathy/tropical spastic paraparesia (HAM/TSP), adult T-cell leukemia (ATL) and uveitis. Other complications include Sjogren’s syndrome, cataract, arthropathies, polymiosites and dermatological manifestations. The possibility of Sjogren’s syndrome occurrence, in addition to drugs that may have side effects on saliva and/or causing lesions in oral mucosa, should be considered. Decreased salivary flow and worsening of periodontal disease have also been reported in the literature. The aim of this work was to give general information about HTLV-1 virus and present possible relationships between this infection and oral health. The bibliographic research was performed using PUBMED, LILACS and SCIELO data bases using HTLV-1, saliva and oral health as keywords. The possibility that the oral health in these individuals is more impaired than in non infected ones leads to the necessity of a special attention from dentists with this group of patients to preserve the integrity of the mineralized structures and soft tissues to improve more life quality. The salivary examination is suggested as an aid in developing the dental treatment plan of these individuals. Health professionals, in particular those who work in endemic areas, should have knowledge about HTLV-1 and the consequences of infection on the health of infected individuals.

Keywords
HTLV-1; Oral health; Sialometry

Abbreviations
HTLV-1: Human T-cell Lymphotropic Virus type 1; HTLV-2: Human T-cell Lymphotropic Virus type 2; HAM: HTLV-1 Associated Myelopathy; TSP: Tropical Spastic Paraparesia; ATL: Adult T-cells Leukemia/Lymphoma; MTCT: Mother-To-Child-Transmission; ID: Infectious Dermatitis

Introduction
The T Lymphotropic Virus type I (HTLV-I) is a human retrovirus originally identified as the aetiological agent of T cell leukemia/lymphoma (ATL) [1]. It is a member of the Retroviridae and was the first human retrovirus identified in laboratory and the second to be discovered implicated in neurological disease.

The vertical transmission of the T-cell lymphotropic virus type I (HTLV-I) occurs predominantly through breast-feeding [2]. The infection can be transmitted through sexual contact, blood transfusion, and through needle sharing among drug users. Its transmission is active in many areas such as parts of Africa, South and Central America, the Caribbean region, Asia and Melanesia [3]. It is estimated that about 15 to 20 million persons, mostly HTLV-1 seropositive, are infected worldwide [4].

The association between HTLV-1 and myelopathy/tropical spastic paraparesia (HAM/TSP) is based on the increased prevalence of this neurological disorder in endemic areas and in the presence of antibodies to HTLV-1 in most patients [5]. There are others medical manifestations associated in HAM/TSP patients including abnormalities in radiographs, Sjogren’s syndrome, cataract, arthropathies, uveites, polymiosites and dermatological manifestations [6].

Considering the various aspects of HTLV-1 infection on the health of patients, the knowledge of this virus and the consequences generated by their presence in human body should not be disregarded by any specialists in human health. The general aspects that affect the patients, physical and social limitations, low self-esteem, psychological disorders represent important variables for which HTLV-1 seropositive patients have to be considered as special patients. In addition, the use of medication that may alter salivary flow and the possibility of Sjogren’s syndrome occurrence associated with the infection are reasons to arouse the attention of the surgeon-dentists. This work aims to provide general information about HTLV-1 infection from the literature review, highlighting the possible oral manifestations resulting from the presence of this virus in humans. The bibliographic research was performed using PUBMED, LILACS and SCIELO data bases using HTLV-1, saliva and oral health as keywords.

The HTLV-1 virus
The HTLV-1 virus was the first human retrovirus described. Initially associated with adult T-cell leukemia (ATL), it was isolated in 1980 from a case of cutaneous T cell lymphoma [7]. The HTLV has a morphological structure similar to other retroviruses, showing a complex construction, consisting of an envelope, a nucleocapsid and a nucleoid. The envelope is composed of a surface protein (SU) and extracellular transmembrane protein.
that passes through this structure and fixes SU. The capsid, with an icosahedral symmetry, is composed mainly by proteins encoded by gag and constitutes the viral particle core. This structure has the nucleocapsid proteins, as well as the reverse transcriptase and integrase, that are essential in the process of proviral DNA integration into the host cell genome. In addition to the standard repertoire of structural proteins and enzymes shared by all retroviridae (gag, pol, pro, env), the 3′ region of the HTLV-1 genome (pX region) also encodes a number of accessory genes as tax, p12, p21, p13, p30 and others [8].

**Epidemiology**

The geographic distribution of the virus has been defined, with Japan, Africa, Caribbean islands and South America emerging as the areas of highest prevalence. The reasons for HTLV-I clustering, such as the high ubiquity in southwestern Japan but low prevalence in neighboring regions of Korea, China and eastern Russia are still unknown. The major modes of transmission are well understood, although better quantitative data on the incidence of transmission, and on promoting/inhibiting factors, are needed. Epidemiologic proof has been obtained for HTLV-I’s causative role in major disease associations: adult T-cell leukemia (ATL), HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP), HTLV-associated uveitis and infective dermatitis. However, more and better studies are needed for other apparent disease outcomes such as rheumatologic, psychiatric and infectious diseases [2].

Recently, a new work about epidemiology and world distribution of HTLV-1 estimated that are 5-10 million persons infected worldwide. However, these results were based on only approximately 1.5 billion of individuals originating from known HTLV-1 endemic areas with reliable available epidemiological data. Correct estimates in other highly populated regions, such as China, India, the Maghreb, and East Africa, is currently not possible, thus, the current number of HTLV-1 carriers is very probably much higher [9].

**Transmission**

Vertical transmission of HTLV-1 can be of transplacental form or through breastfeeding. In endemic areas for the virus, approximately 25% of breastfed children born from HTLV-1 infected mothers, acquire the infection. In Japan, a study showed that the prevalence of HTLV-1 in children of mothers with the virus was 16% [10]. The data supporting the importance of breast-milk transmission included:

1. The demonstration of HTLV-1 antigen in breast milk derived from infected mothers
2. Oral administration of fresh human milk derived from HTLV-1 infected mothers to uninfected marmosets led to HTLV-1 infection
3. A significantly increased HTLV-1 infection rate in breastfed children compared with bottle-fed children
4. Long-term prospective data showing that mother-to-child-transmission (MTCT) rates were 20.5% in infants breastfed for 6 months or more, 8.3% in those breastfed for <6 months and 2.4% in infants exclusively formula-fed.

These data indicate that breastfeeding is the most prevalent, but not the sole route of MTCT of HTLV-1, and that a longer duration of breastfeeding increases the risk of MTCT [11]. Similarly to other sexually transmitted infections, sexual transmission of HTLV-1 is associated with unprotected sex, multiple sexual partners, lifetime contact with an HTLV-1-infected partner, the presence of genital sores or ulcers, and paying or receiving money for sex [3]. Sexual transmission is more effective for women than the other way around. In Japan were described 60.8% rates of transmission from man to woman and only 0.4% in reverse [10].

Transmission through blood and blood products was reported in 1991 with a transmission rate of 12.1% [12]. The possibility of transmission of HTLV-1 and HTLV-2 through blood products has led public health authorities in many countries throughout the world to institute routine screening procedures for these retroviruses in donated blood. Systematic HTLV screening in blood banks is already mandatory in Brazil, Canada, Peru, the United States, Uruguay, and Jamaica and some other countries in the Caribbean, as well as in endemic regions of Argentina and Venezuela [13].

**Diagnostic tests**

The diagnosis of the HTLV-1 virus infection is performed in two steps: screening and confirmation. The tests used for screening are the ELISA or latex particle agglutination or gelatin. Confirmatory tests include the Western blot technique. Molecular tests, using the PCR technique (polymerase chain reaction), are important tools for confirmation and discrimination. The advantage of these tests comparing with the serology is the fact they can reveal the proviral DNA, regardless of antibody production by the host [3].

**HTLV-1 associated diseases**

Most individuals infected with HTLV-1 remains as an asymptomatic carrier. Only a minority of HTLV-1 infected individuals develop disease. Depending on ethnicity and gender, approximately 2-3% of infected individuals develop ATL and 0.25-4% develop HAM/TSP. The majority of infected individuals remains lifelong asymptomatic carriers [14].

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HTLV-1 is the etiological agent of mainly two severe diseases: a malignant T CD4+ cell lymphoproliferation, of very poor prognosis, named Adult T cell Leukemia/Lymphoma (ATL), and a chronic neuro-myelopathy named Tropical spastic paraparesis/HTLV-1 Associated Myelopathy (HAM/TSP). The lifetime risk among HTLV-1 carriers is estimated to be around 0.25 to 3%. HAM/TSP mainly occurs in adults, with a mean age at onset of 40 - 50 years and it is more common in women than in men. Blood transfusion is a major risk factor for HAM/TSP development. Clinically, HAM/TSP is mainly defined as a chronic spastic paraparesis and minor sensory signs. The onset is insidious
with often gait disturbance and urinary symptoms. In more than 90% of the cases, the neurological features involve: spasticity and/or hyperreflexia of the lower extremities, urinary bladder disturbance, lower extremity muscle weakness, and in around 50% of the cases, sensory disturbances with low back pain [15].

The association between infectious dermatitis (ID) and HTLV-1 was suggested by La Grenade et al. [16] in 1990, in Jamaica, presenting as acute eczema in children. This relationship was confirmed with a much larger number of patients in 1998 [17]. Cutaneous manifestations in patients infected by HTLV-1 virus were reviewed by Bittencourt and Oliveira [18].

Ocular manifestations associated with HTLV-1 virus infection have been reported and HTLV-1 uveitis was the main observed. HTLV viral sequences could be detected in vitreous fluid in conjunction with higher numbers of HTLV-infected T lymphocytes compared with the peripheral blood compartment [19]. This article describes the ocular manifestations and pathology of ATL. In 2010, Liu et al. [20] report for the first time a case of a 34-year-old male with systemic ATL and prominent atypical lymphoid cell infiltration in the choroid. This is the first report defining prominent choroidal involvement as a distinct ocular manifestation of ATL. The authors stated that ATL may masquerade as a variety of other conditions, and molecular techniques involving microdissection and PCR have proven to be critical diagnostic tools.

An association between HTLV-1 infection and Sjogren’s Syndrome was reported by Vernant et al. [21], in regions where patients infected and with HAM/TSP, commonly developed the syndrome. Concordant results were obtained by NAKAMURA et al., 1997 [1], studying the prevalence of Sjogren’s syndrome in patients admitted at the school of Medicine of the University of Nagasaki, an endemic area for HTLV-1 in Japan. All patients with HAM/TSP showed an infiltration of mononuclear cells in labial salivary glands. Ohyama et al. [22] showed that Sjogren’s syndrome associated with HTLV-1 is not essentially different from idiopathic form of this syndrome, and suggested the occurrence of an accumulation of T cells infected by the virus in salivary glands of patients with this syndrome. It was observed an accumulation of common T-cell clones in salivary glands of patients with idiopathic Sjogren’s syndrome and in that associated to HTLV-1 [23]. The tax protein of HTLV-1 was suggested as a potential pathogenic factor and a marker for dry syndrome associated with HAM/TSP. Cartier et al. [24] showed that only in patients with HAM/TSP and dry syndrome, the presence of tax protein was observed in CD4+ and CD8+ lymphocytes and in glandular acini.

Although the majority of individuals infected with HTLV-1 remain asymptomatic, recent studies have reported the occurrence of erectile dysfunction, peripheral neuropathy and functional alterations in bladder in subjects positive for the virus, even without present HAM/TSP [25-28].

**Oral health in HTLV-1 infected patients**

Oral health conditions of populations of industrialized countries and developing countries, have improved significantly over the past three decades. In the past, virtually all the individuals were affected by caries and many lost their teeth due to periodontal disease. It is known, currently, that the periodontal disease and tooth decay are differentiated pathologies showing peculiar characteristics according to the factors of aggression (dental biofilm) and the conditions of the host (defense/immune response). The health/disease process depends on balance/imbalance between all factors involved, including systemic conditions of the individual. Therefore, to maintain oral health, there is a need to address not only the oral cavity, but the patient as a whole [29]. The relationship between oral health and systemic diseases is widely discussed in scientific literature. Diseases such as diabetes, obesity, hypertension, heart and renal failure are medical conditions that should require a special attention of dental professionals when performing the dental work [30].

The hypothesis that there is an association between viral infections and depression is quite old, and there are many reports in the literature on the occurrence of depressive episodes after viruses [31]. The association between HIV and depression was well documented in literature. There are evidences that the prevalence of this disorder in HIV-infected individuals is greater than that found in seronegatives. Moreover, studies concluded that depression is associated with a worse course of infection. In 2011, Galvao-Phileto et al. [32] reported a study that confirmed the high prevalence of depression in individuals infected with HTLV-1 (34.7%). It also shows that depression significantly affected the quality of life of these individuals.

HTLV-1 infection seems to be related to the development of Sjogren’s syndrome, particularly in patients with HAM/TSP. Sjogren’s syndrome oral manifestations have as main symptom dryness of mouth (xerostomia). Patients complain of difficulty in chewing and swallowing, mouth pain and recurrent caries. On physical examination, the oral mucosa is dry, erythematous and sticky, being frequent the atrophy of filiform papillae and clefts. The enlargement of salivary gland, mainly involving parotid, is commonly noted in primary Sjogren’s syndrome and, less frequent in secondary form of the syndrome. Diagnostic tests are made, including sialometry, sialography and salivary gland scintigraphy, however the best diagnosis is the labial salivary gland biopsy, which characteristically shows infiltration of lymphocytes [33].

Saliva carries out several functions in higher organisms, such as, the protective action on teeth surface, the buffer capacity, control of the oral microbiota, lubrication, moisturizing, remineralization, and the aid of sensory processes [34]. An important function of saliva is to dilute and eliminate substances produced in the oral cavity, a physiological process referred to as rate of salivary cleansing or oral cleaning. The oral cleaning charge is an individual property and fairly constant over time. However, if changes occur in health and these cause decrease of salivary flow, a drastic change in cleaning charge will occur. The salivary flow is one of the most important parameters related to the oral health, since the saliva composition is directly related to the oral health, since the saliva composition is directly related to the salivary flow [34,35]. The assessment of buffer capacity...
and salivary flow is of great importance to oral health. Early diagnosis of patients with low buffer capacity or salivary flow, or, when these two factors are associated, allows that properly preventive procedures have been adopted, thus avoiding further damage occurring to teeth and oral tissues [35].

Salivary flow in asymptomatic HTLV-1 infected patients and in those with HAM/TSP was analyzed in comparison with a control group of uninfected individuals. Results showed that the salivary gland hypofunction, measured by means of flow reduction, was more common in patients with HAM/TSP than in asymptomatic carriers and controls [36]. Caskey et al. [28], examined several clinical manifestations associated with HTLV-1 infection in a cross sectional study, including 115 individuals infected blood donors without myelopathy and 115 negative controls. Between the clinical manifestations observed, the authors reported oral dryness, gingivitis and periodontitis. The authors concluded that infection by HTLV-1 is associated with a variety of clinical manifestations, even in those patients who have not developed HAM/TSP.

Oral manifestations were studied in Brazilian HTLV-1 infected patients and the most common manifestations were xerostomie (26.8%), candidiasis (20.8%), fissured tongue (17.9%) and loss of tongue papillae (17.9%). Patients with HAM/TSP showed a 3 times greater likelihood of developing xerostomie when compared with HTLV-1 carriers [37]. Similar results were described by Lins et al. [38] in a study about the oral health profile in HTLV-1 infected patients. The relative proportions of complaints of dry mouth, decreased salivary flow, periodontal disease, and gingival attachment loss were higher in the HTLV-1 positive group. Garlet et al. [39] noted the worsening of periodontal disease in HTLV-1 seropositive and have suggested that the virus may play a critical role in the pathogenesis of periodontal disease through the deregulation of local cytokines network, resulting in an exacerbated response against the infection by periodontal bacteria. Recently, Ávies [40] investigated the severity degree of periodontitis and a possible relationship between this disease and cytokines expression and proviral load in HTLV-1 infected patients with and without HAM/TSP. The results showed that HTLV-1 infection may influence the periodontitis severity, but cytokines expression and proviral load in Peripheral Blood Mononuclear Cells (PBMC) were not associated with the severity of this disease.

The disease can be controlled by multidisciplinary treatment using anti-inflammatory agents, antidepressants, antibiotics and hormones. The anti-inflammatory agents may cause herpetic lesion. Antibiotics and antidepressants, in the vast majority, cause dry mouth. Antiretroviral drugs and anticonvulsants may cause oral ulceration. Some antidepressants in addition to causing dry mouth and gum problems may also increase the effects of vasoconstrictors used in oral anesthesia [41].

Conclusion

The numerous variables related to HTLV-1 infection, since the psychosocial implications, the coincidence with other systemic diseases, the use of medication that may alter the salivary flow, the possibility of Sjogren’s syndrome development, compete for the need for a special attention to HTLV-1 virus carriers by health professionals, including dentists working in endemic area. Salivary flow measurement should be performed as support in establishing procedures for the maintenance of oral health. Information related to a complaint of dry mouth, burning, pain and a thorough examination of the oral cavity (teeth, gums, mucous) should be considered as relevant. The possibility that the oral health of HTLV-1 infected individuals is more compromised when compared to non infected ones leads to the need of a special attention to the oral health of this group of patients in order to preserve the integrity of mineralized and soft tissue structures, as well as to improve their quality of life.

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Conflict of Interest

The authors declare that they do not have any conflicts of interest relating to this study. None of the authors has a financial relationship with other people or organizations that could inappropriately influence its findings.

References


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