

# Origin and Diversity of Human Retroviruses

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## Abstract

*Simian immunodeficiency viruses, simian T-cell lymphotropic viruses, and simian foamy viruses from nonhuman primates have crossed the species barrier to humans at several time points, leading to the HIV and human T lymphotropic virus epidemic and to sporadic cases of human infections with simian foamy viruses, respectively. Efficient infection and spread in humans differs between simian foamy virus, simian lymphotropic virus, and simian immunodeficiency virus, but seems also to differ among the different viruses from the same simian lineage, as illustrated by the different spread of HIV-1 M, N O, P or for the different HIV-2 groups. Among the four HIV-1 groups, only HIV-1 group M has spread worldwide, and the actual diversity within HIV-1 M (subtypes, circulating recombinants) is the result of subsequent evolution and spread in the human population. HIV-2 only spread to some extent in West Africa, and similarly as for HIV-1, the nine HIV-2 groups have also a different epidemic history. Four types of human T lymphotropic virus, type 1 to 4, have been described in humans and for three of them simian counterparts (simian T lymphotropic virus-1, -2, -3) have been identified in multiple nonhuman primate species. The majority of human infections are with human T lymphotropic virus-1, which is present throughout the world as clusters of high endemicity. Humans are susceptible to a wide variety of simian foamy viruses and seem to acquire these viruses more readily than simian immunodeficiency viruses or simian T lymphotropic viruses, but neither signs of disease in humans nor human-to-human transmission of simian foamy virus have been documented yet. The current HIV-1 M epidemic illustrates the impact of a single cross-species transmission. The recent discovery of HIV-1 P, HIV-2 I, new human T lymphotropic virus-1 and -3 variants, as well as simian foamy virus infections in humans in Central Africa, show that our knowledge of genetic diversity and cross-species transmissions of simian retroviruses is still incomplete.*

(AIDS Rev. 2014;16:23-34)

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## Key words

**SIV. STLV. SFV. Non-human primates. HIV. HTLV.**

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## Introduction

The majority of emerging infectious diseases have a zoonotic origin and more than 70% originate from wildlife<sup>1</sup>. As such, simian immunodeficiency viruses (SIV), simian T-cell lymphotropic viruses (STLV), and simian foamy viruses (SFV) from nonhuman primates (NHP) have crossed the species barrier to humans on several occasions, leading to the HIV and human T lymphotropic virus (HTLV) epidemic and sporadic cases of human infections with SFV, respectively. Since description of the first AIDS cases in the 1980s, the estimated cumulative number of HIV infections worldwide is around 60 million<sup>2</sup>. HTLV infections affect between 10 and 20 million people worldwide<sup>3</sup>, but in contrast to HIV, only 5% of infected individuals develop a disease associated with this virus<sup>4</sup>. The sporadic human SFV infections are apparently without any health consequences and human-to-human transmission has not been reported yet<sup>5</sup>. The most plausible routes for cross-species transmissions with simian retroviruses are exposure to infected blood or tissues when NHP are hunted or butchered for bushmeat, but injuries from pet NHP can also play a role<sup>6,7</sup>. This review will present actual data on the origin, genetic diversity, and actual spread of these three retroviral infections in humans.

## Origin and diversity of HIV

### Simian immune deficiency viruses

Shortly after the identification of HIV-1 as the cause of AIDS in 1983, the first simian lentivirus, SIVmac, was isolated in 1984 from captive rhesus macaques (*Macaca mulatta*), with clinical symptoms similar to AIDS, at the New England Primate Research Center (NPRC)<sup>8,9</sup>. Since SIVmac induced a disease in rhesus macaques with remarkable similarity to human AIDS, a simian origin of HIV was suspected. However, it soon became clear that macaques are not natural hosts of SIV infection, but became infected with SIV from captive sooty mangabeys (SIVsmm) that are naturally infected with this virus<sup>10,11</sup>. SIVs have since been isolated from many wild African NHP species, but not from wild Asian or new world NHP<sup>7,12</sup>. Moreover, all these viruses seemed also non-pathogenic for their host, in contrast to what was observed in the captive Asian macaque

species, suggesting that Asian NHP are not natural hosts for SIV.

To date, SIVs have been identified in at least 45 different NHP species from Africa. SIVs are named according to the host species, and a three letter code refers to the common name of the corresponding NHP species; ex. SIVrcm for SIV from red-capped mangabey, SIVgsn for greater spot-nosed monkeys, etc (Table 1)<sup>7</sup>. The genetic diversity of NHP lentiviruses is complex and includes examples of co-evolution between virus and host, cross-species transmission, recombination between distant SIV lineages, and certain species can even harbor different SIV lineages. Co-evolution over long time periods is the case for SIV of the four different African green monkey species (*Chlorocebus* spec), SIVs from the *Ihoesti* superspecies (i.e. SIV *Iho* from *C. Ihoesti*, SIVsun from *C. solatus*, and SIVpre from *C. preussi*), and SIV from arboreal *Cercopithecus* species<sup>13-15</sup>. There are also numerous examples of cross-species transmissions of SIV between NHP species with overlapping habitats or among species that live in polyspecific associations. For example, SIV from African green monkeys has been transmitted to patas monkeys (*E. patas*) in Senegal, West Africa, and to yellow and chacma baboons in South Africa<sup>16-18</sup>. There are also more complex examples of cross-species transmission of SIV, followed by recombination between distant SIV lineages. This is the case for SIVcpz from chimpanzees: the 5' region of SIVcpz is most similar to SIVrcm from red-capped mangabeys, and the 3' region is closely related to the SIVgsn/mus/mon lineage infecting greater spot-nosed (*C. nictitans*), mustached (*C. cephus*), and mona (*C. mona*) monkeys<sup>19</sup>. Subsequently, chimpanzees have transmitted their virus to sympatric gorillas<sup>20</sup>. Finally, some NHP are infected with more than one SIV lineage, often as a result of cross-species transmission and recombination, e.g. SIVmnd-1 in mandrills from southern Gabon, and SIVmnd-2 in animals living in northern Gabon and Cameroon or SIVmus in mustached monkeys in which three different variants have been described<sup>21,22</sup>.

Despite the complex evolutionary history of SIV, each NHP species is in general infected with a species-specific SIV, which form monophyletic lineages in phylogenetic trees. The closest simian relatives of HIV-1 are SIVcpz from chimpanzees and SIVgor from gorillas. SIVs from sooty mangabeys are the closest relatives of HIV-2. These observations suggest that these NHP species are at the origin of HIV-1 and HIV-2,

Table 1. African nonhuman primates infected with simian immune deficiency virus and simian T lymphotropic virus

Genus	Species/subspecies	Common name	SIV lineage	SIV prevalence*	STLV type	STLV prevalence*	Human counterparts of SIV and STLV†
<b>HIV-1 group M and N, HTLV-1 subtype B</b>							
<i>Pan</i>	<i>troglodytes troglodytes</i>	Central African chimpanzee	SIVcpzPtt	0-30%	1	na	
	<i>troglodytes schweinfurthii</i>	Eastern chimpanzee	SIVcpzPts	0-30%	na	na	
	<i>troglodytes verus</i>	West African chimpanzee	neg	0%	1	70%	HTLV-1 subtype J?
	<i>troglodytes ellioti</i>	Gulf of Guinea chimpanzee	neg	0%	1	na	
	<i>paniscus</i>	Bonobo	neg	na	2	na	STLV-2 from bonobos are closest simian strains to HTLV-2
<i>Gorilla</i>	<i>gorilla gorilla</i>	Western lowland gorilla	SIVgor	0-5%	1	na	<b>HIV-1 group P and O?, HTLV-1 subtype B</b>
<i>Colobus</i>	<i>guereza</i>	Mantled guereza	SIVcol-1, col-2	18%	?	na	
	<i>angolensis</i>	Angolan colobus	only serology	na	3	8%	
	<i>satanus</i>	Black colobus	SIVbcl‡	30%	na	na	
<i>Piliocolobus</i>	<i>badius badius</i>	Western red colobus	SIVwrcPbb	50-80%	1	50%	HTLV-1 subtype J?
	<i>badius femminckii</i>	Temminck's red colobus	SIVwrcPbt	10%	na	na	
	<i>tholloni</i>	Tshuapa red colobus	SIVtrc‡	24%	1,3	na	
	<i>rufomitratus tephrosceles</i>	Ugandan red colobus	SIVkr‡	23%	1	6%	
<i>Procolobus</i>	<i>verus</i>	Olive colobus	SIVolc	na	na	na	
<i>Lophocebus</i>	<i>albigena</i>	Gray-cheeked mangabey	only serology	na	1,3	20%	HTLV-1 subtype F?
	<i>aerinus</i>	Black-crested mangabey	SIVbkm‡	na	3	12%	
<i>Papio</i>	<i>anubis</i>	Olive baboon	only serology	na	1	9%	
	<i>cynocephalus</i>	Yellow baboon	(SIVagm-ver)‡	na	3	na	
	<i>ursinus</i>	Chacma baboon	(SIVagm-ver)‡	na	1	na	
	<i>hamadryas</i>	Sacred baboon	na	na	3	50%	
<i>Theropithecus</i>	<i>gelada</i>	Gelada baboons	na	na	3	na	
<i>Cercopithecus</i>	<i>atys</i>	Sooty mangabey	SIVsmm	50%	1	23%	<b>HIV-2 group A to I, HTLV-1 sm subtype</b>
	<i>torquatus</i>	Red-capped mangabey	SIVcm	50%	1,3	na	HTLV-3 subtype B
	<i>agilis</i>	Agile mangabey	SIVagi	na	1,3	80%	HTLV-1 subtype F?

(Continue)

Table 1. African nonhuman primates infected with simian immune deficiency virus and simian T lymphotropic virus (continued)

Genus	Species/subspecies	Common name	SIV lineage	SIV prevalence*	STLV type	STLV prevalence*	Human counterparts of SIV and STLV†
<i>Mandrillus</i>	<i>sphinx</i> <i>leucophaeus</i>	Mandrill Drill	SIVmd-1, mnd-2 SIVdrl	33% 22%	1 na	20% na	HTLV-1 subtype D and F
<i>Allenopithecus</i>	<i>nigroviridis</i>	Allen's swamp monkey	SIVasm‡	na	1	na	na
<i>Miopithecus</i>	<i>talapoin</i> <i>ogouensis</i>	Angolan talapoin Gabon talapoin	SIVta‡ SIVtaI	na 17%	na 1	na na	na
<i>Erythrocebus</i>	<i>patas</i>	Patas monkey	(SIVagm-sab)‡	7%	1	na	na
<i>Chlorocebus</i>	<i>sabaeus</i> <i>aethiops</i> <i>tantalus</i> <i>pygerythrus</i>	Green monkey Grevet Tantalus monkey Vervet monkey	SIVagn-sab SIVagn-gri SIVagn-tan SIVagn-ver	47% na 50% na	1 1 1 1	na na na na	na
<i>Cercopithecus</i>	<i>diana</i> <i>nictitans</i>	Diana monkey Greater spot-nosed monkey	only serology SIVgnsn	na 1%	na 1,3	na 2%	HTLV-3 subtype D?, HTLV-1 subtype F?
	<i>mitis</i> <i>albogularis</i>	Blue monkey Slykes's monkey	SIVblu‡ SIVsyk	na 46%	na 1	na 1,3	na
	<i>mona</i>	Mona monkey	SIVmon	na	1,3	na	HTLV-3 subtype D?
	<i>lowei</i>	Lowe's mona monkey	only serology	na	na	na	na
	<i>campbelli</i>	Campbell's monkey	only serology	na	na	na	na
	<i>pogonias</i>	Crowned guenon	only serology	na	1	7%	HTLV-1 subtype D?
	<i>denti</i>	Dent's mona monkey	SIVden	na	na	na	na
	<i>cebus</i>	Mustached guenon	SIVmus-1,mus-2, mus-3	1%	1	3-30%	na
	<i>erythrotis</i>	Red-eared monkey	SIVery‡	33%	na	na	na
	<i>ascanius</i>	Red-tailed monkey	SIVasc‡	25%	1	1.5%	na
	<i>hoesti</i>	IHoest's monkey	SIVho	na	na	na	na
	<i>solatus</i>	Sun-tailed monkey	SIVsun	na	na	na	na
	<i>preussi</i>	Freuss's monkey	SIVpre‡	22%	na	na	na
	<i>hamlyni</i>	Owl-faced monkey	only serology	na	na	na	na
	<i>neglectus</i>	De Brazza's monkey	SIVdeb	20-40%	1	20%	na
	<i>wolff</i>	Wolf's monkey	SIVwol	12%	1	12%	na

\*Prevalence observed in wild nonhuman primate populations are shown; †HIV strains indicated in bold; ‡only partial sequences are available; ?: precise nonhuman primate species at the origin of the HTLV cannot be identified because multiple nonhuman primate species are infected with same STLV subtype. ( ): SIV infections resulting from cross-species transmissions of local African green monkey species; na: not available.

respectively. More in-detail studies showed that SIV from chimpanzees and gorillas have crossed the species barrier on at least four occasions, leading to HIV-1 group M, N, O, and P in humans<sup>6,23</sup>. The different HIV-2 groups are the result of at least nine independent transmissions of SIV from sooty mangabeys in West Africa<sup>6,23,24</sup>.

### **The origin and simian reservoirs of HIV-1 in apes from west Central Africa**

The first SIVcpz strains were identified in two captive wild-born chimpanzees in Gabon<sup>25</sup>. Subsequent studies on captive chimpanzees from different geographic origins and subspecies showed a high degree of genetic diversity among SIVcpz strains that was associated with the chimpanzee subspecies<sup>26</sup>. These initial observations showed also that all HIV-1 strains were more closely related to SIVcpzPtt from Central chimpanzees (*Pan troglodytes troglodytes*) in west Central Africa than to SIVcpzPts from eastern chimpanzees (*P. t. schweinfurthii*) in east Central Africa. However, data on SIV from captive chimpanzees do not reflect the SIVcpz diversity and prevalence in the wild, and studies on wild chimpanzees were needed to better document the origin and reservoirs of the HIV-1 strains that circulate today in humans. Given the difficult access to and the endangered status of chimpanzees, methods were first optimized for antibody and viral detection in fecal samples that can be collected non-invasively<sup>27</sup>. Subsequently, large-scale studies have been conducted and today more than 4,000 fecal samples have been collected from the four different chimpanzee subspecies across Africa<sup>27-30</sup>. These studies showed that only the two subspecies from Central Africa are infected with SIVcpz, and confirmed also that *P. t. troglodytes* and *P. t. schweinfurthii* are each infected with a subspecies-specific lineage. Within the SIVcpzPtt and SIVcpzPts lineages, phylogeographic clusters were observed, which allowed tracing the reservoirs of the ancestors of the pandemic HIV-1 group M in southeast Cameroon<sup>28-30</sup>. Similarly, the ancestors of HIV-1 group N have been identified in chimpanzee communities in south-central Cameroon<sup>28-30</sup>. In both chimpanzee subspecies, SIVcpz prevalences are heterogeneous, with an overall prevalence of 6-13%, which can reach even 30% or more in certain chimpanzee communities<sup>28-30</sup>. Despite the fact that both chimpanzee subspecies represent significant reservoirs, only SIVcpzPtt strains have been transmitted to humans.

In 2006, SIV infection was described for the first time in wild western lowland gorillas (*Gorilla gorilla gorilla*) in Cameroon<sup>20</sup>. SIVgor formed a monophyletic group within the HIV-1/SIVcpz radiation, and was more closely related to HIV-1 group O and P<sup>20,31</sup>. The close phylogenetic relationship of the recently discovered HIV-1 group P and SIVgor suggested that group P is derived from SIVgor<sup>31,32</sup>, and this was confirmed by a recent study that identified gorilla populations in southwest Cameroon that are infected with a strain that has equal or more homology to HIV-1 P than the SIVcpz ancestors to HIV-1 M and N<sup>33</sup>. Today, more than 4,000 fecal samples from gorillas, mainly western lowland gorillas from Cameroon, have been tested. Compared to SIVcpz in chimpanzees, SIVgor is less widespread and prevalence is lower, although it can reach up to 20% or more in certain gorilla groups<sup>20,31,33,34</sup>. Despite the lower spread of SIVgor, gorillas have also transmitted their SIV to humans.

### **Different HIV-1 epidemics**

The four HIV-1 groups thus have their origin in chimpanzees or gorillas from west Central Africa, and the initial genetic diversity of HIV-1 is associated with the different introductions of SIV into humans. Among the four HIV-1 groups, only HIV-1 group M has spread worldwide. The other HIV-1 groups are less prevalent and remain mainly restricted to Cameroon. The geographic areas where HIV-1 O, N, and P have been documented correspond to the areas where their ancestors or closely related SIV have been identified<sup>35</sup>. The situation is different for the pandemic HIV-1 M lineage for which the epicenter is located in the western part of the Democratic Republic of Congo (DRC), 1,000 km from where the SIVcpz ancestors have been identified in Cameroon<sup>28,36</sup>. Although it cannot be excluded that SIVcpzPtt strains closely related to HIV-1 M exist in chimpanzee populations living between southern Cameroon and Kinshasa, the virus most likely arrived in Kinshasa at the end of the 19th and beginning of the 20th century due to commercial activities and exchanges with southern Cameroon<sup>37</sup>. As shown in a biopsy from 1960 and a serum from 1959, HIV-1 M strains circulated already among humans in Kinshasa 20 years before the first AIDS cases were observed in the USA<sup>38,39</sup>. Molecular clock analyses showed that HIV-1 group M started to diverge in the human population at the beginning of the 20th century, around 1908 (95% CI: 1884-1924)<sup>39</sup>.

## ***Genetic diversity and molecular epidemiology of the pandemic HIV-1 group M strain***

Whereas the initial diversity of HIV-1, i.e. groups, is related to different cross-species transmission events, the actual diversity within HIV-1 M is the result of subsequent evolution and spread in the human population. Based on phylogenetic analysis, HIV-1 group M can be further subdivided into nine subtypes (A-D, F-H, J, K), sub-subtypes (A1-A4 and F1 and F2), and numerous circulating (CRF) and unique recombinant strains (URF). Currently, more than 60 CRFs and numerous URF have been reported<sup>40</sup>. Certain CRFs, like CRF01\_AE and CRF02\_AG, were already present early in the epidemic, but many other CRFs have emerged more recently. The genetic diversity within subtypes and CRFs increases also over time. Subtype C predominates in the actual global epidemic, representing almost half of HIV-1 infections, followed in decreasing order by subtype A (12%), subtype B (11%), CRF02\_AG (8%), CRF01\_AE (5%), subtype G (5%), and subtype D (2%)<sup>55</sup>. Other subtypes (F, H, J, K) and all other CRFs represent about 5% of infections in the world<sup>41</sup>.

The classification of HIV strains has helped in tracking the course of the HIV pandemic. The highest genetic diversity, in terms of intra-subtype diversity and number of co-circulating subtypes and recombinants, is seen in the western part of the DRC<sup>36</sup>. This observation, together with the fact that HIV-1 subtype A and D strains circulated already in Kinshasa, the capital city of the DRC, around 1960, suggest that the epidemic is ancient in the DRC<sup>38,39</sup>. Therefore, this part of Africa is considered as the epicenter where the initial diversification of HIV-1 group M strains occurred and from where different HIV-1 M variants started to spread across Africa and subsequently to other continents in the world. A high genetic diversity is also seen in the surrounding countries like Cameroon, Angola, Central African Republic, Gabon, and Equatorial Guinea. In southern Africa, the epidemic is almost exclusively due to subtype C. In East Africa, subtype C predominates also in Burundi and Ethiopia, but subtypes A, C, and D co-circulate in different proportions together with numerous unique recombinants involving subtypes A, C, and D in other countries like Kenya, Tanzania, or Rwanda. In West Africa, 50-80% of infections are caused by CRF02\_AG. In the other continents, subtype/CRF distribution is also heterogeneous; subtype B predominates in North America and Western

Europe; subtype A and CRF03\_AB are widely present among intravenous drug users (IDU) in eastern Europe; subtypes B and F predominate in South America; CRF01\_AE and subtype B co-circulate in southeast Asia; subtype C predominates in India<sup>41,42</sup>. However, as a result of increasing human mobility and migration, new HIV-1 variants are introduced and intermix with existing strains in different parts of the world. The geographic distribution of HIV-1 variants is thus a dynamic process. For example, only subtypes B and F were initially introduced in South America, but today a wide diversity of B/F recombinants circulate, including at least 11 CRF and numerous URF<sup>40</sup>. A similar scenario has been observed in southeast Asia, where subtype B predominated in the IDU population and CRF01\_AE among heterosexually transmitted infections. Today, at least 10 CRF and numerous URF involving subtype B and CRF01\_AE have been described<sup>40</sup>. Overall, with the intermixing of subtypes and CRF, new recombinant viruses are generated and their numbers and complexity will increase since recombination involving viruses that are already recombinant will occur.

## ***Genetic diversity and molecular epidemiology of non-pandemic HIV-1 group N, O, and P***

HIV-1 group O, described in 1990, remained restricted to west Central Africa and especially Cameroon, where they represent today less than 1% of HIV-1 infections and the proportion of group O strains seems to be declining over time<sup>43,44</sup>. Sporadic cases of HIV-O infection have been described in East and West Africa, Europe, and the USA, but always in Cameroonians or in patients with a link to Cameroon<sup>35</sup>. The oldest case of HIV-1 group O infection was documented in a sailor from Norway who visited west Central Africa during the 1960s<sup>45</sup>. A high genetic diversity is seen among HIV-1 group O, and the time of the HIV-1 group O radiation is estimated to be around 1920 (1890-1940)<sup>46</sup>. However, phylogenetic tree analysis of numerous HIV-1 O strains did not allow identifying subtypes as in HIV-1 M and a consensus classification for HIV-1 group O is still pending<sup>35</sup>. As a consequence of the co-circulation of HIV-1 M and O, cases of dual M and O infection, and several HIV-1 M/O recombinant viruses have been observed in Cameroon and also in France<sup>47-50</sup>.

HIV-1 N has been documented in less than 20 patients since its first description in 1998. With the exception of

one case, all are documented in Cameroon<sup>35,51</sup>. The low numbers of HIV-1 N infections and the lower intra-group genetic diversity suggest a more recent introduction of the HIV-1 N lineage into the human population around 1963 (1948-1977)<sup>46</sup>. Finally, HIV-1 group P was described in 2009 and, despite extensive screening, only two patients have been identified today and estimates on dates are uncertain, but probably between 1845 and 1989<sup>32,52,53</sup>.

## Origin and spread of HIV-2 in the human population

HIV-2 is most closely related to SIVsmm infecting sooty mangabeys (*Cercocebus atys*) in West Africa<sup>54,55</sup> and at least nine cross-species transmissions have been observed, leading to nine HIV-2 groups<sup>6,23,24</sup>. HIV-2 only spread to some extent in West Africa, and similarly as for HIV-1, the different HIV-2 groups have also a different epidemic spread. Only groups A and B were able to spread to some extent in the human population in West Africa. Overall, HIV-2 group A predominates. HIV-2 group B is less prevalent and co-circulates with HIV-2 A mainly in Ivory Coast and Ghana<sup>56</sup>. Recombinants between HIV-2 groups A and B have also been reported, and the first CRF of HIV-2 (CRF01\_AB) has been identified recently in three patients living in Japan<sup>57,58</sup>. Detailed analysis showed that this CRF most likely originated in West Africa because a similar strain was isolated in 1990 from a patient living in Ivory Coast<sup>58</sup>. The other HIV-2 groups have been documented in one or two individuals (group F only) and represent most likely dead end infections or infections associated with very low spread. Except for groups G and H, groups C, D, E, F, and I were isolated in rural areas where people are frequently in contact with SIV-infected mangabeys (pets or bushmeat)<sup>23,24</sup>. The ancestors of the epidemic HIV-2 group A and B viruses, as well as those for group C, G, H, and I, were identified in wild sooty mangabey populations from the Tai forest in Ivory Coast, in the eastern part of the sooty mangabey range<sup>24,59</sup>. HIV-2 D, E, and F strains have been isolated in Sierra Leone and Liberia and are most closely related to SIVsmm strains from that area<sup>23</sup>.

Today, HIV-2 prevalences are decreasing and HIV-1 is becoming predominant in West Africa, most likely because HIV-2 is less pathogenic and less transmissible<sup>60</sup>. Dual infections with HIV-1 and HIV-2 have been frequently observed in areas where both viruses co-circulate, but today no recombinant virus between HIV-1 and -2 has been documented yet.

## Origin and diversity of human T lymphotropic viruses (HTLV-1 to 4)

### Simian T lymphotropic viruses

Four types of HTLV, types 1 to 4, have been described in humans and for three of them simian counterparts (STLV-1, STLV-2, STLV-3) have been identified. The first STLV was isolated in 1982 in Japan<sup>61</sup> and subsequent studies on NHP showed that STLV is endemic in many NHP species from Africa and Asia but absent in NHP from the new world<sup>3,62</sup>. Table 1 summarizes STLV infections in African NHP. STLV-1 has been characterized in at least 30 different African and Asian NHP species<sup>4,7</sup>. Today, the STLV-2 lineage is composed of only two strains isolated from two captive bonobos (*Pan paniscus*) but from different captive groups<sup>63,64</sup>. Despite extensive surveys on STLV infection in wild NHP, there is no evidence today for STLV-2 infection in other NHP species. STLV-3 has a wide geographic distribution among NHP in Africa<sup>65</sup>.

A high genetic diversity is seen among the different STLV-1 and -3 strains, with presence of numerous subtypes. Phylogenetic analyses show that STLV-1 and -3 strains from different NHP species cluster geographically and not according to species origin as is seen for SIV. This means that different NHP species living in the same area can be infected with identical STLV, and suggests that these viruses are easily transmitted among different NHP species. For example, in Gabon, greater spot-nosed monkeys, red-capped mangabeys, and mustached monkeys are all infected with subtype D<sup>22</sup>; in the Tai National Park in Ivory Coast, western red colobus monkeys and chimpanzees are infected with the same STLV-1<sup>66</sup>; in Asia, different macaque species are infected by STLV-1 of the Asian/Austronesian PTLV-1 clade<sup>67</sup>. On the other hand, different subtypes co-circulate also within the same NHP species, and co-circulation of STLV-1 and -3 within the same species has also been documented<sup>68,69</sup>.

### Origin of HTLV

Primate T lymphotropic virus-1 (PTLV-1), including HTLV-1 and STLV-1, are the most widely spread variants and at least 10 subtypes (A-J) of closely related HTLV-1 and/or STLV-1 have been described. In certain subtypes, human and simian viruses are interspersed,

and others are mainly comprised of simian strains, including or not sporadic human counterparts. For the cosmopolitan subtype A, which has spread globally, no simian counterpart has yet been observed<sup>3</sup>. For example, in Central Africa, STLV-1 strains from chimpanzees or mandrills cannot be distinguished from HTLV-1 strains of subtype B or D, respectively<sup>70</sup>, and human and simian subtype F strains from Gabon and Cameroon are also very closely related<sup>22,71</sup>. Like STLV-1, STLV-3 is also widespread among African NHP. Four separate subtypes are reported for STLV-3, and human HTLV-3 strains are interspersed with STLV-3 strains from subtype B and D<sup>65</sup>. This intermixing and the close relatedness between certain simian and human strains in the PTLV-1 and -3 lineages suggest that many independent cross-species transmission events are at the origin of the genetic diversity of HTLV-1 and -3 in humans, and suggest also past and probably ongoing cross-species transmissions of STLV from numerous NHP species to humans<sup>72</sup>. On the other hand, HTLV-2 and STLV-2 form distinct monophyletic clades, without evidence for recent interspecies transmissions. Also, for the recently described HTLV-4, no simian counterpart has been identified yet.

### **Genetic diversity and molecular epidemiology of human T lymphotropic virus**

Since the first descriptions of STLV-1 and HTLV-1 around 1980, the virus has infected 10-20 million people worldwide<sup>3</sup>. HTLV-1 is present throughout the world, but in contrast to HIV, the HTLV epidemic is characterized by clusters of high endemicity<sup>3</sup>. The majority of HTLV-1 strains belong to the cosmopolitan subtype A, which has spread globally. Subtype A can be further subdivided in a transcontinental, West African, North African, and Japanese subgroup. Subtype B and D are present in Central Africa, and the Melanesian subtype C counts for almost all HTLV infections in the different islands of the Pacific area<sup>3,73</sup>. The other HTLV subtypes are documented in few individuals, mainly in Central Africa.

HTLV-2 is less widespread and four subtypes are observed. The major subtypes, A and B, are both documented in Amerindians and intravenous drug-using populations in the USA and Europe, and subtype C is nearly exclusively found in Brazilian populations<sup>74,75</sup>. These observations led initially to the hypothesis that HTLV-2 was restricted to the New World. However,

sporadic cases of HTLV-2 infection have been described in different areas from Central Africa. More precisely, a unique divergent subtype D strain was identified in a pygmy living in the DRC<sup>76</sup> and HTLV-2 subtype B strains were isolated from pygmies living in Cameroon and Gabon<sup>77,78</sup>.

HTLV-3 infections have only been recently identified in a handful of individuals, all living in rural areas in southern Cameroon<sup>65</sup>. HTLV-4 consists so far of a unique human strain obtained from a hunter living in Cameroon<sup>79</sup>. The recent discovery of HTLV-3 and HTLV-4 and novel STLV-1-like viruses among people who hunt and butcher NHP suggests that cross-species transmissions are still ongoing<sup>66,72,79</sup>.

## **Foamy viruses**

### **Simian foamy virus**

Simian foamy viruses have been identified in almost all African and Asian NHP, but also in several NHP species in South America<sup>65,80</sup>. These SFV are ancient and co-evolved with their NHP primate hosts 30-40 millions years ago<sup>81</sup>. Although SFV are species-specific, occasional cases of cross-species transmissions among NHP have been documented. The transmission of SFVwrc from western red colobus to chimpanzees in a predator/prey system has been documented in the Tai forest in Ivory Coast, and SFV from a *Cercopithecus* species has been detected in a wild chimpanzee in Cameroon<sup>82,83</sup>.

### **Simian foamy virus infections in humans**

Importantly, humans are not naturally infected with a foamy virus, but several cases of zoonotic transmissions have been reported around the world among individuals who are exposed to NHP, like zoo workers, animal handlers, and hunters<sup>5,84-86</sup>. In Cameroon, about 1% of villagers exposed to NHP through hunting, butchering, or keeping of pet monkeys were found to be SFV antibody positive, and genetic analysis showed infection with SFV strains from De Brazza's monkeys, mandrills, and gorillas<sup>87</sup>. Persons living in rural villages in the DRC were infected at a 0.5% SFV prevalence rate, and molecular characterization of the SFV strains confirmed infection with SFV from local NHP species, i.e. Angolan colobuses and red-tailed monkeys<sup>88</sup>. Between 18-36% of individuals who were severely bitten and injured while hunting wild chimpanzees and gorillas in Cameroon and Gabon had

Table 2: Comparison of simian immune deficiency virus, simian foamy virus, simian T lymphotropic virus, and simian T lymphotropic virus infections in their natural hosts and humans

SIV	STLV	SFV
Spread in NHP	Africa	Africa and Asia
Evolution in natural NHP host	Species-specific lineage: result of virus-host co-evolution, cross-species transmission, recombination	No species-specific lineage but geographic clustering: frequent cross-species transmission, co-circulation of several STLV types and subtypes in same NHP species
Cross-species transmissions to humans	Chimpanzee, gorilla, sooty mangabey	Chimpanzee, gorilla, bonobo, mandrill, Angolan colobus, Tshiaga red colobus, several Cercopithecus species, Macaca species in Asia
Human infections	60 million HIV infections since discovery early 1980s	10-12 million HTLV infections
Human epidemics	HIV-1 M global HIV-1 O 1% of HIV in Cameroon HIV-1 N < 20 cases in Cameroon HIV-1 P, 2 patients from Cameroon	HTLV-1 A global HTLV-1 B and D, West and Central Africa HTLV-1 C Melanesia HTLV-1 E, F, G, H, J, sporadic cases in West and Central Africa
	HIV-2 A West Africa HIV-2 B, eastern part of West Africa HIV-2 C-I sporadic cases in West Africa	HTLV-2 A USA and Europe HTLV-2 B, Europe, USA and Central Africa HTLV-2 C Brazil HTLV-2 D sporadic case in Central Africa
Human disease	AIDS	HTLV-3 sporadic cases in Central Africa HTLV-4 single case in Central Africa Adult T-cell leukemia/lymphoma, Tropical spastic paraparesis and HTLV-1 associated myopathy No disease

SIV: simian immune deficiency virus; STLV: simian T lymphotropic virus; SFV: simian foamy virus; HIV: human immunodeficiency virus; NHP: nonhuman primate; HTLV: human T lymphotropic virus.

detectable SFVcpz or SFVgor sequences in their blood<sup>84,89</sup>. An SFV prevalence of 16% was observed in zookeepers in China, and studies from Thailand, Nepal, Bangladesh, and Indonesia reported that 8% of persons in various contexts (including zookeepers, hunters, Temples and urban) were SFV-infected<sup>85,90</sup>. Finally, up to 5.3% of SFV infection is seen in persons with occupational NHP exposure in research institutions or zoos in the USA<sup>86</sup>.

Humans are thus susceptible to a wide variety of SFV and seem to acquire these viruses more readily than SIV or STLV, but no signs of disease in humans or human-to-human transmission of SFV has, however, been documented. Therefore, the lack of human-to-human SFV transmission represents an informative marker of contact between humans and NHP.

## Conclusion

As discussed, a wide diversity of simian retroviruses have been transmitted to humans, most probably through exposure to blood or other secretions of infected animals, during hunting and butchering of bushmeat, or by injuries like bites or scratches during hunting or from pet NHP. The chance for cross-species transmissions certainly increases when frequency of exposure and retrovirus prevalence is high, which could partially explain the higher rate of cross-species transmissions observed for SFV. In addition to the type and intensity of contacts between NHP and humans, host and viral characteristics play a role in subsequent efficient infection in the new host. SIVwrc infecting western red colobus illustrates the role of viral adaptation and host factors. Overall, 50-80% of them are infected with SIV and, together with mangabeys, they are heavily hunted for bushmeat<sup>91,92</sup>. However, in contrast to SIVsmm, which has been transmitted at least nine times to humans, no SIVwrc cross-species transmission to humans has been documented yet. Efficient infection and spread in humans differs between SFV, STLV, and SIV, but seems also to differ among the different viruses from the same simian lineage, as illustrated by the different spread of HIV-1 M, N, O, and P or for the different HIV-2 groups. Table 2 summarizes the different characteristics of SIV, STLV, SFV in their natural primate host and humans.

Efficient spread of the virus in the human population depends on the capacity of the virus to adapt to the new host, and then on transmission modes together with social and environmental factors. The current

HIV-1 M pandemic illustrates the impact of a single cross-species transmission and its transmission among different human populations where conditions for efficient epidemic spread were present. Already 13 transmissions involving three different NHP species to humans have been documented, four for HIV-1 and nine for HIV-2. Most likely, other cross-species transmission occurred in the past, but remained undetected because the virus could not adapt to its new host or was not introduced into an environment where conditions for efficient and rapid spread were present. Today, humans are still exposed to a wide diversity of SIV through hunting and butchering NHP for bushmeat<sup>22,68,69,93-97</sup>. The recent discovery of HIV-1 P in 2009 in two Cameroonian patients, a new HIV-2 in 2013 in Ivory Coast, new HTLV-1 and HTLV-3 variants as well as SFV infections in humans in Central Africa, clearly illustrate that our knowledge of genetic diversity and cross-species transmissions of simian retroviruses are still incomplete<sup>24,32,65,66,72,84,87,89</sup>. Cross-species transmission of other SIV from mangabeys, chimpanzees, gorillas, or other NHP species has to be considered, given the high prevalence of SIV in some primate populations and species (> 50%). The increasing presence of humans in tropical forest areas (logging and mining industries) and subsequent increasing contact and exposure to SIV-infected primates through hunting and bushmeat preparation, together with the socioeconomic and demographic factors today, are in favor of global expansion with new viral infections.

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