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Genetic Diversity of Lentiviruses in Non-Human Primates

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Abstract

Simian immunodeficiency viruses (SIVs) can be found naturally in a large number of African primate species; already 31 species have been identified with serological evidence of SIV infection, and in 21 this was confirmed by partial or full-length genome sequencing. So far, the primate lentiviruses, for which full-length genome sequences are available, fall into six approximately equidistant major lineages and are represented by, 1) the HIV-1/SIVcpz lineage, 2) the HIV-2/SIVsm lineage, 3) the SIVagm lineage from African green monkeys, 4) the SIVsyk lineage from Sykes' monkeys, 5) the SIVlhoest lineage including viruses from mandrills, l'Hoest and sun-tailed monkeys and, 6) the SIVcol lineage from a colobus monkey. SIVs from other African primates have been partially characterised, but the exact phylogenetic relationship between these SIVs and other nonhuman primate lentiviruses requires the analysis of the complete genome. Most of the SIV-positive primates are the natural hosts of these viruses, and do not seem to develop any clinical symptoms. Nevertheless, if cross-species transmission occurs, the virus may be pathogenic for the new host. The two major viral types infecting humans, HIV-1 and HIV-2, represent zoonotic transmissions from chimpanzees *(Pan troglodytes)* and sooty mangabeys *(Cercocebus atys)* respectively. Therefore, the identification and characterisation of new SIV strains are important to better understand the origins of HIV-1 and-2 and to assess the potential risk for additional lentiviruses into the human population.

Key words

SIV. Lentiviruses. Phylogeny.

Introduction

Simian immunodeficiency viruses (SIV) and the closely related human immunodeficiency viruses (HIV-1 and HIV-2) belong to the lentivirus subfamily of retroviruses. It is now clear that the SIVs are a large group of viruses that can be found naturally in an extensive number of African primate species belonging to Cercopithecinae, Colobinae and great apes[1,2]. Most of the SIV positive primates are the natural hosts of these viruses, and do not seem to develop any clinical symptoms. The two major viral types infecting humans, HIV-1 and HIV-2, represent zoonotic transmissions from two different sources of non-human primates, namely chimpanzees *(Pan troglodytes)*[3] and sooty mangabeys *(Cercocebus atys)*[4,5], respectively. Therefore, the identification and characterisation of new SIV strains are important to better understand the origins of HIV-1 and-2 and to assess the potential risk for additional lentiviruses into the human population. Serological evidence for SIV infection has now been reported for 30 different species of African non-human pri-

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Table 1. *African non-human primates infected with SIV.*

Genus	Species	Common name	SIV		Geographic distribution in Africa	Ref
Chlorocebus	*aethiops*	grivet monkey	SIVagmGri	sequence(full-length)	south	17
	pygerythrus	vervet monkey	SIVagmVer	sequence(full-length)	east	18
	sabaeus	green monkey	SIVagmSab	sequence(full-length)	west	20
	tantalus	tantalus monkey	SIVagmTan	sequence(full-length)	central	14,19,20
Cercopithecus	*l'hoesti*	l'hoest monkey	SIVlhoest	sequence(full-length)	west central	28
	solatus	sun-tailed monkey	SIVsun	sequence(full-length)	central (Congo)	29
	diana	diana monkey	?	serology	central(Congo)	59
	neglectus	de brazza monkey	SIVdeb	sequence(partial)	central	33,34
	mona	mona monkey	SIVmon	sequence(partial)	west-central (Niger Delta)	33,34
	wolfi	wolfi monkey	?	serology	central (Congo)	60
	pogonias	crowned monkey	?	serology	west central	34
	hamlyni	owl-faced monkey	?	serology	central (western rift)	60
	nictitans	grey spot nosed monkey	SIVgsn	sequence(partial)	west central	34
	albogularis	sykes monkey	SIVsyk	sequence(full-length)	east	25
	mitis	blue monkey	SIVblu	sequence(partial)	east	33
	cephus	cephus monkey	?	serology	west central	34,59
Cercocebus	*atys*	sooty mangabey	SIVsm	sequence(full-length)	west	5
	torquatus	red-cap mangabey	SIVrcm	sequence(partial)	west central (Nigeria /Cameroon)	30
	agilis	agile magabey	?	serology	west central	34
Lophocebus	*albigena*	grey cheeked mangabey	?	serology	central	34
Allenopithecus	*nigroviridis*	Allen's swamp monkey	?	serology	central	59
Miopithecus	*talapoin*	talapoin monkey	SIVtal	sequence (partial)	west central	32
Erythrocebus	*patas*	patas monkey	SIVagmSab*	sequence (partial)	west to east	64
Colobus	*guereza*	guereza colobus	SIVcol	sequence (full-length)	central	2
Papio	*anubis*	olive baboon	?	serology	west to east	34
	cynocephalus	yellow	SIVagmVer*	sequence (partial)	south	61,62
	ursinus	chacma	SIVagmVer*	sequence (partial)	south	63
Mandrillus	*sphinx*	mandrill	SIVmnd-1/ SIVmnd-2	sequence (full-length)	west central (Gabon/ Cameroon)	27
	Leucophaeus	drill	SIVdrl	sequence (partial)	west central (Cameroon)	31
Pan	*troglodytes*	chimpanzee	SIVcpz	sequence(full-length)	west to east	3,6,9,10

Represent cross-species transmissions with SIVagm from the sympatric African green monkey populations)

mates, and this is confirmed by sequence analysis for 21 species (Table 1).

Phylogeny of primate lentiviruses

So far, the primate lentiviruses for which full-length genome sequences are available fall into six major lineages, which are based on comparisons of their sequences and the functional similarity of their genes[2] (Fig. 1). These six lineages are approximately equidistant and are represented by:

– SIVcpz from chimpanzees *(Pan troglodytes)* together with HIV-1[3,6-10],

– SIVsm from sooty mangabeys *(Cercocebus atys)* together with HIV-2[4,5,11-13],

– SIVagm from four species of African green monkeys (members of the *Chlorocebus genus*)[14-23],

– SIVsyk from Sykes' monkeys (Cercopithecus *mitis albogularis*)[24,25],

– SIVmnd from a mandrill *(Mandrillus sphinx)*[26,27] together with SIVlhoest from l'Hoest monkeys *(Cercopithecus lhoesti)*[28], and SIVsun from Sun-tailed monkeys *(Cercopithecus solatus)*[29]

– SIVcol from a colobus monkey *(Colobus guereza)*[2].

SIVs from other non-human primates from Africa have been partially characterised, mainly in the *pol* gene[30-34]. They may represent additional distinct lineages, but analysis of the complete genome will be necessary to establish the exact phylogenetic relationship between these SIVs and other non-human primate lentiviruses.

Genomic organization

The common structure for primate lentiviruses is *LTR-gag-pol-vif-vpr-tat-rev-env-nef-LTR*. This basic structure is observed in the SIVagm, SIVsyk, SIVlhoest and SIVcol lineages[2,17-20,23,28,29]. The viruses belonging to the SIVcpz and SIVsm lineages each have one additional gene; a *vpx* gene upstream of the *vpr* gene for SIVsm and HIV-2[36] and a *vpu* gene upstream of *vpr* and overlapping *env* in SIVcpz from chimpanzees and HIV-1[3,6,9,10]. It will be interesting to see whether these supplementary genes can be present in other primate lentiviruses. Indeed, the only SIVs actually known to have been transmitted to humans carried either a *vpx* or a *vpu* gene.

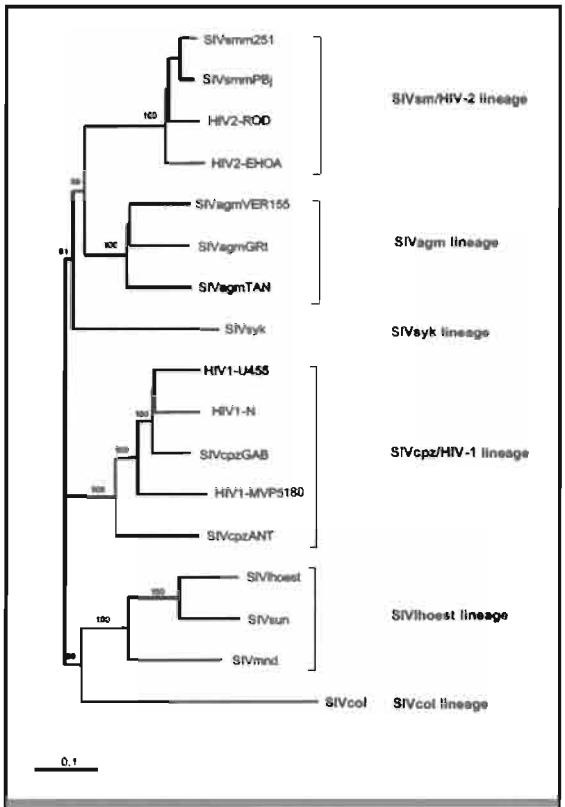

Fig. 1: *Phylogeny of primate lentiviruses. This tree was derived by neighbour-joining analysis from a concatenated Gag-Pol-Vif-Env-Nef protein alignment. The reliability was estimated by 1,000 bootstrap replicates; only values above 75% are shown. Branch lengths are drawn to scale, with the bar indicating 0.1 amino acid replacement per site.*

The SIVcpz/HIV-1 lineage

The only SIVs that are closely related to HIV-1 were isolated from chimpanzees. Chimpanzees *(Pan troglodytes)* can be divided into four subspecies[36,37]: *P.t. verus* from west Africa, *P.t. troglodytes* from west central Africa, *P.t. schweinfurthii* from east Africa and *P.t. vellerosus* in Nigeria. Natural SIVcpz infection has been identified only in the west and east African subspecies. The west African animals were from Gabon, Cameroon and one was an animal living in captivity in the US[3,7,8,10]. Only for one of the two east African chimpanzees, the virus (SIVcpz-ant) was genetically characterised. The SIVcpz-ant strain was obtained from a wild, caught animal of Congolese origin, intercepted by Belgian customs officers after illegal export from Kinshasa[9]. The SIVcpz-ant sequence represents the most divergent strain from the HIV-1/SIVcpz-lineage, while all the other SIVcpz strains form a distinct cluster in the HIV-1/SIVcpz lineage (Fig. 2). Since the sequences from west and east African chimpanzees form distinct phylogenetic lineages, it was assumed that the SIVcpz viruses have a common ancestor in chimpanzees and evolved in parallel with their hosts. Recently, another SIVcpz-infected east African chimpanzee was identified in the wild using non-invasive screening assays[38]. Genetic characterisation of this new virus will allow confirming or refuting of this theory.

Up to now, no SIVcpz infection of *P.t. verus* has been reported and the only reported SIVcpz (SIVcpz-cam4) infection of *P.t. vellerosus* was in an animal infected by his cage-mate, which was a naturally infected P.t.troglodytes (SIVcpz-cam3)[10].

HIV-1 isolates have been classified into 3 distinct groups, M, N and O, with the predominant M group consisting of subtypes (A-K)[39], and all three groups of HIV-1 are more closely related to the SIVcpz strains from west central chimpanzees. Therefore, the cross-species transmissions giving rise to HIV-1 most probably all occurred in west central Africa from P.t. troglodytes subspecies[3]. In addition, the greatest diversity of group M strains is in west Equatorial Africa, this being consistent with the region of group M origin[40-42], this region corresponds to the area inhabited by West Central chimpanzees. Moreover, chimpanzee and group-N human viruses from Cameroon form a unique sub cluster in phylogenetic trees of *env* and *nef* regions (Fig. 2)[3,10]. The question now remains, when and how the transmission from chimpanzees to humans occurred. Two independent studies, using different methods, recently showed that the HIV-1 subtypes started to diverge in humans around 1930[43,44]. This means that the zoonotic transmission occurred before this period and the separation between HIV-1 and SIVcpz was calculated to have occurred around 1700[44]. How SIV could be transmitted to humans will be discussed below in this paper.

The SIVsm/SIVmac/HIV-2 lineage

HIV-2 was isolated from patients with acquired immune deficiency syndrome (AIDS) originating from west Africa. Molecular analyses revealed that HIV-2 was genetically related to SIV from macaques with lymphomas and immunodeficiency-associated disorders (similar to AIDS in humans)[45-47]. Soon after the identification of macaques with AIDS-like disease in primate centres, the molecular characterisation of a virus from healthy captive sooty mangabeys *(Cercocebus atys)*, SIVsm, revealed that it was closely related to HIV-2 and SIVs from macaques[5]. Since only few macaques in captivity and none in the wild in Asia, were found to be infected with SIV[48], it seems likely that SIVs from macaques resulted from transmissions of SIV from sooty mangabeys to macaques in captivity. This theory was confirmed by the fact that several reports showed that free-ranging and pet sooty mangabeys in their natural habitat in west Africa (Guinea-Bissau to Côte d'Ivoire) are indeed infected with SIVsm[11-13,50].

Similarly as for HIV-1 and SIVcpz, the close relationship between SIVsm and HIV-2 from humans suggested that SIV-infected sooty mangabeys in west Africa might be the natural source for HIV-2 infection in humans[5]. The various HIV-2 subtypes are not more closely related to each other than to SIVsm strains[4,11,12,50,51] and in a phylogenetic tree, SIVsm and HIV-2 sequences are interspersed and the geographic clustering between SIVsm and HIV-2 strains in Sierra Leone and Liberia has been demon-

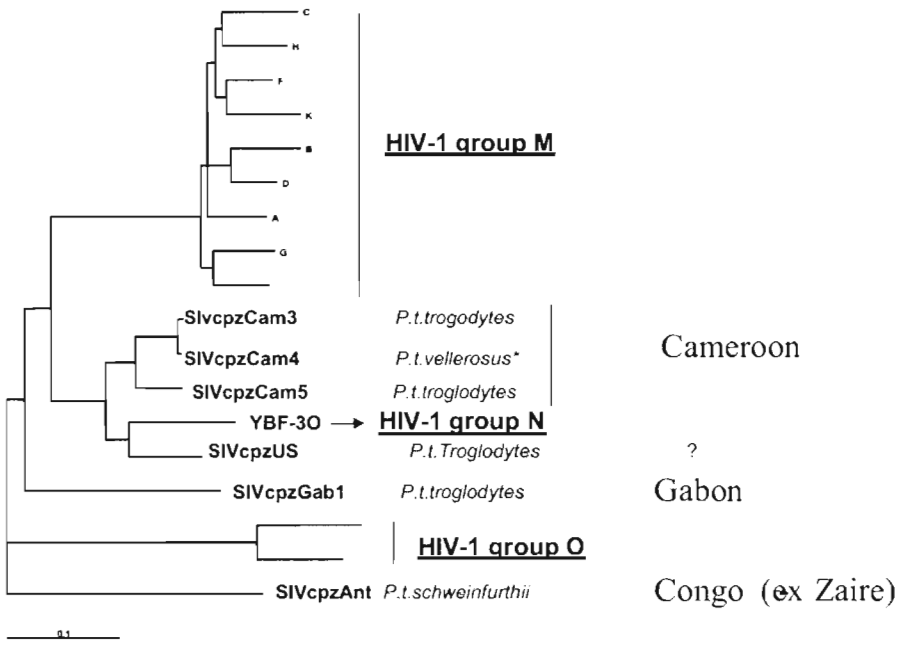

Fig. 2: *Phylogeny of the HIV-1/SIVcpz lineage. This tree was derived by neighbour-joining analysis of envelope nucleotide sequences. Horizontal branch lengths are drawn to scale.*
**Represents an inter-cage transmission from the SIVcpzCam-3 infected animal.*

strated (Fig. 3). Moreover, SIVsm has been shown to be transmissible to humans after accidental exposure to monkey blood[52].

The SIVagm lineage

African green monkeys have been recently classified as a separate new genus *(Chlorocebus)*, which is comprised of four species: grivet *(Chlorocebus aethiops)*, vervet *(Chlorocebus pygerythrus)*, tantalus *(Chlorocebus tantalus)*, and sabaeus *(Chlorocebus sabaeus)*. The 4 species are geographically separated; grivets live in east Africa but are restricted to Ethiopia and the Sudan, vervets can be found from east to south Africa, tantalus monkeys are prevalent in Central Africa and sabaeus monkeys are restricted to west Africa. Each of the four species carry their own species-specific SIV forming four distinct monophyletic clusters, which are more closely related to each other than to other SIVs (Fig. 4). These observations indicate that, similarly as for SIVcpz, the distinct forms of SIVagm may have evolved in parallel to their hosts[1].

However, SIVagm from sabaeus monkeys (SIVagmSab) are unusual because they have a mosaic genome structure. Parts of the genome (3' end of gag and 5 'end of pol) cluster with the SIVsm/HIV-2 lineage, whereas the rest of the genome groups with the SIVagm lineage[20]. This indicates that recombination between divergent SIVs occurred during the evolution of SIVagmSab, implying cross-species transmission of SIVs among simians. It has to be determined if all sabaeus monkeys in west Africa are infected with a similar mosaic virus.

High seroprevalences have been observed in the wild among the different African green monkey species[22,53,54].

The SIVsyk lineage

So far, only one full-length sequence of SIVsyk has been described and characterised[25]. Similar to African green monkeys, Sykes' monkeys *(Cercopithecus albogularis)* exhibit a high SIV seroprevalence[24].

The SIVlhoest lineage

This lineage includes viruses isolated from three different primate species, the l'hoest monkey *(Cercopithecus lhoesti)*, the sun-tailed monkey *(Cercopithecus solatus)*, and the mandrill *(Mandrillus sphinx)*. In the primate evolution, l'hoest and suntailed monkeys are closely related and belong to the same super-species, whereas mandrills have a different origin. The ranges of mandrills and sun-tailed monkeys overlap in west equatorial Africa, and l'hoest monkeys inhabit an area approximately 1,600 km to the east. The close relationship of SIVlhoest and SIVsun parallels the close relationship between their two host species (Fig. 1), and are an additional example of host-dependent evolution[28,29]. L'hoest monkeys are infected with SIV at quite high frequencies in the wild[55].

Since mandrills are only distantly related to the l'hoest super-species, this suggests that the origin of the SIVmnd-GB-1 strain is possibly the result of a cross-species transmission. In addition, recent data

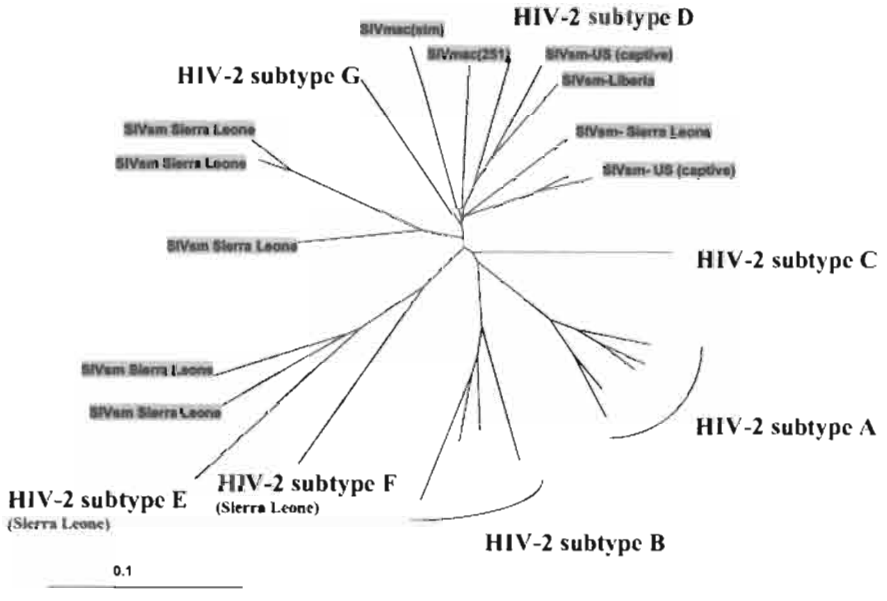

Fig. 3: *Subtype classification of HIV-2. Un-rooted phylogenetic tree based on partial gag nucleotide sequences from HIV-2 and SIVsm/mac sequences.*

suggest that mandrills are infected with at least two different SIVs. A highly divergent SIV (SIVmnd2) has recently been reported from mandrills[56] in north Gabon and southern Cameroon, whereas the SIVmnd-1 virus was isolated from a mandrill originating from central Gabon[26,27]. Characterisation of more SIVs from mandrills in different geographic locations will be necessary, to find out the exact origin of SIVs in mandrills.

The SIVcol lineage

During a recent sero-survey in Cameroon, 25 wild-born Colobus monkeys *(Colobus guereza)* were screened and 7 were identified with HIV/SIV cross-reactive antibodies. The full-length genome was sequenced for one of these viruses, named SIVcol. Genetic and phylogenetic analyses confirmed that SIVcol is genetically distinct from all other known previously characterised SIV/HIV isolates and clusters independently, forming a novel lineage, the sixth in the current classification[2]. Cercopithecidae monkeys (Old World monkeys) are subdivided into two subfamilies, the Colobinae and the Cercopithecinae[57] and until recently, all *Cercopithecidae* monkeys from which lentiviruses have been isolated belonged to the Cercopithecinae subfamily. SIVcol from Colobus monkeys *(Colobus guereza)* is the first primate lentivirus identified in the Colobinae subfamily and the divergence of SIVcol may reflect divergence of the host lineage. The fact that SIVcol is very divergent from all known SIVs also suggests that SIVcol in Guereza Colobus monkeys is not the result of a recent cross-species transmission. The presence of this virus in this species could be very ancient (although we don't know the specific rate of evolution for this virus), and the divergence of SIVcol may reflect divergence of the host lineage. Colobids split off from other Old World monkeys at least 11 million years ago[58] so the screening of other Colobus species, including Asian Colobus monkeys, will help to clarify whether, i) the common ancestor of SIV was already present in the common ancestor of the Cercopithecidae family, or ii) a cross-species transmission occurred between Cercopithecinae and Colobinae, or from a yet unidentified species. Colobus monkeys share habitats with Cercopithecus species and mangabeys, therefore an exchange of ancestral SIVs between these species could have been possible in the past.

Partially characterized primate lentiviruses

SIVrcm was isolated from the red-capped mangabey *(Cercocebus torquatus)*, which are closely related to sooty mangabeys. However, based on partial sequences, SIVrcm is not closely related to SIVsm and seems to have a mosaic genome[30].

Mandrills *(Mandrillus sphinx)* and drills *(Mandrillus leucophaeus)* are closely related primate species, but SIVdrl was not found to be closely related to SIVmnd-1[31]. The genetic characterisation of the full length genome sequence from the drill virus and the comparison with the SIVmnd-GB1 and SIVmnd-2 viruses will help to elucidate the origin SIV in mandrills and drills.

Talapoin monkeys *(Miopithecus talapoin)* are infected with SIVtal. A small fragment of *pol* SIVtal was found to be most closely related to SIVsyk, albeit with a quite significant distance[32].

Partial *pol* sequences have also been reported from de Brazza monkeys *(Cercopithecus neglectus)* and mona monkeys *(Cercopithecus mona)* from

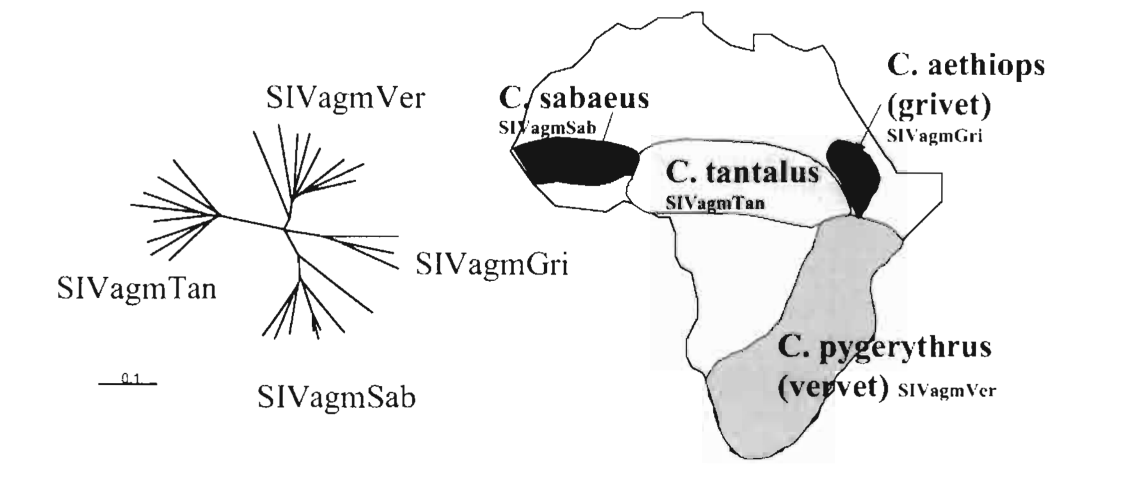

Fig. 3: *Subtype classification of HIV-2. Un-rooted phylogenetic tree based on partial gag nucleotide sequences from HIV-2 and SIVsm/mac sequences.*

Cameroon as well as from Blue monkeys *(Cercopithecus mitis)* from Kenya. Based on these partial sequences, they seem to cluster with the SIVsyk lineage, but again full-length genome sequencing will be necessary to define their exact phylogenetic position in the primate lentivirus family[33]. Partial sequences were also obtained from putty nosed monkeys *(Cercopithecus nictitans)*[34].

Serological evidence for other primate species infected with SIV

The viruses identified to date probably only represent a small part of the lentiviruses in African non-human primates. In fact, serological surveys have indicated that numerous species may harbour lentiviruses, including Allen's swamp monkey *(Allenopithecus nigrovidis)*, Diana monkey *(Cercopithecus diana)*, Moustached monkey *(Cercopithecus cephus)*, Hamlyn's or owl-faced monkey *(Cercopithecus hamlyni)*, Wolf's mona monkey *(Cercopithecus wolfi)*, crowned monkeys *(Cercopithecus pogonias)*, agile mangabeys *(Cercocebus agilis)*, and grey cheeked mangabeys *(Lophocebus albigena)*[1,34,59,60].

Simian to simian cross-species transmission

Although host-specific evolution of SIVs is often observed, examples of simian-to-simian cross-species transmission in the wild have also been documented. A yellow baboon *(Papio hamadryas cynocephalus)* in Tanzania[61,62], a chacma baboon *(Papio ursinus)* in South Africa[63], and a patas monkey *(Erythrocebus patas)* in Senegal[64], were infected by viruses derived from the local sympatric species of African green monkeys. Similarly, a white crowned mangabey in Kenya, became infected with an SIVagm virus in captivity[65].

The observation of recombinant SIVs in sabeus monkeys, red cap mangabeys, and SIVmnd-2 are all additional arguments for the occurrence of simian-to-simian cross-species transmission. This means that super-infection with distant related viruses can occur and can lead to the recombination of different SIVs resulting in the emergence of new variants.

Exposure of humans to simian immunodeficiency viruses in west Central Africa

Possible routes of transmissions are direct exposure to primate blood, by hunting or handling bush-meat and from pet animals through bites and contact with faeces and urine. The risk for cross-species transmission from SIVs to humans is highest among individuals involved in hunting and butchering of primate carcasses, as well as in individuals in contact with pet animals. Bush-meat hunting is not limited to chimpanzees and mangabeys, the majority of non-human primates in the bush-meat trade are represented by multiple *Cercopithecus* species, *colobus* monkeys, mandrills, drills etc.[66,67].

Given that viruses from chimpanzees and sooty mangabeys have both crossed the species to humans on multiple occasions, the risk of ongoing zoonotic transfers has to be considered.

A recent study documented for the first time that humans are continuously exposed to a large variety of SIVs through contact with monkeys, either as pets or by handling bush-meat. Blood samples from more than 300 primates wild-born in Cameroon and representing 17 species were tested for antibodies cross-reacting with HIV-1/HIV-2. Cross-reactive antibodies were detected in 17.7% of the samples derived from 13 species and an additional 13.5% of the samples exhibited at least some degree of cross-reactivity. Amplification of a subgenomic fragment in *pol* confirmed that the majority of serologically cross-reactive samples were indeed derived from SIV infected primates[34].

Bush-meat hunting, to provide animal protein for the family and as a source of income, is a common

component of rural household economies in the Congo Basin, and more generally throughout sub-Saharan Africa, since a very long time period[67-70]. However the bush-meat trade has increased in the last decades, due to the expanding logging industry in certain central African countries and demand for bush-meat delicacies in cities. Thus the potential for human exposure to a wide range of different SIVs has increased substantially along with the conditions that facilitate their dissemination.

Public health implications

SIVs do not cause AIDS in their natural hosts, suggesting that these viruses have been associated and evolved with their hosts over an extended period of time. Nevertheless, if cross-species transmission occurs, the virus may be pathogenic for the new host. For example, SIV isolated from sooty mangabey monkeys (SIVsmm) causes AIDS when transmitted to a new host such as rhesus or pig-tailed macaques *(Macaca mulatta* or *nemestrina)*, which are not infected by SIV in their natural habitat[49]. Both groups of viruses giving rise to AIDS in humans appear to have resulted from several independent transmissions from non-human primate species[1]. As a result, AIDS emerged in the 1980's and has become established in the human population, representing one of the most important infectious diseases, especially in developing countries. HIV has already infected 40 million individuals and more than 70% of them live in sub-Saharan Africa[71].

One major public health implication is that these SIVs are not recognised by commercial HIV-1/HIV-2 screening assays. As a consequence, human infection with such variants can initially go unrecognised and lead to another epidemic. The ability of several SIVs to infect human PBMCs in vitro suggests that these viruses have the potential to infect human populations[7,13,28]. Identification of SIVs in wild primates will help to elucidate the origins and evolution of HIV infection in man, but more importantly they can serve as sentinels by signalling which pathogens may be a risk for humans.

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