**Open Access Library Journal**
2021, Volume 8, e7281
ISSN Online: 2333-9721
ISSN Print: 2333-9705

# Human Leukemia Virus HTLV: An Overview

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**How to cite this paper:** Vicento, B.D. and Kamangu, E.N. (2021) Human Leukemia Virus HTLV: An Overview. *Open Access Library Journal*, **8**: e7281.
https://doi.org/10.4236/oalib.1107281

**Received:** July 22, 2021
**Accepted:** August 13, 2021
**Published:** August 16, 2021





## Abstract

The human leukemia virus HTLV-1 is caused by an oncogenic retrovirus responsible for adult T cell leucemia associated with tropical myelopathy/paraparesis. The mode of transmission of the HTLV-1 virus from one individual to another occurs by following three routes namely: vertical *i.e.* from mother to child by breastfeeding, sexually and intravenously on contact with blood-contaminated objects. In Africa, the disease remains little known and is endemic in the tropical region of Africa. This review presents the origin of the virus, the molecular aspects as well as the molecules involved in the penetration of the virus into the host cell, the genomic structure. Whatever epidemiological and prevalence data from certain studies carried out in Africa on the human leukemia virus are included in this work.

## Subject Areas

Public Health

## Keywords

HTLV-1/HTLV-2, Molecular Epidemiology, Seroprevalence, Africa, World

## 1. Introduction

Human T-cell leukemia virus type 1 (HTLV-1), identified as the first human oncogenic retrovirus 30 years ago, is not a ubiquitous virus. HTLV-1 is found worldwide, with highly endemic clusters often located near areas where the virus is almost absent. The main regions highly endemic for HTLV-1 are the southwestern part of Japan, Sub-Saharan Africa and South America, the Caribbean region and foci in the Middle East and Australo-Melanesia. The origin of this surprising geographical or rather ethnic distribution is probably linked to a founding effect in certain groups with the persistence of a high rate of viral transmission. Despite different socio-economic and cultural backgrounds, the prevalence

of HTLV-1 gradually increases with age, especially among women in all highly endemic areas [1]. The first human retrovirus discovered, the human lymphotropic type 1 virus (HTLV-1), is the etiologic agent of several pathologies, mainly a very severe T cell lymphoproliferation called adult T cell lymphoma (ATLL) and chronic disabling neuromyelopathy, myelopathy associated with tropical spastic paraparesis/HTLV-1 (TSP/HAM) [2] [3] [4] [5].

HTLV-1 is not distributed all over the world. Indeed, it is mainly present in homes where the viral prevalence can reach 2% to 40% in adults, depending on age, sex and geography. It is the human oncoretrovirus which is thought to infect at least 5 to 10 million people worldwide [1] [6]. While the vast majority of people infected with HTLV-1 remain asymptomatic throughout their lives, ATLL and TSP/HAM infections occur in 2% - 7% of them [7]. The three main routes of transmission of HTLV-1 are mother to child through prolonged breastfeeding (usually more than 6 months) [8], sexually (mainly from male to female) [9] and by blood products contaminated with infected cells [10].

HTLV-1 is derived from its simian counterpart STLV-1, which is widely distributed in several species of non-human primates (NHP). Sub-Saharan Africa is considered the largest endemic area for HTLV-1, accounting for at least half of those infected worldwide (2.5 to 5 million). However, the status of HTLV-1 in Africa is not well known. Indeed, the majority of previous studies have been conducted either on very specific populations such as pregnant women, blood donors or series of hospitalized patients, or on heterogeneous groups and relatively small rural or urban inhabitants of a city or town or region. All of these groups are far from representative of the population of a particular region or country. Additionally, many of these prevalence studies only include serologic analyzes, without molecular detection of the proviral DNA of HTLV-1. Finally, there are still few epidemiological studies on the risk factors for acquiring HTLV-1 on the African continent [1] [11].

## 2. History of HTLV-1 and Origin STLV-1

The HTLV-1 virus, the first exogenous oncoretrovirus discovered in humans, was isolated in the United States, in the laboratory of R. Gallo in 1980 from a culture of CD4 + T cells. These cells were obtained from the peripheral blood of a patient with T hematoderma, initially considered to be cutaneous T lymphoma with a leukemic phase [12]. Independently, an identical virus was isolated in Japan a few months later in a T cell line established from the blood of a patient with adult T leukemia/lymphoma (ATLL) [13]. This malignant T lymphoproliferation associated with HTLV-1 had been clinically described as early as 1977, in southern Japan, by Takatsuki's team. The Japanese virus was first called ATLV, then it was quickly established that ATLV and HTLV-1 corresponded to only one and the same retrovirus, and the name HTLV-1 was retained. In 1985, infection with this virus was associated in Martinique with a chronic neuromyelopathy, called tropical spastic paraparesis (TSP) [14]. In 1986, a Japanese team reported the ex-

istence of a similar disease also associated with this retrovirus which was called HTLV-1, associated myelopathy (HAM). This chronic myelopathy is currently called TSP/HAM. Another human retrovirus, different from the HTLV-1 virus, is called HTLV-2, was isolated in 1982, again in the laboratory of R. Gallo, from a culture of spleen cells from a patient with malignant hemopathy initially considered to be a variant form of "hairy cell T leukemia" [15]. Further isolates of HTLV-2 were subsequently obtained from intravenous drug addicts, Native Americans living in different parts of the Americas and, more recently, from Central African Pygmies [16] [17] [18]. These inter-species transmission events have occurred in Africa until recently [19] [20]. In 2005, Wolfe ND [21] and Calattini S, [22] reported the discovery of the third and fourth types of HTLV (HTLV types 3 and 4) in asymptomatic Cameroonian hunters. Some studies had revealed Western blot profiles compatible with HTLV-1 and HTLV-2 in these individuals suggesting an appreciable cross-reaction between these viruses [23] [24]. Isolated as early as 1982 in Japan, this simian retrovirus is highly endemic in many species of Old World monkeys [25]. In contrast, New World monkeys and prosimians do not appear to be infected with these viruses. While to date around ten cases of leukemia or T lymphoma similar to ATLLs (with in particular clonal integration of STLV-1 provirus into tumor cells) have been described in monkeys infected with STLV-1 (gorilla, macaque, African green monkey, etc.), no case of neuromyelopathy similar to TSP/HAM has been reported in infected monkeys [26]. Almost all of the monkeys infected with STLV-1 show a serological profile in Western blot very close to, if not similar to that observed in humans infected with HTLV-1. There are only a few exceptions, usually corresponding to widely divergent strains of STLV-1 [27] [28]. The hypothesis of STLV-1 transmissions from monkeys to humans was mainly based on the discovery of a quasi-sequence identity (97/98%) between the sequence of the gp21 envelope protein of chimpanzee STLV-1 and that of HTLV-1, subtype B, present in inhabitants of Zaire. Subsequently, several studies have reinforced the idea of the origin of some HTLV-1, especially subtype B and D, from STLV-1 transmissions, originating from chimpanzees and mandrills respectively. The simian equivalents of HTLV-1 subtypes B, D and probably F therefore seem to have been found [21] [29] [30] [31]. On the other hand, in Africa, many monkeys are kept in captivity as pets and can sometimes be the cause of wounds and bites [32] [33]. The identification of closely related retroviruses (simian immunodeficiency virus SIV and simian lymphotropic T virus STLV) in non-human primates (NHPs), particularly in West and Central Africa, strongly indicates a simian origin for types of HIV and HTLV. Five had been bitten by gorillas and had been infected with strains of subtype B; However, a 12-year-old girl severely bitten by a *Cercopithecus nictitans* was infected with a strain of subtype D closely related to the simian T lymphotropic virus (STLV-1) which infects this species of monkey. His mother was infected with a strain of subtype B. These data confirm that hunters in Africa can be infected with HTLV-1, closely related to strains

circulating in local NHP-based game. Our results strongly suggest that a severe bite represents a risk factor for the acquisition of STLV-1. Recently, two new divergent STLVs were discovered in nonhuman African primates. STLV-L PH969, distantly related to HTLV-1/STLV-1 and HTLV-2, was isolated from a wild hamadryas baboon captured in Eritrea and is considered to be a third type of T-cell lymphotropic virus primate (PTLV) [34] [35]. Another new STLV has been isolated from wild-caught bonobos (pygmy chimpanzees) born in the colony, which are only found in the wild in the Democratic Republic of the Congo, formerly Zaire [36] [37]. Although distinct, this bonobo virus is more closely related to HTLV-2 than to HTLV-1 and may be referred to as STLV-2 [38] [39] [40]. The recent discovery of endemic HTLV-2 infections in isolated Pygmy populations [41] [42] [43] [44] [45] and the identification of a simian virus closely related to HTLV-2 in bonobos indicate that the HTLV-2 appears to have its origin in Africa. Molecular characterization of an HTLV-2b isolate from a Cameroonian pygmy [42] confirms the ancient African origin of HTLV-2, but also raises questions about the extremely close phylogenetic relationship with Native American strains of HTLV-2b [46].

## 3. Virus Structure

HTLV is a member of the delta retrovirus family. These viruses are complex retroviruses which express regulatory and accessory genes, in addition to the structural and enzymatic genes common to all retroviruses. The proviral genomes of HTLV-1 and HTLV-2 are shown in **Figure 1(b)**. Both genomes are approximately 9 kb in length and have terminal repeats of 5' and 3' long (LTR), which are direct repeats. generated during the reverse transcription process. The 5' parts of both genomes encode structural and enzymatic gene products (***Gag***, ***Pol***, ***Pro*** and ***Env***). Regulatory and accessory genes are expressed from the region historically called "***pX***" of the genome. The ***pX*** region is located 3' of the env structural gene. The two HTLVs encode an antisense gene, ***HBZ*** for HTLV-1 and ***APH***-2 for HTLV-2, located on the negative or negative strand of the proviral genome. After integration of the proviral genome, several different HTLV transcripts will be produced (**Figure 1(a)**, **Figure 1(b)** show a summary of these transcripts). Both viruses use the viral regulatory protein Tax and the viral promoter located in the 5' LTR to direct transcription of the viral gene. The viral ***Rex*** protein ensures the export of unspliced viral mRNAs. The full-length, unspliced viral mRNA serves as the viral genome for future virions and also as a source of ***Gag***, ***Pol*** and ***Pro*** proteins. Several mRNAs of different splice variants are also expressed to generate ***env***, regulatory proteins and accessory proteins. Expression of HTLV antisense genes is not regulated by the ***Tax*** or ***Rex*** proteins, but rather depends on host cellular factors to promote transcription. The next sections will cover the different proteins expressed by HTLV-1 and HTLV-2 [47]. The whole is surrounded by the capsid (***CA*** or ***p24***) within which are also the reverse transcriptase, integrase and protease. The matrix (**MA** or ***p19***) pro-

tects the whole. This structure is, finally, covered by the envelope consisting of a lipid bilayer of cellular origin which contains the viral glycoproteins (***gp*46** and ***gp*21**) resulting from the cleavage of a common precursor [48]. The ***gp*46** and ***gp*21** proteins are encoded by the viral ***env*** gene. The ***gp*46** and ***gp*21** proteins are encoded by the viral ***env*** gene. It is the ***gp*46** protein that binds and then enters the virus into target cells [49].

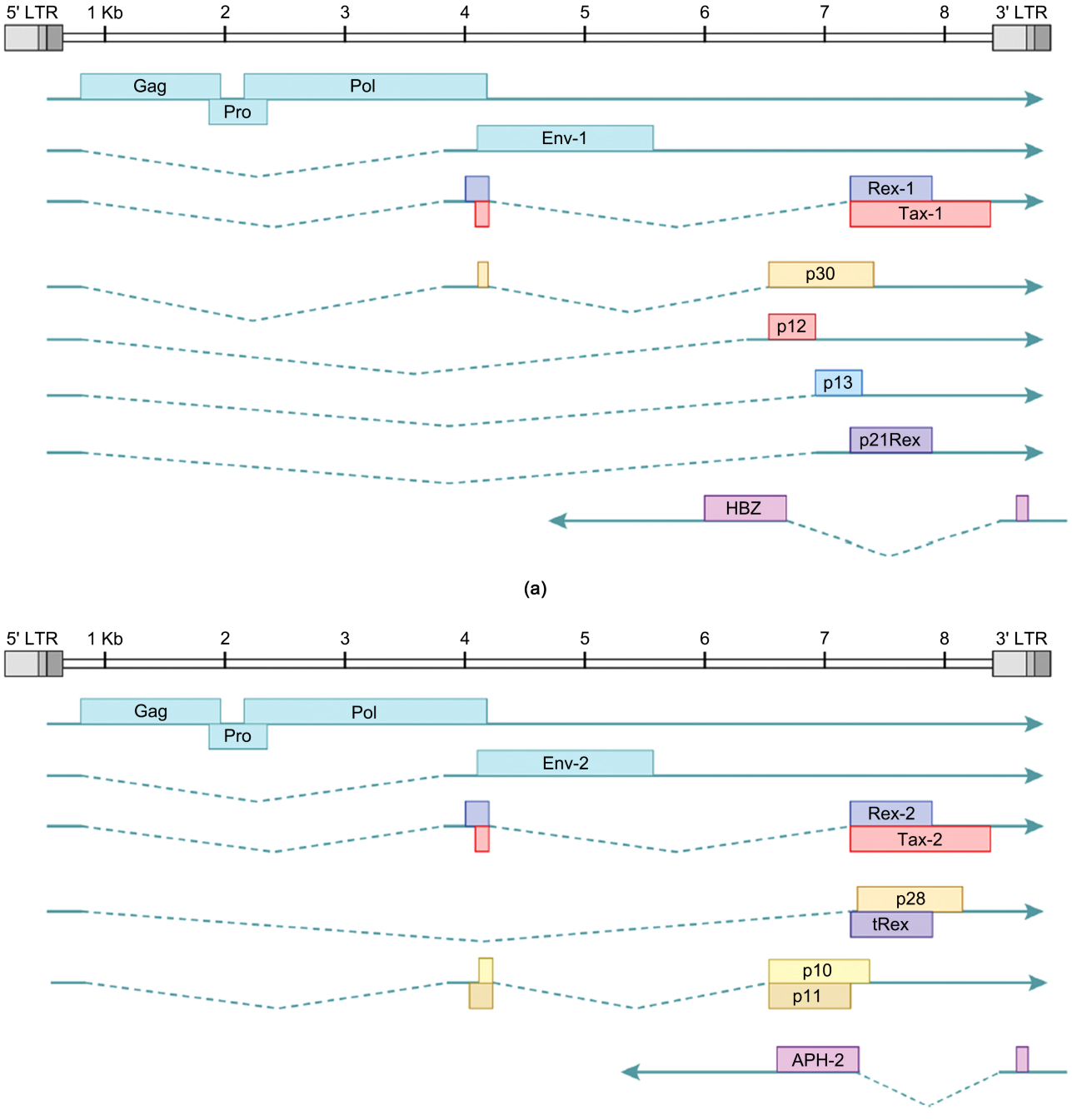


**Figure 1.** HTLV-1 and HTLV-2 genomes and transcriptions. (a) HTLV-1 genome, transcripts and associated proteins. (b) HTLV-2 genome, transcripts and associated proteins [49].

### 3.1. *Tax* 1 and *Tax* 2

In vivo, the provirus is mainly detected in CD4 + T lymphocytes. It is also, but less commonly, found in CD8 + T lymphocytes, B lymphocytes, monocytes, macrophages, dendritic cells and other non-lymphoid cells. As the free HTLV-1 virus is mildly infectious, its transmission depends on intercellular contact. This mode of transmission relies on the increased ability of infected cells to migrate, a function performed by the viral transcriptional activator Tax via the reorganization of the cytoskeleton [50]. After integration of the proviral genome, several different HTLV transcripts will be produced (**Figure 1(a)**, **Figure 1(b)** show a summary of these transcripts). Both viruses use the viral regulatory protein Tax and the viral promoter located in the 5' LTR to direct transcription of the viral gene. The viral Rex protein ensures the export of unspliced viral mRNAs. The full-length, unspliced viral mRNA serves as the viral genome for future virions and also as a source of ***Gag***, ***Pol*** and ***Pro*** proteins. Several mRNAs of different splice variants are also expressed to generate ***Env***, regulatory proteins and accessory proteins. Expression of HTLV antisense genes is not regulated by the ***Tax*** or ***Rex*** proteins, but rather depends on host cellular factors to promote transcription. The next sections will cover the different proteins expressed by HTLV-1 and HTLV-2 [47]. HTLV-1 and HTLV-2 encode the pleiotropic transactivator proteins ***Tax*-1** and ***Tax*-2**, respectively, which share 85% amino acid identity [51]. Both proteins contain CREB activating domains (N-terminal), zinc finger domains (N-terminal), nuclear localization signals (***Tax*-1**, in the first 60 amino acids; ***Tax*-2**, in the First 42 amino acids), nuclear export signals (amino acids 189 - 202) and ATF/CREB activation domains (C-terminal regions) (**Figure 2(a)**, **Figure 2(b)**) [51]-[58]. Unlike ***Tax*-2**, ***Tax*-1** has two leucine zipper-like regions (amino acids 116 - 145 and 225 - 232) responsible for activating canonical and non-canonical NF-κB pathways, a PDZ binding motif (PBM; C-terminal 4 amino acids) and a secretion signal (C-terminal) [59] [60] [61]. Conversely, ***Tax*-2** has a cytoplasmic localization domain (amino acids 89 - 113), which ***Tax*-1** lacks [62]. Although ***Tax*-1** and ***Tax*-2** have been found in the nuclear and cytoplasmic compartments of infected cells, the ***Tax*-2** cytoplasmic localization domain explains its predominantly cytoplasmic distribution compared to the predominantly nuclear distribution of ***Tax*-1** [58] [60] [61] [63]. Despite their functional domain similarities, the ***Tax*-1** and ***Tax*-2** interactomes and subsequent effects on cellular pathways are divergent (**Figure 3**).

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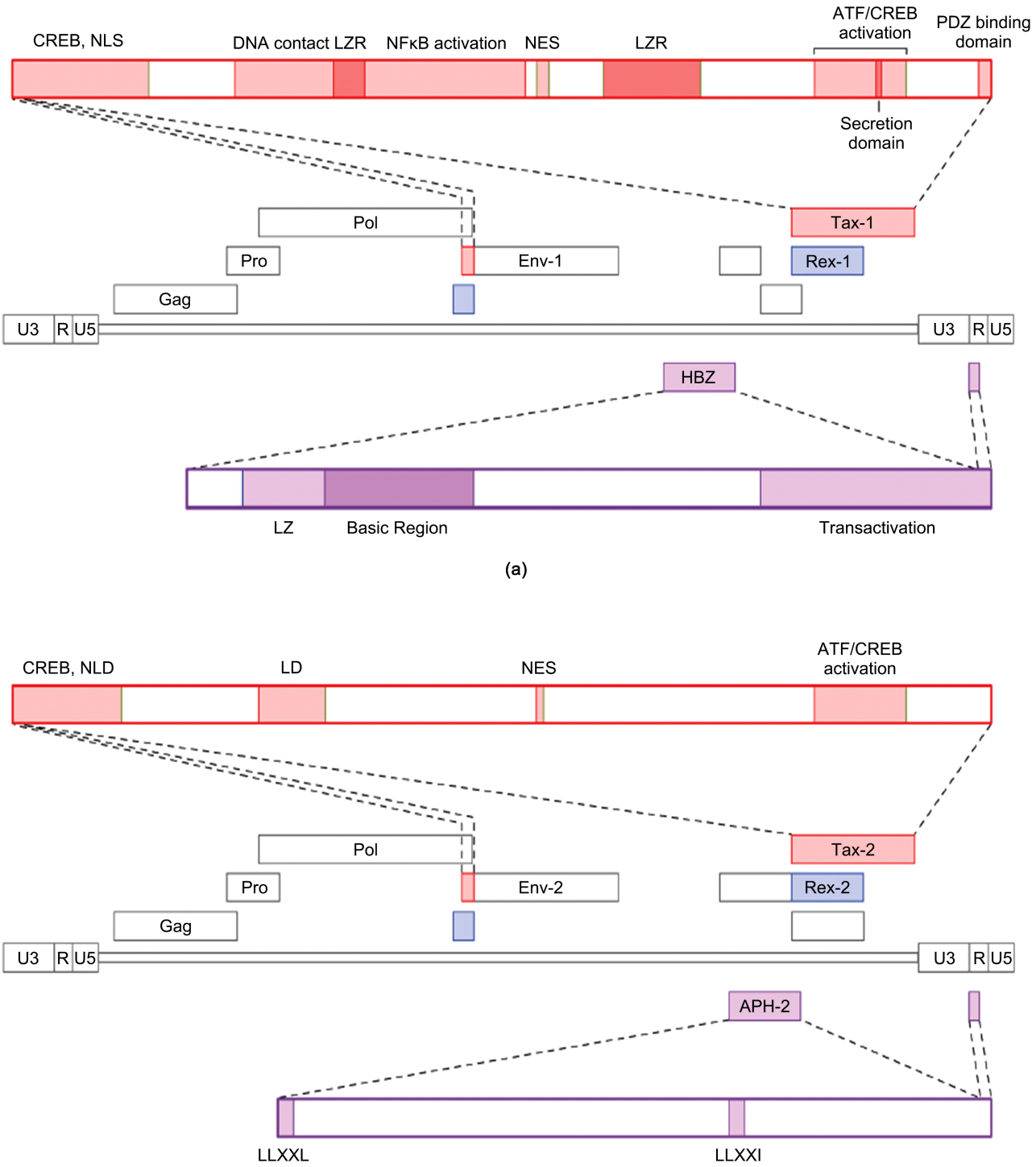


**Figure 2.** Functional domains of ***Tax*-1**, ***Tax*-2**, ***HBZ***, and ***APH*-2**. (a) HTLV-1 protein products and functional domains ***Tax*-1** and ***HBZ***. (b) HTLV-2 protein products and functional domains of ***Tax*-2** and ***APH*-2** [49].

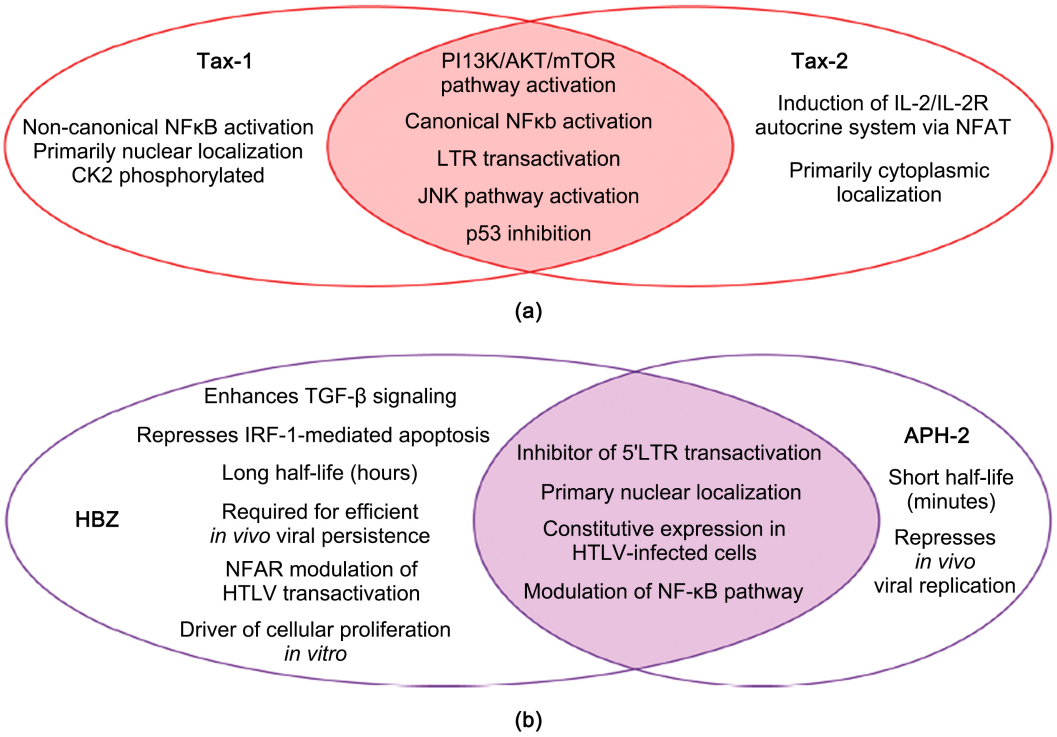


**Figure 3.** Functional comparison of ***Tax*-1** compared to ***Tax*-2** and HBZ compared to APH-2 [49].

### 3.2. Molecules Involved in Viral Entry

The ability of the HTLV-1 virus to infect many human and animal cells in vitro has long been an obstacle to the identification of its receptors. Several molecules are involved in binding the virus to target cells and then entering the virus into the cells (**Table 1**) [64]. The binding of viral particles to target cells depends on the expression of heparan sulfate proteoglycans (HSPGs), which are a primary attachment factor. GLUT-1, a glucose transporter strongly expressed by activated T cells, is then involved in the entry of the virus. The level of GLUT-1 expression at the cell surface is not however correlated with the level of binding of the viral envelope protein SU [65], suggesting that GLUT-1 is involved in late entry events. (fusion step) [66]. A third molecule contributes to the entry of the virus. It is neuropilin-1 (NRP-1 or BDCA4 9 (blood dendriticcell antigen 4), CD304 or VEGF165R (vascular endothelial growth factor isoform 165 receptor). Its expression in vivo is limited to activated T lymphocytes and dendritic cells, endothelial cells and certain tumor cells [67]. NRP-1 is in fact expressed in the vast majority of transformed cells, including laboratory lines [68], which correlates with the tropism of HTLV-1 in vitro It is a receptor for VEGF isoform A (VEGF165), which plays a role in particular in the survival of tumor cells [69]. Productive entry of the virus requires sequential interactions between the proteins of envelope and these three molecules [70]. According to the model proposed by Pique and Jones [71], HSPGs interact with SU, allowing the initial attachment of virions and their concentration on the cell surface. HSPGs also ensure recruitment of NRP-1.

Table 1. Dentritic cells and Cellular receptors of HTLV-1. D dendritic cells [52].

| HTLV-1 receptors | Cellular localization | Role in viral entry | Exception |
|---|---|---|---|
| GLUT-1 or carrier of glucose-1 | Ubiquitous in all laboratory lines Overexpressed after activation of cells or in cells in proliferation | Late entry events such as the merger | Glioblastoma/Astroglioma lines do not express GLUT-1 but are susceptible to HTLV-1 infection |
| BDCA-4 or NRP-1 or CD304 or VEGF165R | In vivo: activated T lymphocytes, dendritic cells (DC), endothelial cells and certain tumor cell lines In vitro: expression in almost all lines, particularly dendritic cells | Binding of the HTLV-1 (SU) env protein to the surface of the target cell, formation of syncytia | Possible infection in the presence of antibodies blocking the interaction between HTLV-1 and NRP-1 in dendritic cells |
| Heparin Sulphate Proteoglycans (HSPG and syndecan 1 and 2) | All cells. HSPGs are a component of the matrix extracellular | Attachment factors and virion concentration on the surface of the target cell Ensure the recruitment of NRP-1 | Unactivated CD4 + T cells express little or no HSPG. Possible infection in the presence of antibodies blocking the interaction between HSPG and HTLV-1 in dendritic cells |
| DC-SIGN | Dendritic cells, dendritic cells derived from monocytes (MDDC), myeloid dendritic cells and B cell lines | Attachment factor and virion concentration to the dendritic cell membrane. Also involved in virus transmission from dendritic cells to T lymphocytes | Expression restricted to a few subtypes of dendritic cells, but no expression in pDC |

An interaction then occurs between the 90-94 region of SU and the "b" domain of NRP-12, stabilized by HSPGs. A second conformational change allows SU tyrosine 114 to interact with GLUT-1, leading to fusion of viral and cell membranes. This model has been validated in CD4 + T lymphocytes, but may not be generalizable to all primary cells. In particular, infection of dendritic cells derived from monocytes remains possible in the presence of antibodies blocking the interaction of SU with HSPG or NRP-1. In this case, virus uptake may depend on the expression of DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin), a C-type lectin expressed by dendritic cells [72]. Likewise, although not expressing GLUT-1, cells of the U87 line (from tumor astrocytes) are infectable by HTLV-1 [73]. Their infection is believed to depend on the expression of NRP-1 [74]. These two examples suggest the possible existence of other receptors specific for certain target cell types of HTLV-1, or an alternative use of receptors depending on cell types.

## 4. Geographic Distribution and Molecular Subtypes of HTLV-1

### 4.1. Subtype A or Cosmopolitan

This is the first subtype described: the prototype strain ATK is one of them. It is also the most geographically dispersed molecular subtype. This genotype is indeed present in many regions and in very diverse human populations. Thus, by way of example, this subtype is most frequently encountered in Japan, the Americas, the Caribbean region, North, West and South Africa, the Middle East and India, as well as in some Pacific Islands. In addition, it is the subtype present

in Europe, on the one hand in the rare endemic foci of HTLV-1 such as Romania, and on the other hand especially in immigrants from highly endemic areas (mainly Antilles and West Africa). Despite this very wide geographical distribution, this subtype is surprisingly made up of a set of viral strains with very low divergence. It is however possible to define, within this subtype, molecular groups strongly supported by phylogenetic analyzes and/or by specific mutations. So, if we analyze the LTR, which is the most studied region of the virus because it is the most variant, at least four major molecular subgroups exist. They often correspond to aggregates of isolates with the same geographical origin (North Africa, Japan, West Africa) [75]-[83].

### 4.2. Subtype B or Central African Subtype

Subtype B (prototype EL), the sequence of which diverges by almost 3% from the ATK strain in the env gene, was initially discovered in 1985 in a patient of Zairian origin with ATL [42]. Several teams subsequently described other isolates of subtype B, mainly in different regions of the Democratic Republic of Congo (DRC, former Zaire). Recently, after studying 36 new isolates of HTLV-1 in inhabitants of Central Africa, it was demonstrated the existence of a great diversity of strains within this subtype with, once again, genotypes specificto the geographic origin of the isolates (DRC, Gabon, Cameroon) [84].

### 4.3. Subtype C or Melanesian Subtype

This subtype was first described in Melanesians living in Papua New Guinea (PNG), and the Solomon Islands [85] [86] [87] [88]. Surprisingly, the sequence of these viral strains diverged, in ***gp*21**, by nearly 6% to 8% compared to the strain ATK, prototype of the Cosmopolitan subtype. In addition, the PNG subtype C sequences themselves differed by 3% - 4% from other, but isolated, subtype C strains from the Solomon Islands. This demonstrated the existence of a high variability even within this subtype. Interestingly, the study of a strain from an inhabitant of the island of Bellona (island of the Solomon archipelago, but whose population is of Polynesian origin, therefore much more recent), showed that it was a strain of the Cosmopolitan subtype and not the Melanesian subtype. More recently, strains of subtype C have also been isolated and characterized in Australian aborigines [88].

### 4.4. Subtype D or Central African, Subtype Pygmies

This subtype, has been described [84] in three inhabitants of the western part of central Africa (Cameroon, Gabon and Central African Republic) including two Pygmies, seems to represent only a small proportion of the HTLV-1 viral strains of these regions compared to the more frequent subtype B [84] [89] [90] [91]. At the phylogenetic level, this subtype occupies an intermediate position between subtype B and subtype C. Finally, more recently still, two new viral strains of HTLV-1, distinct from known genotypes, have been characterized in inhabitants of central Africa, one living in Gabon, and the other in the east of the DRC

(Pygmée Effé) [92]. These new human isolates, unique for the moment, could be considered as potential prototypes of new viral subtypes (E and F).

Small arrows indicate the very likely interspecies transmission with passage of STLV-1 from monkeys (S) to humans (H) responsible for the current HTLV-1 subtypes. A = Cosmopolitan subtype with its different subgroups: TC (transcontinental, the most common and most widely distributed), Awa (West Africa), Ana (North Africa), Ajp (Japanese). B = Central Africa, most frequent in this highly endemic region, C = Melanesia, D = Central Africa, present particularly in certain groups of Pygmies and E, F, G of which very few strains have been described (all in Central Africa). Other minor genotypes have also been characterized in Central Africa: the -d, -e, -f and -g genotypes [92]. There is no definitive rule for the definition of each genotype, but each genotype is supported by phylogenetic studies, and intragenotypic variability is less than intergenotypic variability [95]. The initial classification included the Transcontinental A subgroup, the Japanese subgroup B, the West African subgroup C and the North African subgroup D; they are now called a-TC, a-Jpn, a-WA and a-NA, respectively [76] [94] [95]. More recently, the E/a-Per subgroup, comprising 2 strains of Black Peruvian, has been defined [96]; on the basis of a partial segment of LTR, a subgroup F was also identified, in particular in an Ethiopian patient [97]. Finally, in 2006, a Senegalese subgroup (a-Sen), which was also named "trans-Saharan" or W clade within the HTLV-1aD subgroup [98] [99] [100]. The transcontinental sub-group (TC) is present on all continents. The overall nucleotide variability within the a-TC subgroup is low: it can reach 0% - 2.5% in the gp21-env gene and 0% - 2% in the LTR region [101]. This low genetic variability is believed to reflect the recent spread of these strains. In particular, the slave trade from Africa to America, which peaked in the 18th century, may represent one of the major routes of recent diffusion [99] [102] [103]. In fact, the strains of HTLV-1 found in South Africa, Mozambique, Zimbabwe, Swaziland and Angola cannot be distinguished from the strains found in Brazil [1] [104] [105] [106] [107]. Additionally, in some studies, clades within the a-TC subgroup have been identified as South African clusters, Latin American clusters, and a Middle East [96] [108] [109].

The proportion of the different genotypes and subgroups of HTLV-1 is presented for each African country. Regarding the situation of Benin, Sierra Leone, Western Sahara and Madagascar, no data was available. Countries with no indication do not have published informative data on HTLV-1 genotypes between 1994 and 2019. The size of the circles is proportional to the number of strains identified. The smallest size corresponds to 1 characterized strain, the intermediate sizes to a maximum of 5 or 29 strains and the largest to a minimum of 30 strains. HTLV-1a-North Africa (HTLV-1 a-NA), HTLV-1a-Senegalese (HTLV-1 a-Sen), HTLV-1a-West Africa (HTLV-1 a-WA), HTLV-1b and HTLV-1a-Transcontinental (HTLV-1a-TC) are most prevalent throughout the continent in the North, West, Central and Austral regions respectively. HTLV-1 d, -e, -f and-g have been identified in Central Africa (Cameroon, Central African Re-

public and Gabon) [93]. In Côte d'Ivoire and Ghana, the majority of HTLV-1 strains belong to the West African subgroup [110] [112]. Strains of a-WA were also introduced to South America via the slave trade: strains of a-WA are found among the populations of Black-Brown living in Guyana and Suriname [110]. The Black-Maroons are the descendants of the slaves who escaped from the plantations of the Dutch colony of Suriname in the 16th and early 17th centuries. The Noir-Marron have strong genetic affinities close to the African populations of the bay of Benin, which is consistent with their predominant genetic subtype HTLV-1 [56] [111]. The Senegalese subgroup represents, by definition, the major subgroup present in Senegal [99] [100]. It is also present in neighboring countries such as The Gambia, Guinea-Bissau and Mali [98] [112]. In addition, a-Sen strains are found, but more rarely, in Côte d'Ivoire and Ghana. This is probably a testament to frequent migrations, some still ongoing, of people from Senegal and neighboring countries to other parts of West Africa. The North African subgroup is mainly present in Algeria, Morocco, Mauritania, Western Sahara and Mali [95] [110]. It can also be found sporadically in other West African countries such as Senegal, Guinea, Cote d'Ivoire, and Ghana. The Central African genotype b is most frequently found in Central Africa, *i.e.* Cameroon, Gabon, CAR, DRC and Nigeria. It represents more than 90% of the strains found in Gabon and the DRC [101] [113] [114]. The strains of HTLV-1b differ from HTLV-1a by 2% to 3% at the nucleotide level (compared to the reference strain ATK) [101]. As for HTLV-1a, the strains can be grouped according to the geographical origin: the HTLV-1 strains from DRC are closer to each other than strains found in South Cameroon and Gabon, for example [114]. Other d, e, f and g genotypes have been reported from Central Africa, mainly Cameroon, Gabon, DRC and CAR [101] [115] [116]. HTLV-1d can represent up to 3% of HTLV-1 strains in this region [113]; strains of HTLV-1 e - g have been reported sporadically. Sub-Saharan Africa is considered to be one of the largest endemic areas for HTLV-1 infection, with an estimated 2 - 4 million people infected with HTLV-1. However, most of the early seroepidemiologic studies performed in Africa applied Western blot criteria for HTLV-1 seropositivity, which were subsequently found to be weak [117]-[122]. This has led to an overestimation of the seroprevalence of HTLV-1 in several African regions. Thus, to date, there are only a few studies on HTLV-1 infection on the African continent in which the authors have used rigorous serological and/or molecular criteria for the diagnosis of HTLV infection [123] [124] [125] [126]. In addition, most epidemiological studies have been carried out in hospitalized patients or in people at risk of contracting HTLV-1 (prostitutes, patients infected with the human immunodeficiency virus, etc.) or in rural populations [122] [127] [128] [129] [130]. Therefore, very little data has been reported to date for large blood donor populations in West or Central Africa [131] [132]. The molecular characterization of a Congolese pygmy strain Efe HTLV-2 belonging to a potential new subtype, HTLV-2d, which is genetically and possibly also phenotypically different

from HTLV-2a, HTLV-2b or HTLV-2c. The Efe Pygmies belong to the Bambuti (or Mbuti) Pygmies of the Ituri Forest and are the least mixed of all the Pygmies. The flow of genes (including sexually transmitted viruses) almost always goes from Pygmies to other Africans and is rarely reversed. They are generally thought to represent the oldest "Proto-Africans" [133] [134].

## 5. HTLV-1 and HIV-1 Co-Infection

HTLV-1/HIV-1 co-infection is more frequently reported in South America, the Caribbean and Africa [135] [136] [137]. Studies suggest that HTLV-1/HIV-1 co-infection is associated with a change in the natural history of HIV-1, with faster clinical progression to AIDS and shorter survival time [138]. HIV-1 appears to upregulate HTLV-1 expression, leading to an increased risk of HTLV-1-associated diseases, such as TSP/HAM and T-cell leukemia in adults. However, the clinical evidence remains controversial due to methodological issues in the majority of currently published studies [139]. An early study of HIV and HTLV-1 co-infection by Leung *et al.* in 1988 [140] reported that co-infection with HTLV-1 led to increased production of host cell specific proteins, resulting in stimulation of HIV replication. In 1994, Schechter *et al.* published a case-control study of 27 patients with HIV/HTLV-1 co-infection [141] and concluded that co-infection was associated with higher CD4 counts, but at the same time with evidence of more advanced clinical HIV disease. A retrospective case-control study, published in 2001 by Brites *et al.* [135] of 198 patients infected with HIV-1, including 63 cases co-infected with HTLV-1, concluded that patients co-infected with HIV-1/HTLV-1 had a shorter mean survival than patients mono-infected with HIV-1, regardless of gender or baseline CD4 cell count. Sobesky *et al.* found an increased risk of death for patients co-infected with HIV-1/HTLV-1 from Guyana, compared to patients mono-infected with HIV-1, but the power of their finding was limited by the small size of the sample. Of 151 patients infected with HIV included in this study, only 18 patients were co-infected [142]. In 2004, Beilke *et al.* published a longitudinal study, carried out in New Orleans, which examined 62 patients with HIV/HTLV-1 co-infection and compared them to a group of 824 patients who were mono-infected with HIV. They found no significant difference in progression to AIDS, the presence of opportunistic infections or death between these two groups [143]. Certain methodological issues may have influenced their results. This study included patients who were taking antiretroviral drugs, while some of the earlier studies were done in the pre-HAART era. Beilke et al. report that they adjusted the analysis for the use of antiretroviral drugs, but there is no description in the article on how long HAART took, patient follow-up, or when antiretroviral therapy was started initiated in patients mono-infected with HIV, compared to co-infected [144].

## 6. HTLV-1 and HTLV-2 Co-Infection

HIV-1/HTLV-2 co-infection is predominant in North America and Europe, par-

ticularly among intravenous drug users [145]. The available evidence suggests a possible protective role of HTLV-2 co-infection with slowing the progression to AIDS [146]. Patients co-infected with HIV/HTLV-2 had lower levels of T cell activation with a lower rate of HIV replication [145]. In the retrospective study published by Beilke *et al.*, 141 patients co-infected with HIV/HTLV-2 were compared to 824 patients mono-infected with HIV. Their conclusion was that HIV/HTLV-2 co-infection was statistically associated with delayed progression to AIDS and death [143]. A longitudinal study by Turci *et al.* of 2371 white HIV-1 infected intravenous drug users in Italy, 6.7% of whom were co-infected with HTLV-2, found that co-infected patients were older, had CD4 counts initially higher and delayed progression to AIDS [147].

HTLV-1 and HTLV-2 co-infection appear to have different effects on people infected with HIV. It appears that HTLV-1 may accelerate clinical progression to AIDS and that the HIV virus may promote a higher risk of diseases associated with HTLV-1. However, some of the data available is contradictory. Co-infection with HTLV-2 appears to have a protective role, decreasing the progression to AIDS. A common denominator between HTLV-1 and HTLV-2 co-infection in HIV patients, is that both have been linked to higher CD4 counts. The higher CD4 counts may have caused a delay in the initiation of antiretroviral therapy in these co-infected patients [139].

## 7. Prevalence, Epidemiological and Molecular Studies Carried Out in Africa

In 1998 Anne-Mieke Vandamme, Marco Salemi and colleagues identified a potential subtype, within the human lymphocyte lymphotropic virus type-2 (HTLV-2), HTLV-2d present in members of a pygmy tribe Efe Bambuti. Two of 23 Efe pygmies were seropositive for HTLV-2, with HTLV-2 Western blot reactivities and enzyme-linked immunosorbent. From one of them, the entire genome of the HTLV-2 Efe2 strain could be amplified and sequenced. In all the gene regions analyzed, this strain was the most divergent HTLV-2 strain, differing from 2.4% (***tax/rex***) to 10.7% (long terminal repeat) of the two subtypes HTLV-2a and HTLV-2b, but the main functional elements are retained. The similarity between the HTLV-2 Efe2 Gag and Env proteins and the corresponding HTLV-2a and -2b proteins is consistent with the observed serological reactivity. In the proximal ***pX*** region, one of the two alternative splice acceptor sites is abolished in HTLV-2 Efe2. Another interesting feature of this potential new subtype is that it has a Tax protein of 344 amino acids (aa), which is intermediate in length between the HTLV-2a Tax protein (331 aa) and the HTLV-2b proteins and ***-2c Tax*** (356 aa) and similar to the tax protein PP1664 of the simian T cell lymphotropic virus type 2 (STLV-2). Together, these two results suggest a different phenotype for the HTLV-2 strain Efe2. Phylogenetic analyzes confirmed that the Pygmy strain Efe2 potentially belonged to a new and quite divergent subtype, HTLV-2d [89]. In 2002, out of 4900 samples in a seroepidemiological

and molecular study of HTLV-1 in a large population of blood donors in Senegal, the seroprevalence of human T-cell leukemia virus type 1 (HTLV-1) and HTLV-2 was 0.16% (8/4900) in blood donors from Dakar, Senegal. Most of the positive donors came from the southern region of the country. Seven donors were infected with HTLV-1 (cosmopolitan subtype) and one was infected with HTLV-2. Of the 4900 samples tested, only 14 were repeatedly found to be ELISA positive. Moreover, only 8 of these 14 samples were considered seropositive for HTLV (0.16%) according to strict WB criteria, 7 of them being HTLV-1 and 1 HTLV-2. The other six samples showed either no reactivity (four cases) or an undetermined WB profile (p19 alone and GD21 alone). The seroprevalence of HTLV-1 and HTLV-2 increased with age, ranging from 0.1% in blood donors aged < 30 years to 0.8% in blood donors aged > 50 years. Analysis of the LTR and ***env*** sequences demonstrated that all four new strains of HTLV-1 were closely related with an inter-strain nucleotide difference ranging from 0% to 0.9% for the LTR sequences and from 0% to 0.2% for the ***env*** genomics of 522 bp fragments. In addition, phylogenetic analyzes, using several strains representative of the different molecular subtypes of HTLV-1, clearly indicated that the four new strains belonged to the large cosmopolitan subtype HTLV-1. More specifically, they constituted a strongly phylogenetically supported clade (90% bootstrap in the neighborhood analysis), located between the HTLV-1 subgroups of North Africa and West Africa and comprising most of the others known strains of HTLV-1 from Senegal [148]. A prospective cross-sectional study of 184 subjects by Idris Abdullahi, Abdurrhaman EA *et al*., a study that examined the prevalence as well as the effects of HIV-1/HTLV-1 co-infection on CD4 + cell count found this following: the seroprevalence of anti-HTLV-1/2 IgM antibodies was 4.9%. However, 12 (6.5%) subjects tested positive for HTLV-1 provirus DNA. The CD4 + cell count in those with HTLV-1 and HIV-1 coinfection was significantly higher than those with HIV-1 monoinfection (P = 0.025). There was no significant difference between the other haematological parameters studied and the two groups (P > 0.05). There was no significant difference between the biochemical parameters studied between the two groups (P > 0.05). HTLV-1/HIV-1 co-infection was most detected in the 21 - 30 year age group, 7 (53.3%) and none in the 31 - 50 year old. HTLV-1/HIV-1 co-infection was detected more in women, 7 (58.3%), than in men, 5 (41.7%) subjects co-infected with HTLV-1/HIV-1 had a normal number of CD4 + cells [149]. In Uganda, in a study of blood donors in the Mbarara region of Uganda, of the 366 blood donors 229 men (62.2%) and 139 women (37.8%), only two male donors aged 20 and 21 tested positive for HTLV-1/2, for a prevalence of 0.54%. The prevalence of HTLV-1/2 is low among blood donors from the Mbarara regional blood bank. Studies among other categories of people at risk of HTLV 1/2 infection should be conducted. An HTLV seroprevalence of 2.3% was obtained from a similar study carried out in blood donors in Mozambique (the country closest to Uganda where a similar study had been carried out) by Caterino-de-Araujo *et*

*al*., 2010 [148] [149]. The genetic diversity of Mozambican HTLV-1 detected in the study by Ana Carolina, Eduardo samo reveals that although the strains belong to the most widespread and globally distributed Transcontinental subgroup of the Cosmopolitan subtype, there is a High HTLV diversity which could be correlated with at least 3 different introductions of HTLV-1 in the country. The differential rates of HIV-1/HTLV-1 co-infection in the three HTLV-1 clusters demonstrated the dynamics of the two viruses and the need to implement control measures focused on the two retroviruses [148].

## 8. Conclusion

Human T-cell leukemia virus type 1 remains unrecognized in parts of Africa. To date, very few studies have been carried out on the general population and because of its asymptomatic nature, the virus continues to progress. Hence the need to conduct an in-depth systematic study in target subjects namely: prostitutes, pregnant women and voluntary blood donors, but also HIV and HTLV co-infection based on serological and molecular criteria. The use of molecular tools should also allow us to subtype HTLV.

## Conflicts of Interest

The authors declare no conflicts of interest.

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