

EMBARGOED UNTIL MAY 10, 2018 18:30 EDT

Time to eradicate HTLV-1: an open letter to WHO

10, May 2018

On behalf of Human T Cell Leukemia Virus-1 (HTLV-1) positive patients, expert clinicians and scientists working in the field of HTLV-1 clinical and laboratory research.

Dear Dr. Tedros Ghebreyesus,

We are writing to you today to ask you to support the promotion of proven effective transmission prevention strategies against one of the most potent human carcinogens, Human T Leukemia Virus subtype 1 (HTLV-1).

As experts in this field, we offer our support to co-develop a **WHO HTLV-1 webpage** under Health Topics, and a **WHO HTLV-1 Fact Sheet** detailing specifically HTLV-1 prevention strategies. In addition, we would like to propose that information on HTLV-1 is included and updated on various WHO webpages such as Sexually Transmitted Infections, Blood Transfusion Safety and Breastfeeding.

With this letter, we hope to raise your awareness about several current shortcomings and potential solutions in this field.

Our global community has been slow to respond to the HTLV-1 predicament, a virus transmitted through body fluids, causing significant morbidity and mortality. This is almost certainly due to having to address many other pressing health priorities. However today we are encouraged by the WHO's mandate to value a healthy sexual life and the availability of many WHO fact sheets on other blood borne and sexually transmitted viruses such as Hepatitis B and C and HIV.

HTLV-1 is transmitted through the same routes as HIV-1 through infected body fluids, via condom-less sexual intercourse (1-4), breastfeeding (5-7), sharing of needles (8-11) and the transfusion (12, 13) and transplantation of infected blood and organ donations (14-17).

Recently published prevalence data from Central Australia (where in some communities 45% of adults live with HTLV-1)(18), Japan (19) and Brazil (20, 21) report the importance of HTLV-1's sexual transmission. The sexual transmission of HTLV-1 was also highlighted in several presentations at the 18th International Retrovirology Conference in Tokyo in Japan in March 2017 (Satake, M. et al O-1-5, Morita, M. et al P-A-6, Fuchi, N. et al P-A-12) and at the 2017 Australasian HIV & AIDS and Sexual Health Conference in Canberra in Australia (22).

In 2012 Antoine Gessain and Olivier Cassar (23) published a systematic review of available data on HTLV-1 origin and prevalence, which we are drawing upon to provide you with an overview of the world distribution of HTLV-1. It is well understood that HTLV-1 originated from non-human primates. It is an ancient virus and its prevalence is complex, in that it is highly endemic in some parts of the world, but regrettably available surveillance data is not comprehensive, and in many regions, accounting for 6 billion persons, HTLV-1 prevalence remains unknown.

HTLV-1 has been detected in most parts of Africa. In Gabon, a HTLV-1 sero-prevalence of 5–10% has been observed in adults, 1-5% in pregnant women and in some villages up to 25% of older women are HTLV-1 positive. In Nigeria, an estimated 850,000 to 1.7 million people are infected with this virus. In Central African Republic, HTLV-1 infection has been reported in 7% of older, female Pygmies of Southern region.

In Japan, an estimated 0.8 million people are HTLV-1 positive and in Southern regions 30–40% of adults > 50 years of age and up to 5.8% of pregnant women carry this virus.

In Jamaica, the estimated mean HTLV-1 sero-prevalence is 6.1% (1.7- 17.4%) in the general population (including older persons) and is as high as 2–3.8% among pregnant women and blood donors. Other Caribbean islands that have been studied have similar prevalence rates.

In areas of Brazil, especially in people of African ancestry, HTLV-1 prevalence has been reported in 1.3% in blood donors, 1.8% in the general population and 1.05% in pregnant women with 33% of their family members including children found to be positive.

In Iran, up to 3% of adults are infected in the Mashad area but HTLV-1 is found across the country.

In Romania, the HTLV-1 prevalence has been reported to be 5.3/10,000 among first-time blood donors, and 3-25% in poly-transfused patients.

In non-endemic areas, due to the migration of people and the sexual transmission of the virus, HTLV-1 and 2 have also been detected. In the UK 20,000 - 30,000 people live with the virus, whilst in metropolitan France an estimated 10,000 - 25,000 people are HTLV-1 infected. In the USA, it is estimated that approximately 266,000 individuals are infected with HTLV-1 or -2, and that 3,600 people with HAM/TSP remain undiagnosed.

In a recent hospital-based cohort study in Central Australia, 635/1889 (33.6 %) tested Indigenous people were HTLV-1 positive. Only one of 77 (1.3 %) children tested positive but with age a sharp increase in prevalence rates were observed (15-29 years, 17.3 %; 30-49 years, 36.2 %; 50-64 years, 41.7 %), reaching 48.5 % in men older than 50 years of age (18).

As with most blood borne and sexually transmitted viruses the majority of HTLV-1 positive people transmit the virus unknowingly and are unaware that they are at risk of developing diseases caused by HTLV-1.

HTLV-1 was the 1st infectious agent discovered to be the direct cause of human cancer and is the most carcinogenic of all oncoviruses (24). HTLV-1 causes Adult T Cell Leukemia/Lymphoma (ATL) which depending on subtype, timing of diagnosis and access to treatment, has a median survival of 8 to 10 months despite all the advances in chemotherapy and supportive therapy (25, 26). The lifetime probability of developing ATL is 4-5 in 100 people infected with HTLV-1 (27, 28), and ATL is attributed to the acquisition of the infection in infancy, through breastfeeding. Thus, it is a preventable malignancy and, in our opinion public health efforts to prevent its transmission should be comparable to other preventable cancers. For instance, the WHO's promotion and prevention strategies to reduce smoking related lung cancers are exemplary (WHO Health Topic: Tobacco), though the lifetime risk of developing lung cancer through smoking cigarettes is only 14: 1000 (29).

In addition, HTLV-1 causes chronic, progressing, disabling and painful conditions such as myelopathy and polymyositis as well as chronic inflammatory pulmonary disease, uveitis and dermatitis (30).

The lifetime risk of HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP) approaches 4 in 100 infected people (31-36), with an average of 8 years delay in diagnosis and treatment due to lack of awareness and testing (37). Patients with HAM/TSP suffer from

decades of progressive walking disability, chronic severe back and leg pain, incontinence and urinary retention, severe constipation and sexual dysfunction, all of which lead to social isolation. HAM/TSP affects both adults and children but mostly women, and has been associated with the acquisition of HTLV-1 through organ donation (17) (18th International Retrovirology Conference in Tokyo in Japan in March 2017: Yuzawa K. et al O-5-7).

Despite its distinct etiology and distinctive pattern there is no International Classification of Disease Code (ICD code) for HAM/TSP, an extraordinary state of affairs for a disease described for the first time by Eric Cruickshank in 1956 (38), linked to HTLV-1 in 1985 and for which WHO has had diagnostic criteria since 1989 (39). Patients living with HTLV-1 and/or suffering from HAM/TSP find this omission incredulous. We truly hope that you can help us rectify this serious oversight in order to reduce the under-diagnosis and under-reporting of this disease.

HTLV-1 was discovered 37 years ago (40), just before the AIDS epidemic. It is acknowledged that HTLV-1 research led to the idea that AIDS might be caused by a new retrovirus and therefore greatly abetted the identification of HIV-1. It is disappointing that despite the significance of HTLV-1 research in the fight against AIDS, in comparison to HIV-1, people who are infected with HTLV-1 have received very little attention in form of publicity, development of international clinical guidelines or financial investment into drug development and clinical trials (41).

Worldwide it is mostly women, who carry the burden of HTLV-1 infection and its associated diseases: Women, who become infected through condom-less sex, and their babies, who are infected through breastfeeding. Therefore HTLV-1 is highly concentrated in families [1:3 to 1:4 of family members carry the virus (42, 43)].

In your speech on 3 July 2017 you fearlessly stated that the WHO is fully committed to 'Every Woman Every Child'. You asked for quality, equity and dignity in services for sexual and reproductive health, equal rights and the empowerment of women, girls and communities. Today we are asking you to include families at risk of HTLV-1 in your list of goals to improve global health.

We would like to support the WHO by using published evidence on HTLV-1's prevalence and

mode of transmission together with the established understanding of effective transmission prevention strategies against blood borne and sexually transmitted viruses, to produce a clear and evidence-based **WHO HTLV-1 Fact Sheet**, which would inform WHO web-users world-wide.

A recent review of WHO’s website revealed that the information on HTLV-1 could benefit from an evidence-based update, supported by HTLV-1 experts and patient representatives living with this virus. We need to visibly share the information that about 80% of HTLV-1 infection is transmitted sexually [4000 cases/annum of sexual transmission in Japan alone (19)] with most of the remaining 20% of transmission being attributed to mother to child transmission, predominantly through breastfeeding [up to 32% risk to the infant depending on the duration of breastfeeding (44)]. We would like to see an emphasis on the fact that HTLV-1 is highly transmissible through infected blood and that the risk through organ transplantation may be 100% with 2 out of 3 organ recipients thus infected developing HAM/TSP within 4 years (18th International Retrovirology Conference in Tokyo in Japan in March 2017: Yuzawa K. et al O-5-7).

So far, an astounding 17 different prevention strategies have been identified to reduce the risk the transmission of other blood borne and sexually transmittable viruses, such as Hepatitis B & C and HIV (Table 1) but not for HTLV-1.

Table 1: List of potentially available strategies to prevent the transmission of blood borne and sexually transmitted viruses. There has been a case report of HIV cure through stem cell transplantation but this intervention is risky, carries considerable morbidity and is not a realistic option as a global strategy. Legend: Not available = NA; The intervention is available = ✓; The intervention could be available = (✓); Could be effective but not researched = ?.

	HBV	HTLV	HIV	HCV
Discovered	1965	1980	1983	1989
Vaccine	✓	NA	NA	NA
Test	✓	✓	✓	✓
Routine blood product screening	✓	✓	✓	✓
Routine organ transplant screening	✓	(✓)	✓	✓

Routine antenatal screening	✓	(✓)	✓	✓
Routine sexual health screening	✓	(✓)	✓	(✓)
Treatment or Cure	✓	(✓)	✓	✓
Mother to child transmission prevention	✓	(✓)	✓	(✓)
Partner notification	✓	(✓)	✓	✓
Needle exchange programs	✓	(✓)	✓	✓
Condoms	✓	✓	✓	✓
Strategies for condom-less anal sex	(✓)	?	✓	(✓)
Post-exposure prophylaxis	(✓)	?	✓	?
Pre-exposure prophylaxis	(✓)	?	✓	?? ?
Voluntary medical male circumcision	NA	?	✓	NA?
Testing and treating sexually transmitted infections	✓	✓	✓	✓
Education of medics, patients, population	✓	(✓)	✓	✓
Total number of widely available interventions	12/16	4/12	16/17	10/13

Without a doubt, the availability and level of access to these strategies varies significantly from region to region, but there is a very clear directive from the WHO that they work and should be implemented. Especially in combination, they are so effective that many nations are now planning the eradication of three of these viruses.

There is irrevocable evidence that the transmission of HTLV-1 would be averted by

- using condoms when having sex,
- avoiding the transfusion and transplantation of infected blood and organs,
- advising HTLV-1 antibody positive mothers not to breast-feed their babies (if deemed safe) or reducing duration to 3 – 6 months,
- using sterile needles, and
- by educating healthcare professionals and the population about prevention strategies.

For HTLV-1, some of the aforementioned strategies are implemented inconsistently most probably due to a lack of an international consensus and directive. For example, universal antenatal care (ANC) screening is implemented only in Japan. In Brazil, HTLV-1 ANC screening is recommended in some regions but not necessarily implemented. In the UK, ANC screening is not recommended at all, despite recent evidence that it would be cost effective to identify positive mothers and counsel against breastfeeding and therefore prevent HTLV-1 transmission and ATL disease in their children long-term (18th International Retrovirology Conference in Tokyo in Japan in March 2017: Malik B. et al O-3-2, submitted for publication). If we add to this the prevention of other HTLV-1 diseases the cost effectiveness would be still greater.

In Japan, it is permitted to transplant HTLV-1 positive organs despite recent evidence showing that 63% of recipients of HTLV-1 positive kidneys developed HAM/TSP [(17), 18th International Retrovirology Conference in Tokyo in Japan in March 2017: Yuzawa K. et al O-5-7].

Nowhere that we know of is HTLV-1 part of routine sexually transmitted infection screening or needle exchange programs despite indisputable knowledge of its mode of transmission.

Here we propose the universal HTLV-1 testing of blood and organ donors, and the prevention of HTLV-1 positive blood transfusion and organ transplantations. We offer to support the WHO to develop a **HTLV-1 Fact Sheet** which provides clear advice that HTLV-1 is an oncovirus and can cause severe inflammation. We wish to inform HTLV-1 infected people that they need lifelong clinical and laboratory monitoring (HTLV-1 pro-viral load, lymphocyte count etc.), so that they are diagnosed early when they develop HTLV-1 diseases, so they can access treatment and clinical trials in a timely fashion. We encourage the WHO to support the recommendation that all people living with HTLV-1 are informed, that HTLV-1 is sexually transmitted and that their partners need to be notified and tested. HTLV-1 positive patients need to be informed that HTLV-1 can be transmitted through breastmilk and we need to advise to have their children tested for HTLV-1.

We are pleased to report that even the variable usage of some of these intervention strategies against HTLV-1 have led to a measurable change in the HTLV-1 prevalence profile. In Japan since the introduction of HTLV-1 ANC in 1987 in the Nagasaki region the HTLV-1 prevalence in mothers has reduced from 7.2% to 1% (<http://www.med.nagasaki->

u.ac.jp/gyneclogy/now/now_htlv-1.html). Following the national roll out of ANC screening the mother to child transmission has reduced from 20% to 2.5% in Japan (45). In 2017 Dr Lezin reported a significant reduction in HAM/TSP incidence due to ANC and blood donor screening in the French island of Martinique, in the West Indies (46).

Therefore, we propose a **WHO HTLV-1 Vision** for the prevention of HTLV-1 transmission:

'Let's eradicate HTLV-1 together!' and a **WHO HTLV-1 Mission:**

'Intervention strategies to achieve the eradication of HTLV-1'.

This may be achieved with the implementation of 5 strategies:

Strategy #1 protects the sexually active population:

Routine HTLV-1 testing in sexual health clinics should be available to all attendees. All people diagnosed with HTLV-1 need to be followed up medically and monitored clinically, immunologically and virologically to be able to access treatment promptly. We need to promote **CMPC: Counsel & Monitor** HTLV-1 positive patients, notify **Partners** and promote **Condom** usage. This strategy also supports HTLV-1 positive parents to test their children for HTLV-1.

Strategy #2 protects blood and organ donors and recipients:

We need to test donors and not use products potentially infected with HTLV and make medical follow up and CMPC available to those infected.

Strategy #3 protects mothers, babies and fathers:

We need routine antenatal care testing and advise against breastfeeding by mothers who are HTLV-1 positive where safe, alternative methods of infant feeding are available.

Alongside we need to promote CMPC.

Strategy #4 protects people who inject drugs:

We need to promote HTLV-1 testing and provide free safe needles through needle exchange programmes together with CMPC promotion.

Strategy #5 supports the population and health care providers:

Access to up-to-date and evidence-based **WHO HTLV-1 Fact Sheet** and its diseases will allow health care providers to diagnose HTLV-1 and its diseases more often and in a timely fashion. Informed people are more likely to protect themselves and ask for a HTLV-1 test.

Words are important. We need to change the way we talk about HTLV-1 to increase its visibility and are guided by the beautiful language used for the USA National HIV/AIDS Strategy:

Vision: International HTLV Strategy

“Our world will become a place where new HTLV infections are very rare and when they do occur, every person, regardless of age, gender, race/ethnicity, sexual orientation, gender identity or socio-economic circumstance, will have unfettered access to high quality, life-extending care, free from stigma and discrimination.”

Thank you for considering our point of view and we are looking forward to hearing from you and to support your efforts to increase the visibility of people living with HTLV-1.

Yours sincerely,



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References

1. Kajiyama W, Kashiwagi S, Ikematsu H, et al. Intra-familial transmission of adult T leukaemia virus. *J Infect Dis.* 1986;154:851-7.
2. Murphy EL, Figueroa JP, Gibbs WN, Brathwaite A, Holding-Cobham M, Waters D, et al. Sexual transmission of human T-lymphotropic virus type I (HTLV-I). *Ann Intern Med.* 1989;111(7):555-60.
3. Roucoux D, Wang B, Smith D. A prospective study of sexual transmission of human T lymphotropic virus (HTLV)-I and HTLV-II. *Journal Infectious Diseases.* 2005;191(9):1490-7.
4. Stuver SO, Tachibana N, Okayama A, Shioiri S, Tsunetoshi Y, Tsuda K, et al. Heterosexual transmission of human T cell leukemia/lymphoma virus type I among married couples in southwestern Japan: an initial report from the Miyazaki Cohort Study. *J Infect Dis.* 1993;167(1):57-65.
5. Kinoshita K, Hino S, Amagaski T, Ikeda S, Yamada Y, Suzuyama J, et al. Demonstration of adult T-cell leukemia virus antigen in milk from three seropositive mothers. *Gan.* 1984;75(2):103-5.
6. Hino S, Sugiyama H, Doi H, Ishimaru T, Yamabe T, Tsuji Y, et al. Breaking the cycle of HTLV-I transmission via carrier mothers' milk. *Lancet.* 1987;158-9.
7. Percher F, Jeannin P, Martin-Latil S, Gessain A, Afonso PV, Vidy-Roche A, et al. Mother-to-Child Transmission of HTLV-1 Epidemiological Aspects, Mechanisms and Determinants of Mother-to-Child Transmission. *Viruses.* 2016;8(2).
8. Dourado I, Andrade T, Galvao-Castro B. HTLV-I in Northeast Brazil: differences for male and female injecting drug users. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998;19(4):426-9.
9. Andersson S, Ahmed R, Bredberg-Raden, Albert J, Krook A, Kall K, et al. HTLV-II infected Swedish intravenous drug users carry subtype A. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1999;10:280.
10. Andrade TM, Dourado I, Galvao-Castro B. Associations among HTLV-I, HTLV-II, and HIV in injecting drug users in Salvador, Brazil. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998;18(2):186-7.
11. Caterino-de-Araujo A, Sacchi CT, Goncalves MG, Campos KR, Magri MC, Alencar WK, et al. Short Communication: Current Prevalence and Risk Factors Associated with Human T Lymphotropic Virus Type 1 and Human T Lymphotropic Virus Type 2 Infections Among HIV/AIDS Patients in Sao Paulo, Brazil. *AIDS Res Hum Retroviruses.* 2015;31(5):543-9.
12. Okochi K, Sato H, Hinuma Y. A retrospective study on transmission of adult T-cell leukaemia virus by blood transfusion: seroconversion in recipients. *Vox Sang.* 1984;46(5):245-53.
13. Okochi K, Sato H. Transmission of Adult T-Cell Leukemia-Virus (Htlv-I) Through Blood-Transfusion and Its Prevention. *Aids Research.* 1986;2:S157-S61.
14. Cook LB, Melamed A, Demontis MA, Laydon DJ, Fox JM, Tosswill JH, et al. Rapid dissemination of human T-lymphotropic virus type 1 during primary infection in transplant recipients. *Retrovirology.* 2016;13(1):3.

15. Montesdeoca Andrade MJ, Correa Diaz EP, Buestan ME. HTLV-1-associated myelopathy in a solid organ transplant recipient. *BMJ Case Rep.* 2016;2016.
16. Ramanan P, Deziel PJ, Norby SM, Yao JD, Garza I, Razonable RR. Donor-transmitted HTLV-1-associated myelopathy in a kidney transplant recipient--case report and literature review. *Am J Transplant.* 2014;14(10):2417-21.
17. Tajima Y, Matsumura M, Yaguchi H, Mito Y. Two Cases of Human T-Lymphotropic Virus Type I-Associated Myelopathy/Tropical Spastic Paraparesis Caused by Living-Donor Renal Transplantation. *Case Rep Neurol Med.* 2016;2016:4203079.
18. Einsiedel L, Woodman RJ, Flynn M, Wilson K, Cassar O, Gessain A. Human T-Lymphotropic Virus type 1 infection in an Indigenous Australian population: epidemiological insights from a hospital-based cohort study. *BMC public health.* 2016;16:787.
19. Satake M, Iwanaga M, Sagara Y, Watanabe T, Okuma K, Hamaguchi I. Incidence of human T-lymphotropic virus 1 infection in adolescent and adult blood donors in Japan: a nationwide retrospective cohort analysis. *Lancet Infect Dis.* 2016;16(11):1246-54.
20. Nunes D, Boa-Sorte N, Grassi MF, 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.
21. Paiva A, Smid J, Haziot MEJ, Assone T, Pinheiro S, Fonseca LAM, et al. High risk of heterosexual transmission of human T-cell lymphotropic virus type 1 infection in Brazil. *J Med Virol.* 2017;89(7):1287-94.
22. Einsiedel L, Purcell D, Schinke S, Haynes K, Taylor GP, Martin F. Highlights from the HTLV-1 symposium at the 2017 Australasian HIV and AIDS Conference held jointly with the 2017 Australasian Sexual Health Conference, November 2017, Canberra, Australia. *J Virus Erad.* 2018;4(1):48-50.
23. Gessain A, Cassar O. Epidemiological Aspects and World Distribution of HTLV-1 Infection. *Front Microbiol.* 2012;3:388.
24. Tagaya Y, Gallo RC. The Exceptional Oncogenicity of HTLV-1. *Front Microbiol.* 2017;8:1425.
25. Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). *Br J Haematol.* 1991;79(3):428-37.
26. Katsuya H, Ishitsuka K, Utsunomiya A, Hanada S, Eto T, Moriuchi Y, et al. Treatment and survival among 1594 patients with ATL. *Blood.* 2015;126(24):2570-7.
27. Murphy E, Hanchard B, Figueroa JP, Gibbs WN, Lofters WS, Campbell M, et al. Modelling the risk of adult T-cell leukaemia/lymphoma in persons infected with human T-lymphotropic virus type I. *Int J Cancer.* 1989;43:250-3.
28. Tajima K. The 4th nation-wide study of adult T-cell leukemia/lymphoma (ATL) in Japan: estimates of risk of ATL and its geographical and clinical features. The T- and B-cell Malignancy Study Group. *Int J Cancer.* 1990;45(2):237-43.
29. Villeneuve PJ, Mao Y. Lifetime probability of developing lung cancer, by smoking status, Canada. *Can J Public Health.* 1994;85(6):385-8.
30. Martin F, Taylor GP, Jacobson S. Inflammatory manifestations of HTLV-1 and their therapeutic options. *Expert Rev Clin Immunol.* 2014;10(11):1531-46.

31. Araujo AQ, Andrade-Filho AS, Castro-Costa CM, Menna-Barreto M, Almeida SM. HTLV-I-associated myelopathy/tropical spastic paraparesis in Brazil: a nationwide survey. HAM/TSP Brazilian Study Group. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998;19(5):536-41.
32. Taylor GP, Tosswill JH, Matutes E, Daenke S, Hall S, Bain BJ, et al. Prospective study of HTLV-I infection in an initially asymptomatic cohort. *J Acquir Immune Defic Syndr.* 1999;22(1):92-100.
33. Murphy EL, Wilks R, Morgan OS, Hanchard B, Cranston B, Figueroa JP, et al. Health effects of human T-lymphotropic virus type I (HTLV-I) in a Jamaican cohort. *Int J Epidemiol.* 1996;25(5):1090-7.
34. Maloney EM, Cleghorn FR, Morgan OS, Rodgers-Johnson P, Cranston B, Jack N, et al. Incidence of HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) in Jamaica and Trinidad. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998;17(2):167-70.
35. 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.
36. Orland JR, Engstrom J, Fridey J, Sacher RA, Smith JW, Nass C, et al. Prevalence and clinical features of HTLV neurologic disease in the HTLV Outcomes Study. *Neurology.* 2003;61(11):1588-94.
37. Martin F, Fedina A, Youshya S, Taylor GP. A 15-year prospective longitudinal study of disease progression in patients with HTLV-1 associated myelopathy in the UK. *J Neurol Neurosurg Psychiatry.* 2010;81(12):1336-40.
38. Cruikshank E. A neuropathic syndrome of uncertain origin: review of 100 cases. *West Indian Medical Journal.* 1956;5:147-58.
39. Organisation WH. WHO diagnostic guidelines of HAM. *Weekly Epidemiological Record.* 1989;49:382-3.
40. Poiesz BJ, Ruscette FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured cells of a patient with cutaneous T-cell lymphoma. *Proc Natl Acad Sci USA.* 1980;77:7415-9.
41. Zihlmann KF, de Alvarenga AT, Casseb J. Living invisible: HTLV-1-infected persons and the lack of care in public health. *PLoS neglected tropical diseases.* 2012;6(6):e1705.
42. Alvarez C, Gotuzzo E, Vandamme AM, Verdonck K. Family Aggregation of Human T-Lymphotropic Virus 1-Associated Diseases: A Systematic Review. *Front Microbiol.* 2016;7:1674.
43. Bandeira LM, Uehara SNO, Puga MAM, Rezende GR, Vicente ACP, Domingos JA, et al. HTLV-1 intrafamilial transmission among Japanese immigrants in Brazil. *J Med Virol.* 2017.
44. Wiktor SZ, Pate EJ, Rosenberg PS, Barnett M, Palmer P, Medeiros D, et al. Mother-to-child transmission of human T-cell lymphotropic virus type I associated with prolonged breast-feeding. *J Hum Virol.* 1997;1(1):37-44.
45. Hino S. Establishment of the milk-borne transmission as a key factor for the peculiar endemicity of human T-lymphotropic virus type 1 (HTLV-1): the ATL Prevention Program Nagasaki. *Proc Jpn Acad Ser B Phys Biol Sci.* 2011;87(4):152-66.

46. Olindo S, Jeannin S, Saint-Vil M, Signate A, Edimonana-Kaptue M, Joux J, et al. Temporal trends in Human T-Lymphotropic virus 1 (HTLV-1) associated myelopathy/tropical spastic paraparesis (HAM/TSP) incidence in Martinique over 25 years (1986-2010). PLoS neglected tropical diseases. 2018;12(3):e0006304.