

# Human T-Lymphotropic Viruses Evolution Possibly Explained by Primate Deltaretrovirus Geographical Segregation

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**Abstract:** The primate T cell lymphotropic virus group comprises pathogenic and apathogenic agents found in human and simian hosts. Up to date, three types of the simian T cell lymphotropic virus/STLV and four types of the human T cell lymphotropic virus/HTLV have been isolated and characterized from non human primates and from human hosts respectively. We have not found evidences of STLV-1 infection among new world monkeys and besides findings of HTLV-1 and HTLV-2 infection among brazilian mixed ethnic populations and Amerindians respectively, some unresolved HTLV indeterminate-Western blot results prevailed among human groups of different ethnic background. Based on recent serologic detection, isolation and characterization of HTLV-3 and HTLV-4 among African populations in central Africa and additional unrefutable evidences of early human migration from Africa and Australia to the American continent previously of Asiatic population migration lead us to hypothesize that human descendents of mixed Amerinds and Africans or remaining Africans explain the very frequent presence of Western blot-indeterminate results for HTLV-1/2 that we and other groups have been detecting and also the unusual absence of HTLV-2 infection among some relatively homogeneous ethnic native human populations in the American continent.

**Keywords:** deltaretrovirus, human T cell lymphotropic virus, simian T cell lymphotropic virus, amerindians, human migration

## Introduction

Recently Kanzaki and Casseb [1] described the unusual finding of HTLV-1 infection among Waiãpi Amazonian Amerindians. Also, among certain ethnic ancient groups, in the American Continent, it is very low the prevalence of both, HTLV-1 and HTLV-2 infection [2–5]. Colin et al. [6] found a very low prevalence to HTLV-1/2 infection in a human population in the Occidental Amazon (Acre/Brazil) despite other works showing high prevalence to HTLV-2 among Amerindian groups mainly in South America [1]. Besides these findings, not so common among Amerindians, we and others have also found frequently HTLV-1/2 seroreactors by the Enzyme-linked immunosorbent assay /Immunofluorescence (ELISA/IF) unconfirmed by the Western blot analysis, but exhibiting isolated bands to one peptide or glycopeptide apparently related to deltaretroviruses [1,7,8]. In the beginning of the pioneering HTLV epidemiological studies in Brazil, we suspected that the high incidence of HTLV-2 among some Amerindian ethnicities were related to a deltaretrovirus circulating among new world monkeys; therefore in order to corroborate this hypothesis we screened amazonian monkeys (58 *Cebus paella*, 5 *Cebus albifrons*, 5 *Cebus nigrivittatus*, 6 *Callicebus moloch*, 13 *Callithrix jacchus jacchus*, 1 *Callithrix argentata argentata*, 34 *Aotus agarae infulatus*, 2 *Alouata belzebu belzebu* and 10 *Chiropotes satanas utahicki*) for HTLV-1/2/STLV-1 antibodies by the ELISA test and found none reactive but we had 6 out of 24 african old world monkeys, *Cercopithecus aethiops*, highly reactive by the ELISA assay [7]. Other authors also could not find HTLV-1/STLV-1 antibodies among new world monkeys [9,10] and confirming that new world monkeys are not susceptible to HTLV-1 infection, new world squirrel monkeys (*Saimiri sciureus*) were experimentally infected by HTLV-1 infected cells as apparently these animals did not share cell receptors for the virus [11]. Despite Chen et al. [12] claims of STLV-2 isolation from *Ateles fusciceps*, a new world monkey in Panama, nobody else could demonstrate antibodies among new world monkeys neither isolate the virus again. Most of these HTLV-1 strains are serologically indistinguishable from

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STLV-1 strains, as their viral genomes exhibit about 96% nucleotide homology which allow us to easily detect STLV-1 antibodies utilizing serologic assays sensitized with HTLV-1 peptides [13]. Presently, it is assumed that the deltaretroviruses evolution occurred in Africa and very probably after the branching of new and old world monkeys' ancestors [13,14].

According to different authors, during the Pleistocene/Holocene transition period, at least two different human populations migrated to the American Continent. Cranial anatomic analysis recognized two peculiar human morphologic patterns related to Asiatics and Africans, so contrary to the common sense, one of these groups, the Asiatics were not the first human groups to migrate to the America continent, but the African group, probably coming from Oceania and/or Africa. Confirming these findings, Neves et al. [15] emphasizes that the colonization of the New World occurred by two distinct, succeeding biological populations: an early one with a cranial morphology similar to that found today in the African and Australian continents, and a later one with a morphology similar to that found today among northeastern Asians.

Neves et al. [16] also have been finding increasing skeletal evidences from U.S.A., Mexico, Colombia, and Brazil strongly suggesting that the first settlers in the Americas had a cranial morphology distinct from that displayed by most late and modern native Americans.

Based on these research results and our unusual findings of HTLV-1 infection among Amazonian amerinds, and indeterminate-Western blot profiles, we hypothesized that early human populations, the Australo-Melanesians and Africans that colonized the American continent 12.000–35.000 years in the past, previously to the migration of asian populations, by some way were not susceptible to HTLV-1 and 2 infection, and probably were mainly infected by other human deltaretroviruses.

## The Primate T cell Lymphotropic Viruses

The Human T cell Lymphotropic Viruses are exogenous deltaretroviruses comprising four types, HTLV-1 to HTLV-4 [17–20]. The HTLVs and the Simian T Lymphotropic Viruses (STLVs) altogether are commonly denominated the Primate T Lymphotropic Viruses (PTLVs) due to their high

nucleotide homology besides their common general genomic organization [21–23]. They were numbered according to their discoveries, not denoting the hierarchic filogenetic positioning. Epidemiological and molecular studies point out to Africa as the motherland of these biological entities, which spread out to Asia, Europe and Oceania accompanying their hosts in their migrations [22,23].

## Human Deltaretroviruses Evolution and Human Disease

As the deltaretroviruses are closely associated to the cell, their transmission mode are generally enclosed in familiar clusters, being transmitted by sexual intercourse, usually from man to woman and during breast-feeding, from mother to lactating children [24,25]. Their low mutation rate also confer them the maintenance of low pathogenicity behavior or depending on the type, their apathogenic role, therefore they are very successfully horizontally transmitted throughout generations [26,27]. Nevertheless, the human cultural development accompanied by population growth which consequently moved huge mass of people to more developed towns adding high levels of demographic density imposing exaggerated levels of stress and besides these factors, the advances in preventive and curative medicine have selected all kind of microorganisms by the survival of their human hosts. Also, climatic changes with elevated exposition to different wave length radiations, mainly ionizing radiation, have played an important role in the mutation rate of all kind of genetic elements in acellular and cellular organisms [28]. Henceforth, taking in account all the facts mentioned, evolution has been in fast course and ultimately it seems to be in a rush at least in our knowledge of the modern civilization, in a way that apathogenic deltaretroviruses have been claimed to be involved in a large spectrum of diseases [29]. Comparing the human and deltaretrovirus genome from different time points, we can assume that the virus in a general way did not change at all, but human populations became much more vulnerable now than in the past to different microorganisms. Different vaccines, a lot of new chemical drugs and modern curative measures have been selecting less adapted human beings, so in these subjects the immune system does not respond appropriately, and an example of it are the

autoimmune diseases associated to HTLV-1 infection among human beings [29–32].

## Primate Deltaretroviruses Geographical Segregation

The emergence of STLVs after the evolutionary splitting of non human primates into new world and old world species avoided the spreading of STLVs to the American continent [22,23]. Several seroepidemiological studies in primate centres in the American continent could not find STLV-1 infection among new world monkeys.

It is interesting to note the distribution and segregation of HTLV-1 and HTLV-2 in cosmopolitan megalopolis and small towns in rural areas respectively, around the world [1,2,8,33]. Among Amerindian communities, HTLV-2 infection is widely spread out while HTLV-1 infection is mainly found among communities of African and Japanese origin, even though the intense human miscegenation in countries like Brazil, contributes to equal distribution of both HTLV types in human population as also, in the U.S. the epidemic HTLV-2 transmission among intravenous drug users changed the usual distribution pattern of human deltaretroviruses among different human ethnicities [8,33,34]. Examining HTLV-1 distribution in the world, historical facts try to explain the virus dissemination carried by their African hosts, in Portuguese commercial ships navigating to India and Japan, and lately in the slave trade period to the American continent and Caribbean basin. High levels of HTLV-1 prevalence is found in the Caribbean basin and Brazil among afrodescendants [35]. In Japan, the high HTLV-1 prevalence is not well understood as initially proposed by Africans transportation in Portuguese trade ships in Japan [36]. Noteworthy to mention that STLV-1 is endemic among protected simians, *Macaca fuscata*, in Japanese sanctuary mountains. Also, HTLV-1 is more related to the African strain of STLV-1 than to the Japanese strain. Would be the origin of HTLV-1 high incidence in Japanese human populations explained by STLV-1 natural human infection transmitted from *Macaca fuscata*? [37] Or by very ancient invasion of Japan archipelago by paleo-Mongoloids human lineages more than 10.000 years ago? [38]. By analogy to what is believed about SIV transmission from chimpanzees to man and SIV mutation/adaptation to human target cells, generating HIV-1/2, which demanded

a large step, while in the case of a possible transmission of STLV-1 from simians to man, would be a short step as both viruses, STLV-1 and HTLV-1 share about 96% nucleotide homology.

Particularly in Brazil, HTLV-1 prevalence is widespread, but mainly concentrates among black communities that arrived in Brazil during the slave trade period, contrasting to HTLV-2 prevalence which is high among Amerindian communities and intravenous drug users [39]. Despite this common sense, some exceptions occur, as the finding of HTLV-1 low prevalence among some Amerindian communities and any known reactivity to HTLV-2 peptides [1]. Reviewing the literature, it seems that not only Amerindians colonized the American continent, but other ethnic groups have arrived earlier in the new world. The most antique of these human groups were Australo-Melanesians African descendents. Despite remnants findings of these human groups spread out all over the continent, mainly abundant in Brazil, there seems actually to be vanished, nevertheless it is believed that few of them mixed to some other populations. Apparently the arrival of Asians to the continent through the Behring strait and the total occupation from north to south, must have annihilated the first human settlers in the American continent and as a common practice, very probably women and children became prisoners and mixed to the conquerors [15,16].

## HTLV-1 and HTLV-2 Differences

When we look at the distribution of deltaretroviruses among human populations, it apparently means that ethnic pattern would determine which HTLV type would be housed by the host [35,36]. As previously mentioned, HTLV-2 is mainly disseminated among native Americans of asian origin, from North to South America [33,34,36,37,38] but curiously, some of these Amerindians groups exhibit low levels of HTLV-2 infection or do not express the virus at all in their cells [1,6]. How close are different human ethnic groups? Are genetic or cultural factors or both involved in more or less susceptibility to HTLVs infection? [34–36] Are these differences related to the levels of HTLV-1 or 2 infection susceptibility? [37,38]. Are so polymorphic the cell receptors for these viruses? [39] Anyway, why HTLV-1 is not reported to be well disseminated among intravenous drug users as it happens with HTLV-2? Would be their different biological behavior? It is very rare to

observe clinical diseases related to HTLV-2 infection, but the frequency of HTLV-1 related disease occurrence is higher compared to HTLV-2. Genomic organization of both viruses are similar, but their cell targets are different [40,41]. While HTLV-1 preferentially infects CD4<sup>+</sup> cells, HTLV-2 exhibits CD8<sup>+</sup> tropism. As it is well known, CD4<sup>+</sup> cells are functionally more important than CD8<sup>+</sup> cells, which mainly exerts a final effector function as a cytotoxic cell. [42,43].

## Hypotheses

In all seroepidemiological surveys we have conducted among Amerindian communities and mixed ethnic populations, there is a high frequency of indeterminate Western blot results [1,7]. Reviewing the literature, recently, two new HTLV types were identified in Africa, HTLV-3 and HTLV-4, and curiously, in serological assays screening for HTLV-1 and 2 antibodies, people infected by HTLV-3 or 4, displayed Western blot isolated bands similarly to indeterminate results as we have found among our samples [17–19]. Future studies would corroborate these assumptions and would reinforce our hypothesis of vestiges of Australo-Melanesians and africans among our isolated native communities, explaining therefore the unusual absence of HTLV-2 infection among some Amerindian communities, interfered by HTLV-3/4 infection.

## Conclusion

Unusual finding of HTLV-1 infection among some Amerindian communities and in some cases, the absence of HTLV-2 infection among some other Amerindian communities besides the frequency of indeterminate-Western blot bands to HTLV-1 and 2 antibodies, strongly suggest the circulation of other deltaretroviruses among Amerindians and mixed ethnic populations in the American continent. Also, we have associated this hypothesis to the recent theory of earlier Australo-Melanesians and African descendents migrations to the American continent, carrying with them HTLV-3 and 4. Very probably remnants of these populations or the dominance of their HLA alleles in the mixed descendents could be responsible for immune response to HTLV-3/4 yielding interference to HTLV-1/2 infection (44–48). As previously discussed, HTLV-1/2 transmission in nuclear families would determine viral antigens immune

tolerance as earlier proposed by Medawar (1983), mainly among newborn [49], but later, 40 or 50 years, a small percentage of these infected subjects would develop an HTLV-1 related disease, as tolerance would break up, favored by the immune system aging associated to a number of environmental factors exposure.

Our preliminary studies corroborated by others could not support the initial hypothesis in the early epidemiological studies in Brazil of a possible transmission of a deltaretrovirus from new world monkeys to native Amazonians. Until now, any known deltaretrovirus has not yet been isolated from new world monkeys.

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## Disclosure

The authors report no conflicts of interest.

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