Diversity and Evolution of Primate Lentiviruses

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INTRODUCTION

The human immunodeficiency viruses (HIV-1 and -2) together with the simian immunodeficiency viruses (SIV) comprise the primate lentivirus family. Since the isolation of the first SIV in 1985 [15], our knowledge of the diversity of these primate lentiviruses has continuously developed by the isolation and characterization of new SIV strains from additional species of African simians. It is now clear that the SIVs are a large group of viruses that can be found naturally in feral and domesticated African primates, such as guenons, mangabeys, mandrills, and chimpanzees; to indicate the species from which each SIV was isolated they are given a short suffix, such as SIVagm for the virus derived from African green monkeys. Most of these African primates are natural hosts for these viruses, but some infections are the result of recent cross-species transmissions. In those species that are natural hosts, the proportion of animals that are seropositive in the wild can be quite high [5, 33, 55, 60], and infected primates do not seem to develop any clinical symptoms [22, 51, 66]. The reasons for this lack of pathogenicity are still not well understood. However the lack of pathogenicity does not seem to be based on inherent properties of the virus, since for example Asian macaques inoculated with SIV from sooty mangabeys or African green monkeys can develop AIDS-like symptoms similar to those of humans after HIV infection [35, 59]. Because SIV is the most closely related lentivirus to HIV, SIV infection of monkeys has become the best animal model for studying the pathogenesis of, and efficacy of vaccines against, HIV infection in humans. In addition, the evaluation of new SIV strains is important to better understand the origins of HIV-1 and -2 and to assess the potential for additional lentiviruses to infect the human population.

PHYLOGENY OF PRIMATE LENTIVIRUSES

SIV infection has been detected in more than 20 different species of African primates, but examples of complete sequences of only 13 of these are available to date (Table 1). As shown in Fig. 1, these fully characterized SIVs can be classified into five distinct lineages based upon phylogenetic analyses of their sequences [37, 68, 70]. These five lineages are represented by (i) SIVcpz from chimpanzees (*Pan troglodytes*) [24, 40, 42, 64, 83], (ii) SIVsm from sooty mangabeys (*Cercocebus atys*) [11, 39, 56, 65, 66], (iii) SIVagm from four species of African green monkeys (recently re-named as the *Chlorocebus* genus) [2, 4, 16, 20, 21, 38, 43, 45, 58, 73], (iv) SIVsyk from Sykes' monkeys (*Cercopithecus albogularis*) [19, 36], and (v) SIVlhoest from L'Hoest monkeys (*Cercopithecus lhoesti*). These five lineages are approximately equidistant, differing from each other at about 40% of amino acid residues in the Pol protein.

Four of these major lineages (the exception being SIVsyk) are represented by multiple strains including isolates from two or more host species; the SIVs within one lineage cluster together with high bootstrap values (Fig. 1). From the evolutionary tree, it is evident that the distinction between HIV and SIV reflects only whether a virus is found in humans or some other species of primate and is not an accurate taxonomic classification since HIV-1 and HIV-2 are not each others' closest relatives. In fact, HIV-1 is closely related to lentiviruses from chimpanzees, while HIV-2 clusters with viruses infecting sooty mangabeys (Fig. 1). Thus, from these and other observations, it can be concluded that the human AIDS viruses have arisen quite recently through cross-species transmissions from these two other primates in Africa.

Table 1 Full length genome sequences of primate lentiviruses

Source	Strain/isolate	Accession#	Author	Reference
1. SIVcpz lineage (*Pan troglodytes* subspecies)				
P. t. troglodytes	SIVcpzGab1	X52154	Huet T (1990)	*Nature* **345**, 356
	SIVcpzUS	AF103818	Gao F (1999)	*Nature* **397**, 436
	SIVcpzCam3	AF115393	Corbet S (2000)	*J Virol* **74**, 529
P. t. schweinfurthii	SIVcpzAnt	U42720	Vanden Haesevelde M (1996)	*Virology* **221**, 346
2. SIVsm lineage (*Cercocebus atys* and *Macaca* species[a])				
C. atys	SIVsmH4	X14307	Hirsch V (1989)	*Nature* **339**, 389
	SIVsmE543	U72748	Hirsch V (1997)	*J Virol* **71**, 1608
	SIVsm9	M80194	Courgnaud V (1992)	*J Virol* **66**, 414
	SIVsmPBjA.4.41	M31325	Dewhurst S (1990)	*Nature* **345**, 636
	SIVsmPBj6.6	L09212	Novembre F (1993)	*J Virol* **67**, 2466
	SIVsmPGm	AF077017	Novembre F (1998)	*J Virol* **72**, 8841
M. mulatta	SIVmm239	M33262	Regier D (1990)	*ARHR* **6**, 1221
	SIVmm251	M19499	Franchini G (1987)	*Nature* **328**, 539
	SIVmm32H	D01065	Rud E (1994)	*J Gen Virol* **75**, 529
	SIVmm1A11	M76764	Luciw P (1992)	*ARHR* **8**, 395
	SIVmm142	M16403	Chakrabarti L (1987)	*Nature* **328**, 543
M. nemestrina	SIVmne8	M32741	Benveniste R (1990)	unpublished
	SIVmne027	U79412	Kimata J (1998)	*J Virol* **72**, 245
M. arctoides	SIVstm	M83293	Novembre F (1992)	*Virology* **186**, 783
3. SIVagm lineage (*Chlorocebus* species)				
C. pygerythrus	SIVagmVerTyo	X07805	Fukasawa M (1988)	*Nature* **333**, 457
	SIVagmVer155	M29975	Johnson P (1990)	*J Virol* **64**, 1086
	SIVagmVer3	M30931	Baier M (1990)	*Virology* **176**, 216
	SIVagmVer9063	L40990	Hirsch V (1995)	*J Virol* **69**, 955
C. aethiops	SIVagmGri677	M66437	Fomsgaard A (1991)	*Virology* **182**, 397
C. tantalus	SIVagmTan1	U58991	Soares M (1997)	*Virology* **228**, 394
C. sabaeus	SIVagmSab1C	U04005	Jin M (1994)	*EMBO J* **13**, 2935
4. SIVsyk lineage (*Cercopithecus albogularis*)				
C. albogularis	SIVsyk173	L06042	Hirsch V (1993)	*J Virol* **67**, 1517
5. SIVlhoest lineage (*Cercopithecus* species and *Mandrillus sphinx*)				
M. sphinx	SIVmndGB1	M27470	Tsujimoto H (1989)	*Nature* **341**, 539
C. lhoesti	SIVlhoest7	AF075269	Hirsch V (1999)	*J Virol* **73**, 1036
	SIVlhoest447	AF188114	Beer B (2000)	*J Virol*, in press
	SIVlhoest485	AF188115	Beer B (2000)	*J Virol*, in press
	SIVlhoest524	AF188116	Beer B (2000)	*J Virol*, in press
C. solatus	SIVsun1	AF131870	Beer B (1999)	*J Virol* **73**, 7734

[a] All isolates originate from sooty mangabeys and have been passaged intentionally or unintentionally to macaques. The first column indicates the species, in which the isolate was first identified. For passage history see *Human Retroviruses and AIDS 1998: A Compilation and Analysis of Nucleic Acid and Amino Acid Sequences*. Korber B, Kuiken CL, Foley B, Hahn B, McCutchan F, Mellors JW, and Sodroski J, Eds. Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, Los Alamos, NM. p. III-94. Brackets indicate that virus isolates/clones share a common passage history.

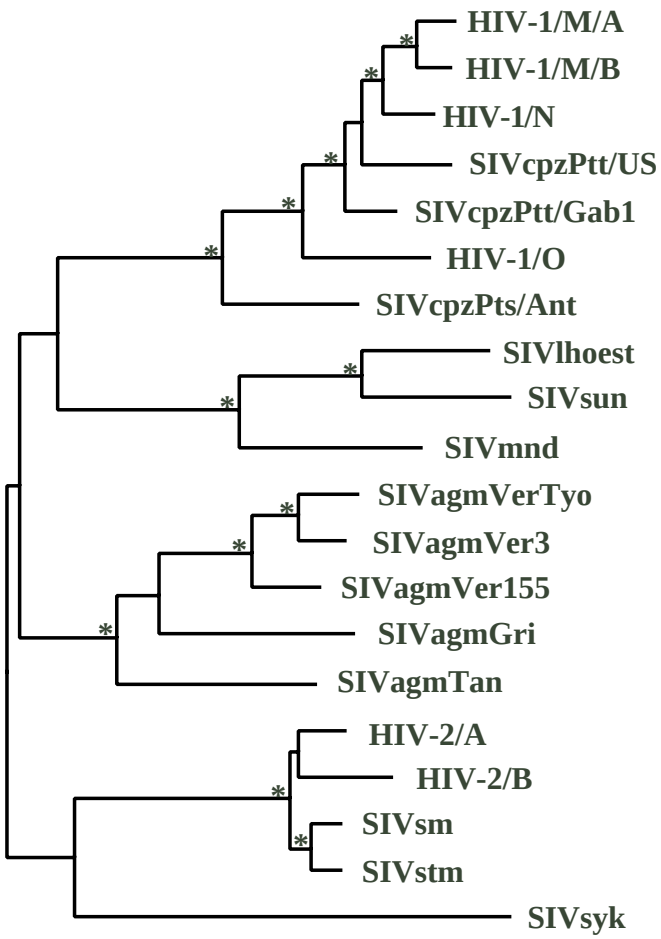

Figure 1: Evolutionary relationships among primate lentiviruses. The tree was derived by maximum likelihood analysis of Pol protein sequences. Horizontal branch lengths are drawn to scale. A similar tree was derived by neighbor-joining analysis; asterisks denote clades (to the right) supported in at least 80% of bootstrap replicates.

GENOMIC ORGANIZATION

The basic common, and presumably ancestral, structure for primate lentiviruses is LTR-*gag*-*pol*-*vif*-*vpr*-*tat*-*rev*-*env*-*nef*-LTR. These viral genes overlap in a number of regions (Fig. 2). The *tat* and *rev* genes consist of two exons (exon 2 lies within the *env* open reading frame) whereas the other six genes have only one exon. This basic structure applies to the members of the SIVagm, SIVsyk, and SIVlhoest lineages [3, 6, 20, 21, 34, 35, 38, 43, 45, 73]. The viruses belonging to the SIVcpz and SIVsm lineages each have one additional gene. SIVsm-related viruses, including HIV-2 and SIVmac, have a *vpx* gene upstream of the *vpr* gene [47]. The deduced Vpx protein shares sequence similarity with Vpr, and therefore could have been arisen through a tandem gene duplication [78], although phylogenetic analyses suggest that *vpx* is more likely to have been acquired by nonhomologous recombination between different SIVs [69]. The *vpu* gene occurs upstream of, and overlapping, *env* in SIVcpz from chimpanzees and HIV-1 [24, 40, 76, 83]. A *vpu* gene has not been found in the genomes of other SIVs, although the extent of divergence of the Vpu protein even among SIVcpz [83] is so great as to indicate that *vpu* homologues elsewhere would be difficult to recognize on the basis of sequence similarity. The origin of *vpu* has not been elucidated.

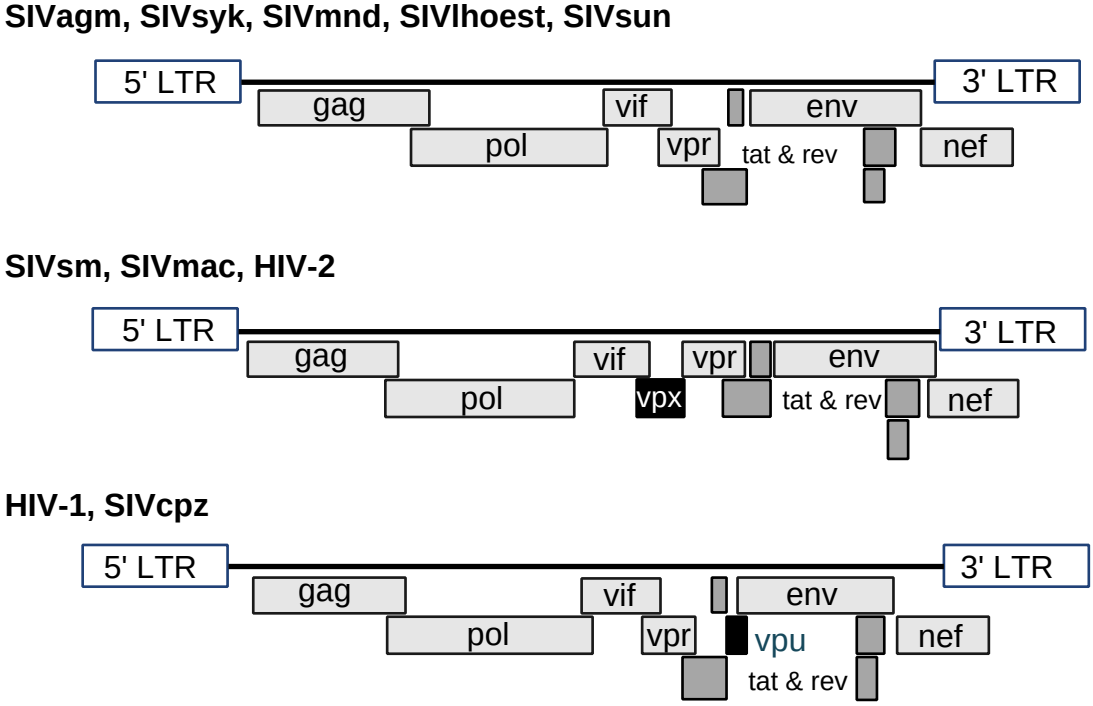

Figure 2: Genomic organization of the primate lentivirus lineages.

PRIMATE EVOLUTION

To understand the evolution of the SIVs, and in particular to ascertain whether SIVs have been evolving in parallel with their hosts for a long period of time, or whether there have been other instances of cross-species transmission (between non-human primates), it is necessary to consider the phylogenetic relationships among those primate hosts (Fig. 3). Within the primate evolutionary tree, apes such as humans and chimpanzees are highly divergent from the Old World monkeys, which include all the other species from which primate lentiviruses have been isolated. Furthermore, within the Old World monkeys, Sykes' and L'Hoest monkeys (both classified in the genus *Cercopithecus*) and African green monkeys (the genus *Chlorocebus*) are much more closely related to each other than to mangabeys (*Cercocebus* spp.). Thus, the approximate equidistance among the five major lineages of SIV does not match the relationships among their hosts. In addition, Asian species of primates such as macaques, as well as some African species such as baboons of the genus *Papio*, do not appear to be naturally infected with their own species-specific SIV. These observations imply that the last common ancestor of the catarrhines (Old World monkeys and apes) around 25 million years ago was not infected by SIV, but that one of these primate species became infected by an ancestral lentivirus from a non-primate source at a later time point. In the last two decades, lentiviruses have been isolated from various other orders of mammals [29, 61, 67, 74, 75], but none of those characterized is specifically closely related to the primate viruses. Once SIV was established in the primate population, simian-to-simian cross-species transmissions occurred, on the deeper branches within the SIV tree.

THE SIVcpz/HIV-1 LINEAGE

The only examples of SIV that are closely related to HIV-1 come from chimpanzees (Fig. 1). Since the vast majority of AIDS cases worldwide are due to infection with HIV-1, sequences of vastly

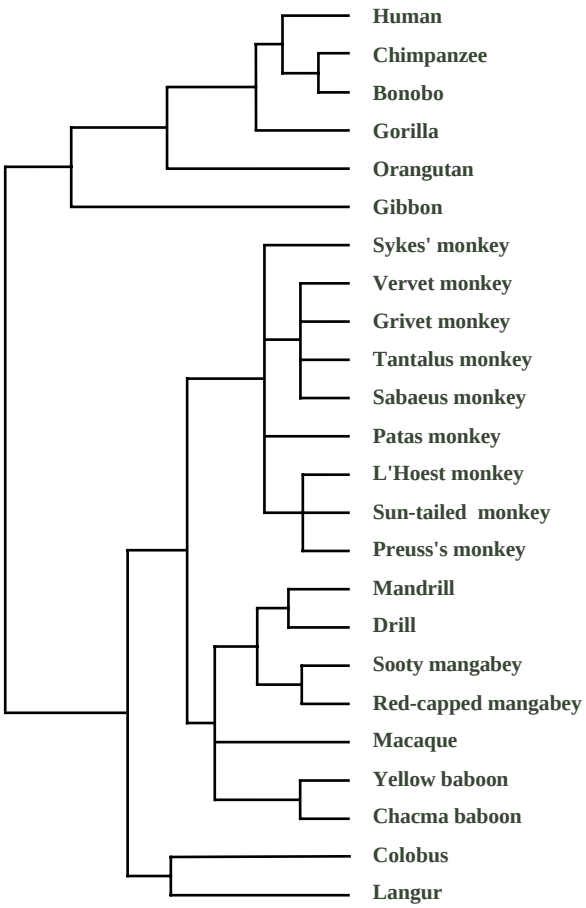

Figure 3: Evolutionary relationships among catarrhine primates (Old World monkeys and apes). The tree is schematic only, having been synthesized from a variety of sources including analyses of genetic and morphological markers: it summarizes what appears to be the consensus of views on relationships among species, but branch lengths are at best approximate. Major sources: references [17, 27, 31, 81].

more isolates of HIV-1 have been determined than of any other primate lentivirus. In contrast, rather few examples of SIVcpz have been characterized as yet. Two wild-caught chimpanzees from Gabon were first reported to be seropositive for HIV-1 antibodies more than 10 years ago [64]. A full-length genome sequence was characterized for one (SIVcpzGab1) [40], but only a 280 bp *pol* fragment for the other (SIVcpzGab2) [42]. A third isolate, SIVcpzAnt, was obtained from a chimpanzee wild-caught in the Democratic Republic of Congo (formerly Zaire) [63, 83]. Only within the last year have four more isolates been reported, one from a captive animal in the United States that had been imported from Africa as a juvenile [24], and three from chimpanzees in Cameroon [14]. In light of recent genetic evidence to support the division of chimpanzees into four distinct subspecies [23, 57], all of these animals have, in some cases retrospectively, been characterized at the mitochondrial DNA level. As expected, the two animals from Gabon, and two of those from Cameroon, were found to belong to the central African subspecies, *Pan troglodytes troglodytes*, while the chimpanzee from the Democratic Republic of Congo was a member of the East African subspecies *P. t. schweinfurthii* [24]. The animal from the US was found to be another *P. t. troglodytes* [24], while the third chimpanzee from Cameroon belonged to the Nigerian subspecies, *P. t. vellerosus* [14].

These subspecies assignments are of particular interest in interpreting the phylogenetic relationships among the SIVcpz isolates, and the relationship between SIVcpz and HIV-1 (Fig. 4). First, since it was first characterized and still to this date, SIVcpzAnt has been recognized as being highly divergent from all other SIVcpz. Since SIVcpzAnt is the only isolate from *P. t. schweinfurthii*, this

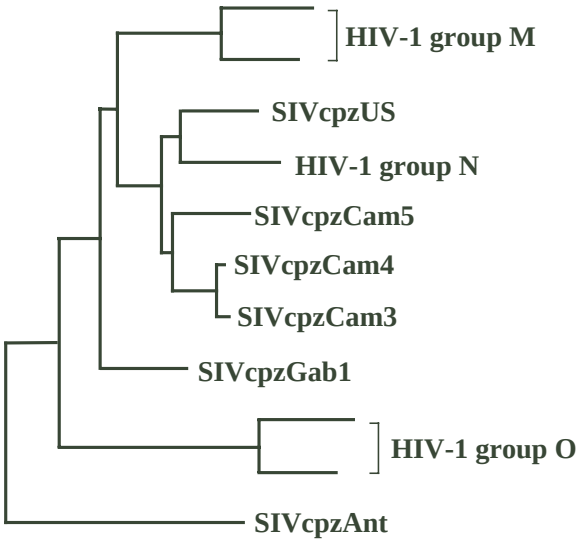

Figure 4: Evolutionary relationships among members of the SIVcpz/HIV-1 lineage. The tree was derived by maximum likelihood analysis of Env protein sequences. Horizontal branch lengths are drawn to scale. Adapted from [30].

could be interpreted as the result of an ancient split between the viruses infecting different subspecies of chimpanzee [24], similar to the divergence among clades of SIV infecting different species of African green monkeys (see below). In contrast, the isolate from *P. t. vellerosus* (SIVcpzCam4) is extremely closely related to one of the isolates from *P. t. troglodytes* (SIVcpzCam3), obtained from an animal at the same location. This level of identity is indicative of epidemiological linkage. This suggests that the *P. t. vellerosus* animal most likely became infected in captivity, and leaves open the question of whether *P. t. vellerosus*, as well as the fourth subspecies, the West African chimpanzee *P. t. verus*, are naturally infected with SIVcpz in the wild.

In the past, the apparently low prevalence of SIV infection in chimpanzees, as well as other factors including the high degree of divergence between SIVcpzAnt and other isolates, had cast doubt on whether chimpanzees are the natural reservoir for this group of lentiviruses. The possibility existed that both humans and chimpanzees had acquired these viruses from some other, unidentified, species of African primate. However, the recent increase in the number of characterized SIVcpz isolates, together with the information about the subspecies from which they were isolated, and considerations about the geographical origins of SIVcpz and HIV-1, have all combined to indicate that chimpanzees have indeed been the proximal source of HIV-1 [14, 24]. On the basis of phylogenetic relationships, HIV-1 isolates have been classified into three distinct clades, groups M, N and O ([71]; see also the article by Robertson *et al*., in this volume). In comparisons involving SIVcpz, the three groups of HIV-1 are not each others' closest relatives, and so they must each have arisen from a separate cross-species transmission event [24, 71]. All three groups of HIV-1 are more closely related to the SIVcpz isolates from *P. t. troglodytes* than to that from *P. t. schweinfurthii* (Fig. 4), indicating that the former subspecies, and not the latter, has been the source of HIV-1 [14, 24]. This is consistent with the geographical origins of the HIV-1 groups. The *P. t. troglodytes* subspecies inhabits Cameroon, Gabon and surrounding countries in west equatorial Africa: group N has only so far been reported in that region, group O is largely restricted to the same area, and while group M has achieved global distribution, the greatest diversity of group M subtypes is found in west equatorial Africa.

THE SIVsm/SIVmac/HIV-2 LINEAGE

The second human AIDS virus, HIV-2, has been found to be closely related to SIVs isolated from macaques and sooty mangabeys. First evidence for a virus of this lineage appeared in the early 1980s when an unusual clustering of lymphomas and immunodeficiency-associated disorders (similar to AIDS

in humans) was noted in a colony of captive rhesus macaques (*Macaca mulatta*) at the New England Regional Primate Research Center [41, 53, 54]. These observations led to the isolation of a T-cell tropic retrovirus, initially called STLV-III (now re-named SIVmac or SIVmm), which was shown to be antigenically related to HTLV-III (now called HIV-1) [46]. Subsequently, SIV was isolated from other macaque species. At the Washington Regional Primate Research Center, SIVmne was recovered from stored lymph node tissue of a pig-tailed macaque (*Macaca nemestrina*) that died of lymphoma in 1982 [7]; and at the California Regional Primate Research Center, SIVstm was isolated from frozen tissues of a stump-tailed macaque (*Macaca arctoides*) that had died of lymphoma and AIDS-like symptoms in the mid-1970s [49]. In 1986, a second human AIDS virus, named 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 [12].

However, very few macaques in captivity, and none in the wild in Asia, were found to be infected with SIV [84]. The natural origin of this form of SIV remained unresolved for several years. Then, molecular characterization of a virus from captive sooty mangabeys (*Cercocebus atys*), designated SIVsm, revealed that it was closely related to HIV-2 and SIVs from macaques [39]. In subsequent years, SIVsm strains were isolated from free-ranging and pet sooty mangabeys in their natural habitat in West Africa (Guinea-Bissau to Ivory Coast) [10, 11, 56]. Thus, it seems likely that SIVmm, SIVmne and SIVstm resulted from unintentional transmissions of SIV from sooty mangabeys to macaques in captivity.

The close relationship between SIVsm and HIV-2 from humans suggested that feral SIV-infected sooty mangabeys in West Africa might be the natural source for HIV-2 infection in humans [39]. In the last decade, several lines of supporting evidence for this epidemiological link have been provided [9–11, 25, 26, 56]. HIV-2 is a diverse group of viruses consisting of six different clades, termed subtypes A–F [9, 25]. Several of the HIV-2 subtypes have only been found in West Africa, in countries within the range of free-living sooty mangabeys. Furthermore, strains of SIVsm from different sooty mangabeys are known to be highly diverse, differing by up to 19% in *gag* nucleotide sequences [10, 11, 56]. Importantly, the various HIV-2 subtypes are not more closely related to one another than to SIVsm strains [11]. Instead, the HIV-2 and SIVsm lineages are phylogenetically interspersed (Fig. 5). Additionally, geographic clustering between SIVsm and HIV-2 strains in Sierra Leone and Liberia has been demonstrated. This indicates that the different clades of HIV-2 cannot all be due to a single mangabey-to-human transmission but must be the result of multiple independent cross-species transmissions of SIVsm into the human population. The observation of cross-species transmission of SIVsm is not surprising as sooty mangabeys are often kept as pets and used for food in West Africa [56]. Moreover, SIVsm has been shown to be transmissible to humans after accidental exposure to monkey blood [48].

THE SIVagm LINEAGE

Among feral primates that are known to be infected with SIV the African green monkeys are the most numerous, most geographically dispersed, and the most commonly infected [1, 2, 33, 38, 58, 60]. African green monkeys are dispersed over most of sub-Saharan Africa and have been classified as a separate genus (*Chlorocebus*) which is comprised of four species [52]: grivet (*Chlorocebus aethiops*), vervet (*Chlorocebus pygerythrus*), tantalus (*Chlorocebus tantalus*), and sabaeus (*Chlorocebus sabaeus*). These four species are distinguishable on the basis of phenotypic and genotypic markers and have different geographic ranges. Grivets live in 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.

Initially, SIVs from AGMs were described as one virus group with a novel and extremely high degree of genetic diversity [4, 45]. Later it was found that the four species of African green monkeys each

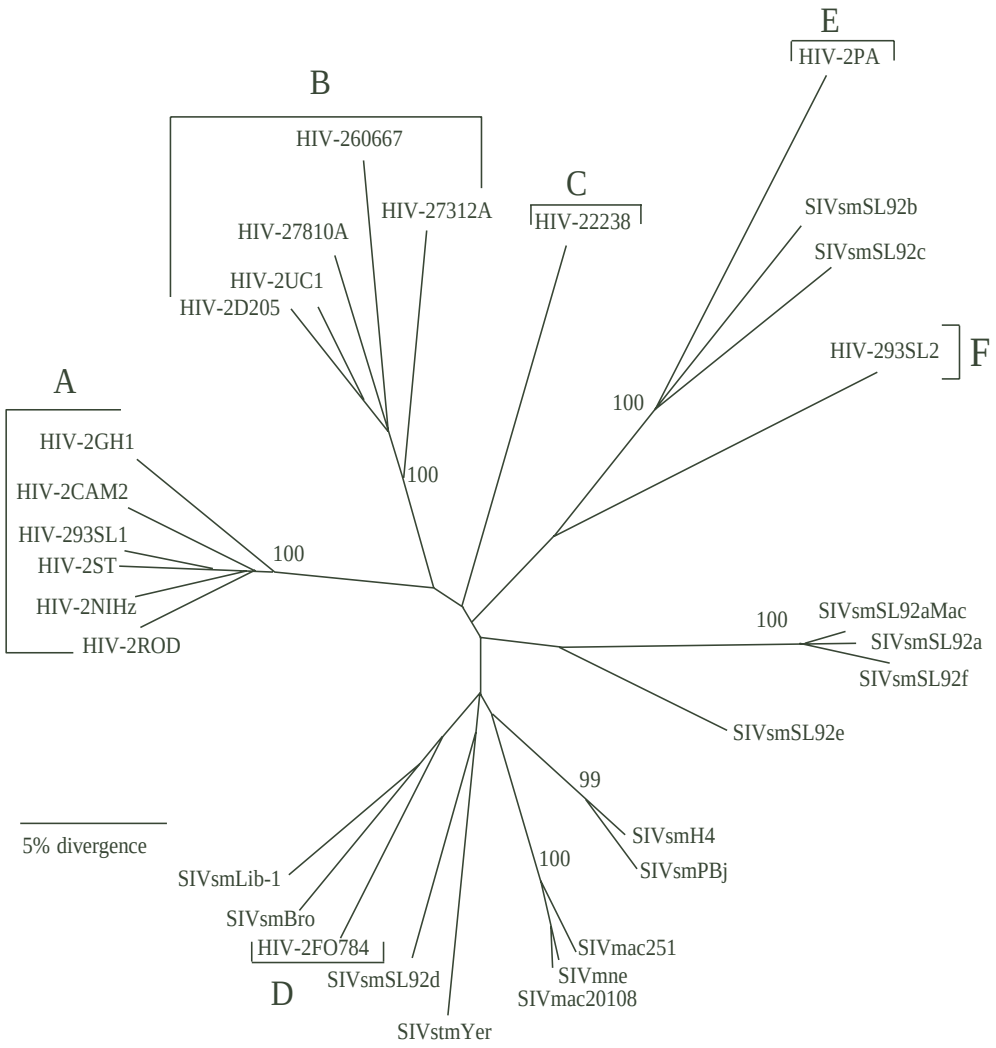

Figure 5: Evolutionary relationships among members of the SIVsm/SIVmac/HIV-2 lineage. The (unrooted) tree was derived by neighbor-joining analysis of partial *gag* nucleotide sequences. Branch lengths are drawn to scale, and percentage bootstrap values greater than 50% are shown. Adapted from reference [9]; kindly provided by Dr. P. A. Marx.

carry their own species-specific SIV indicating that the distinct forms of SIVagm may have evolved in parallel to their hosts. According to their host species, the SIVagm isolates have been named SIVagmVer, SIVagmGri, SIVagmSab, and SIVagmTan [2, 4, 16, 20, 21, 38, 43, 45, 58, 73]. SIVagmVer is the most extensively characterized group and many molecular clones have been generated including SIVagmVer3, SIVagmVer9063, SIVagmVer155, and SIVagmVerTyo (Table 1) [3, 21, 35, 45]. There is as much as 20% divergence in the Pol protein among SIVagmVer isolates [35] and 30% divergence in the Gag protein between SIVagmGri-1 and SIVagmVer155 [45, 73]. SIVagm from sabaeus monkeys (SIVagmSab) is unusual because it was found to 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 [43]. This indicates that recombination between divergent SIVs occurred during the evolution of SIVagmSab, and also implies that cross-species transmission among simians provided the opportunity for this recombination to occur. The two viral lineages involved, SIVagmSab and SIVsm, both infect monkeys from West Africa. The hybrid virus has been successful in that it is the only form of SIV that has been found among sabaeus monkeys.

Sporadic instances of SIVagm-like viruses have been reported from species other than African green monkeys, apparently reflecting recent simian-to-simian cross-species transmission in the wild. For example, two (out of 279 tested) wild-living yellow baboons (*Papio hamadryas cynocephalus*) from an area of Tanzania also inhabited by vervets were reported to harbor antibodies reactive with a SIVagm-like antigen [50]. It was later demonstrated that a virus isolated from one of these animals clustered within the vervet viruses in *gag* and *env* phylogenies [44]. Similarly, a chacma baboon (*Papio ursinus*) from South Africa was found to be infected with a virus strain of SIVagm most closely related to SIV from South African vervets. [82]. In another study, a wild-living patas monkey (*Erythrocebus patas*) in Senegal was found to be infected with a strain of SIVagm most closely related to those from sympatric sabaeus monkeys [8]. Additionally, a captive white-crowned mangabey (*Cercocebus lunulatus*) has been found to be infected with virus closely related to SIVagm from a vervet [77]. This transmission probably occurred in captivity because white-crowned mangabeys are indigenous to West Africa, where sabaeus monkeys are the local species of African green monkeys.

THE SIVsyk LINEAGE

Similar to African green monkeys, Sykes' monkeys (*Cercopithecus albogularis*) exhibit a high rate of SIV seroprevalence [19]. So far, only one full-length molecular clone of SIVsyk has been described and characterized [36], and no closely related viruses have been found in any other species. In contrast to the SIV strains from the other four lineages, SIVsyk has a very restricted host cell tropism *in vitro*, because it preferentially replicates in CD4+ enriched peripheral blood mononuclear cells (PBMC) from Sykes' monkeys and not in human, mangabey, or macaque PBMC [19]. However, macaques inoculated *in vivo* with SIVsyk became persistently infected but remained clinically healthy [36].

THE SIVlhoest LINEAGE

This lineage includes viruses isolated from three different species, the L'Hoest monkey (*Cercopitheucs lhoesti*), the sun-tailed monkey (*Cercopithecus solatus*), and the mandrill (*Mandrillus sphinx*). The mandrill virus, SIVmndGB1, from an animal in Gabon, was first described more than 10 years ago [79, 80], and for many years was the only known representative of the "SIVmnd" lineage. However, recently characterized isolates of SIVlhoest and SIVsun have been found to lie within the same major lineage as SIVmnd [5, 6, 34]. The ranges of mandrills and sun-tailed monkeys overlap in west equatorial Africa, whereas L'Hoest monkeys inhabit an area approximately 1600 km to the east. Nevertheless, SIVlhoest and SIVsun are more closely related to each other than to SIVmnd (Fig. 1). The close relationship of SIVlhoest and SIVsun parallels the close relationship between their two host species (Fig. 3), which have been placed in the same superspecies [32]; mandrills are only distantly related to these guenons. L'Hoest monkeys appear to be infected with SIV at quite high frequencies in the wild [5]. Taken together, these observations suggest that this lineage of SIV has infected monkeys of this *C. lhoesti* superspecies for quite some time, and that the split between SIVlhoest and SIVsun may have occurred when their hosts last shared a common ancestor before they became geographically isolated. This appears to be an additional example of host-dependent evolution paralleling that in SIVs from African green monkeys. Since the frequency of this SIV isolate in wild-living mandrills is unclear, and because a highly divergent form of SIV has recently been reported from other mandrills [72], we have recently suggested that this viral clade should be designated the SIVlhoest lineage rather than the SIVmnd lineage [6].

The presence of quite closely related viruses in quite distantly related hosts (guenons and mandrills) indicates that cross-species transmission must have occurred at some point in the past. Because of their close relationship to one another, neither SIVlhoest nor SIVsun can have been the direct ancestor of SIVmnd. It is possible that SIV was transmitted from mandrills to a common ancestor of L'Hoest and sun-tailed monkeys, although it perhaps seems more likely that the Cercopithecus monkeys were the species infected first. It will be interesting to determine whether Preuss's monkeys (*Cercopithecus preussi*), which are closely related to L'Hoest and sun-tailed monkeys (Fig. 3, [18, 32]), and whose

range also overlaps that of mandrills, are naturally infected with SIV, and how such a virus might be related to SIVlhoest and SIVsun (and SIVmnd).

UNCLASSIFIED PRIMATE LENTIVIRUSES

There is at least serological evidence for SIV infection in a number of other species of African monkeys, and there are even more species that have yet to be tested in any systematic way. Viruses have been isolated from some species, and partial sequence data are available for several. These strains do not seem to be very closely related to any of the previously characterized SIV, although the precise phylogenetic positions of these novel isolates must probably await analysis of full-length sequences.

One of these new variants, SIVrcm, was isolated from the red-capped mangabey (*Cercocebus torquatus*) [28]. Red-capped mangabeys are very closely related to sooty mangabeys (Fig. 3) and in some classifications have been placed within the same species. However, SIVrcm does not appear to be closely related to SIVsm [28]. In a phylogenetic analysis based on partial (318 amino acids) Gag sequences, SIVrcm was approximately equidistant from the SIVsm and SIVagm lineages. However, in an analysis of partial (155 amino acids) Pol sequences, SIVrcm was more closely related to the SIVcpz/HIV-1 clade than to any of the other major lineages. The discordance between these results suggests that there has been recombination between SIV lineages in the past, similar to that inferred to have occurred during the evolution of SIVagmSab.

Another recently characterized SIV was obtained from the drill (*Mandrillus leucophaeus*) [13]. Drills are closely related to mandrills (Fig. 3), but SIVdrl was not found to be closely related to SIVmndGB1. Phylogenetic analysis of partial (787 bp) *pol* sequences suggested that SIVdrl was more closely related to SIVrcm than to any other SIV, although the SIVdrl and SIVrcm nucleotide sequences differ by nearly 30% [13]. It is not known whether SIVdrl and SIVrcm would also cluster together in a *gag* phylogeny.

Serological studies have indicated that talapoin monkeys (*Miopithecus talapoin*) are infected by lentiviruses. A small fragment (550 bp) of *pol* sequence has been obtained from one such virus (SIVtal) and found to be most closely, albeit quite distantly, related to SIVsyk [62]. SIVtal and SIVsyk exhibit only 56% amino acid sequence identity in the region studied, and so SIVtal may represent a sixth distinct lineage of the primate lentiviruses. However, as with SIVrcm and SIVdrl, definitive conclusions about the phylogenetic position of SIVtal should be based on analyses of more extensive sequence data.

Antibodies to SIV proteins have been found in sera from De Brazza's monkeys (*Cercopithecus neglectus*), moustached monkeys (*C. cephus*), Diana monkeys (*C. diana*), greater white-nosed monkeys (*C. nictitans*), Campbell's monkeys (*C. campbelli*), Allen's swamp monkeys (*Allenopithecus nigroviridis*), and Colobus monkeys (*Colobus guereza*) [6, 55, 60]. Clearly, it will be of great interest to isolate and characterize viruses from these species. Such analysis will be necessary to gain a greater insight into the origins and evolution of the primate lentiviruses, to understand exactly how widespread they are among African primates, and to elucidate just how often they have successfully jumped between host species.

CONCLUSIONS

The primate lentiviruses are a diverse group, that naturally infect African species of simians. SIVs from 13 different species have been fully characterized, and within evolutionary trees, they cluster into five approximately equidistant major lineages. However, serological evidence exists for SIVs in a large number of additional species, some of which have been partially characterized, with results that hint at even greater complexity in the primate lentivirus evolutionary tree. Within some major SIV lineages there are viral radiations that seem to reflect speciation events among their hosts, implying that these SIVs may have been evolving in a host-dependent manner for a long period of time. However, there have clearly been many instances of simian-to-simian cross-species transmissions, some of which have led to widespread infection of the new host. Simian-to-human transmissions, from chimpanzees and sooty mangabeys, have led to HIV-1 and HIV-2, respectively, and thus lie at the origin of the AIDS pandemic.

REFERENCES

[1] Allan, J. S., P. Kanda, R. C. Kennedy, E. K. Cobb, M. Anthony, and J. W. Eichberg. 1990. Isolation and characterization of simian immunodeficiency viruses from two subspecies of African green monkeys. *AIDS Res. Hum. Retroviruses* **6**:275–285.

[2] Allan, J. S., M. Short, M. E. Taylor, S. Su, V. M. Hirsch, P. R. Johnson, G. M. Shaw, and B. H. Hahn. 1991. Species-specific diversity among simian immunodeficiency viruses from African green monkeys. *J. Virol*. **65**:2816–2828.

[3] Baier, M., C. Garber, C. Müller, K. Cichutek, and R. Kurth. 1990. Complete nucleotide sequence of a simian immunodeficiency virus from African green monkeys: a novel type of intragroup divergence. *Virology* **176**:216–221.

[4] Baier, M., A. Werner, K. Cichutek, C. Garber, C. Müller, G. Kraus, F. J. Ferdinand, S. Hartung, T. S. Papas, and R. Kurth. 1989. Molecularly cloned simian immunodeficiency virus SIVagm3 is highly divergent from other SIVagm isolates and is biologically active *in vitro* and *in vivo*. *J. Virol*. **63**:5119–5123.

[5] Beer, B. E., E. Bailes, G. Dapolito, B. J. Campbell, R. M. Goeken, M. K. Axthelm, P. D. Markham, J. Bernard, D. Zagury, G. Franchini, P. M. Sharp, and V. M. Hirsch. 2000. Patterns of genomic sequence diversity among their simian immunodeficiency viruses suggest that L'Hoest monkeys (*Cercopithecus lhoesti*) are a natural lentivirus reservoir. *J. Virol*., in press.

[6] Beer, B. E., E. Bailes, R. Goeken, G. Dapolito, C. Coulibaly, S. G. Norley, R. Kurth, J. P. Gautier, A. Gautier-Hion, D. Vallet, P. M. Sharp, and V. M. Hirsch. 1999. Simian immunodeficiency virus (SIV) from sun-tailed monkeys (*Cercopithecus solatus*): Evidence for host-dependent evolution of SIV within the *C. lhoesti* superspecies. *J. Virol*. **73**:7734–7744.

[7] Benveniste, R. E., L. O. Arthur, C. C. Tsai, R. Sowder, T. D. Copeland, L. E. Henderson, and S. Oroszlan. 1986. Isolation of a lentivirus from a macaque with lymphoma: comparison with HTLV-III/LAV and other lentiviruses. *J. Virol*. **60**:483–490.

[8] Bibollet-Ruche, F., A. Galat-Luong, G. Cuny, P. Sarni-Manchado, G. Galat, J. P. Durand, X. Pourrut, and F. Veas. 1996. Simian immunodeficiency virus infection in a patas monkey (*Erythrocebus patas*): evidence for cross-species transmission from African green monkeys (*Cercopithecus aethiops sabaeus*) in the wild. *J. Gen. Virol*. **77**:773–781.

[9] Chen, Z., A. Luckay, D. L. Sodora, P. Telfer, P. Reed, A. Gettie, J. M. Kanu, R. F. Sadek, J. Yee, D. D. Ho, L. Zhang, and P. A. Marx. 1997. Human immunodeficiency virus type 2 (HIV-2) seroprevalence and characterization of a distinct HIV-2 genetic subtype from the natural range of simian immunodeficiency virus-infected sooty mangabeys. *J. Virol*. **71**:3953–3960.

[10] Chen, Z., P. Telfer, P. Reed, L. Zhang, A. Getti, D. D. Ho, and P. A. Marx. 1995. Isolation and characterization of the first simian immunodeficiency virus from a feral sooty mangabey (*Cercocebus atys*) in West Africa. *J. Med. Primatol*. **24**:108–115.

[11] Chen, Z., P. Telfer, A. Gettie, P. Reed, L. Zhang, D. D. Ho, and P. A. Marx. 1996. Genetic characterization of new West African simian immunodeficiency virus SIVsm: geographic clustering of household-derived SIV strains with human immunodeficiency virus type 2 subtypes and genetically diverse viruses from a single feral sooty mangabey troop. *J. Virol*. **70**:3617–3627.

[12] Clavel, F., M. Guyader, D. Guetard, M. Salle, L. Montagnier, and M. Alizon. 1986. Molecular cloning and polymorphism of the human immune deficiency virus type 2. *Nature* **324**:691–695.

[13] Clewley, J. P., J. C. M. Lewis, D. W. G. Brown, and E. L. Gadsby. 1998. A novel simian immunodeficiency virus (SIVdrl) *pol* sequence from the drill monkey, *Mandrillus leucophaeus*. *J. Virol*. **72**:10305–10309.

[14] Corbet, S., M. C. Müller-Trutwin, P. Versmisse, S. Delarue, A. Ayouba, J. Lewis, S. Brunak, P. Martin, F. Brun-Vézinet, F. Simon, F. Barré-Sinoussi, and P. Mauclère. 2000. Env sequences of simian immunodeficiency viruses from chimpanzees in Cameroon are strongly related to those of human immunodeficiency virus group N from the same geographic area. *J. Virol*. **74**:529–534.

[15] Daniel, M. D., N. L. Letvin, N. W. King, M. Kannagi, P. K. Sehgal, R. D. Hunt, P. J. Kanki, M. Essex, and R. C. Desrosiers. 1985. Isolation of T-cell tropic HTLV-III-like retrovirus from macaques. *Science* **228**:1201–1204.

[16] Daniel, M. D., Y. Li, Y. M. Naidu, P. J. Durda, D. K. Schmidt, C. D. Troup, D. P. Silva, J. J. MacKey, H. W. Kestler, P. K. Sehgal, et al. 1988. Simian immunodeficiency virus from African green monkeys. *J. Virol*. **62**:4123–4128.

[17] Disotell, T. R. 1996. The phylogeny of Old World monkeys. *Evol. Anthropol*. **5**:18–24.

[18] Dutrillaux, B., A.-M. Dutrillaux, M. Lombard, J.-P. Gautier, R. Cooper, F. Moysan, and J. M. Lernould. 1988. The karyotype of *Cercopithecus solatus* Harrison 1988, a new species belonging to *C. lhoesti*, and its phylogenetic relationships with other guenons. *J. Zool. Lond*. **215**:611–617.

[19] Emau, P., H. M. McClure, M. Isahakia, J. G. Else, and P. N. Fultz. 1991. Isolation from African Sykes' monkeys (*Cercopithecus mitis*) of a lentivirus related to human and simian immunodeficiency viruses. *J. Virol*. **65**:2135–2140.

[20] Fomsgaard, A., V. M. Hirsch, J. S. Allan, and P. R. Johnson. 1991. A highly divergent proviral DNA clone of SIV from a distinct species of African green monkey. *Virology* **182**:397–402.

[21] Fukasawa, M., T. Miura, A. Hasegawa, S. Morikawa, H. Tsujimoto, K. Miki, T. Kitamura, and M. Hayami. 1988. Sequence of simian immunodeficiency virus from African green monkey, a new member of the HIV/SIV group. *Nature* **333**:457–461.

[22] Fultz, P. N., R. B. Stricker, H. M. McClure, D. C. Anderson, W. M. Switzer, and C. Horaist. 1990. Humoral response to SIV/SMM infection in macaque and mangabey monkeys. *J. Acquir. Immune Defic. Syndr*. **3**:319–329.

[23] Gagneux, P., C. Wills, U. Gerloff, D. Tautz, P. A. Morin, C. Boesch, B. Fruth, G. Hohmann, O. A. Ryder, and D. S. Woodruff. 1999. Mitochondrial sequences show diverse evolutionary histories of African hominoids. *Proc. Natl. Acad. Sci. U S A* **96**:5077–5082.

[24] Gao, F., E. Bailes, D. L. Robertson, Y. Chen, C. M. Rodenburg, S. F. Michael, L. B. Cummins, L. O. Arthur, M. Peeters, G. M. Shaw, P. M. Sharp, and B. H. Hahn. 1999. Origin of HIV-1 in the chimpanzee *Pan troglodytes troglodytes*. *Nature* **397**:436–441.

[25] Gao, F., L. Yue, D. L. Robertson, S. C. Hill, H. Hui, R. J. Biggar, A. E. Neequaye, T. M. Whelan, D. D. Ho, G. M. Shaw, P. M. Sharp, and B. H. Hahn. 1994. Genetic diversity of human immunodeficiency virus type 2: evidence for distinct sequence subtypes with differences in virus biology. *J. Virol*. **68**:7433–7447.

[26] Gao, F., L. Yue, A. T. White, P. G. Pappas, J. Barchue, A. P. Hanson, B. M. Greene, P. M. Sharp, G. M. Shaw, and B. H. Hahn. 1992. Human infection by genetically diverse SIVSM-related HIV-2 in west Africa. *Nature* **358**:495–499.

[27] Gautier-Hion, A., F. Bourlière, J.-P. Gautier, and J. Kingdon. 1988. A primate radiation: evolutionary biology of the African guenons. Cambridge University Press, Cambridge.

[28] Georges-Courbot, M. C., C. Y. Lu, M. Makuwa, P. Telfer, R. Onanga, G. Dubreuil, Z. Chen, S. M. Smith, A. Georges, F. Gao, B. H. Hahn, and P. A. Marx. 1998. Natural infection of a household pet red-capped mangabey (*Cercocebus torquatus torquatus*) with a new simian immunodeficiency virus. *J. Virol*. **72**:600–608.

[29] Gonda, M. A., M. J. Braun, S. G. Carter, T. A. Kost, J. W. Bess, Jr., L. O. Arthur, and M. J. Van der Maaten. 1987. Characterization and molecular cloning of a bovine lentivirus related to human immunodeficiency virus. *Nature* **330**:388–391.

[30] Hahn, B. H., G. M. Shaw, K. De Cock, and P. M. Sharp. 2000. AIDS as a zoonosis: scientific and public health implications. *Science* **287**:607–614.

[31] Harris, E. E., and T. R. Disotell. 1998. Nuclear gene trees and the phylogenetic relationships of the mangabeys (Primates: *Papionini*). *Mol. Biol. Evol*. **15**:892–900.

[32] Harrison, M. J. S. 1988. A new species of guenon (genus *Cercopithecus*) from Gabon. *J. Zool. Lond*. **215**:561–575.

[33] Hendry, R. M., M. A. Wells, M. A. Phelan, A. L. Schneider, J. S. Epstein, and G. V. Quinnan. 1986. Antibodies to simian immunodeficiency virus in African green monkeys in Africa in 1957–62. *Lancet* **2**:455.

[34] Hirsch, V. M., B. J. Campbell, E. Bailes, R. Goeken, C. Brown, W. R. Elkins, M. Axthelm, M. Murphey-Corb, and P. M. Sharp. 1999. Characterization of a novel simian immunodeficiency virus (SIV) from L'Hoest monkeys (*Cercopithecus l'hoesti*): implications for the origins of SIVmnd and other primate lentiviruses. *J. Virol.* **73**:1036–1045.

[35] Hirsch, V. M., G. Dapolito, P. R. Johnson, W. R. Elkins, W. T. London, R. J. Montali, S. Goldstein, and C. Brown. 1995. Induction of AIDS by simian immunodeficiency virus from an African green monkey: species-specific variation in pathogenicity correlates with the extent of *in vivo* replication. *J. Virol.* **69**:955–967.

[36] Hirsch, V. M., G. A. Dapolito, S. Goldstein, H. McClure, P. Emau, P. N. Fultz, M. Isahakia, R. Lenroot, G. Myers, and P. R. Johnson. 1993. A distinct African lentivirus from Sykes' monkeys. *J. Virol.* **67**:1517–1528.

[37] Hirsch, V. M., and P. R. Johnson. 1993. Genetic diversity and phylogeny of primate lentiviruses, p. 221–240. In J. Morrow and N. Haigwood (eds.): HIV Molecular Organization, Pathogenicity and Treatment. Elsevier Science Publishers, The Netherlands.

[38] Hirsch, V. M., C. McGann, G. Dapolito, S. Goldstein, A. Ogen-Odoi, B. Biryawaho, T. Lakwo, and P. R. Johnson. 1993. Identification of a new subgroup of SIVagm in tantalus monkeys. *Virology* **197**:426–430.

[39] Hirsch, V. M., R. A. Olmsted, M. Murphey-Corb, R. H. Purcell, and P. R. Johnson. 1989. An African primate lentivirus (SIVsm) closely related to HIV-2. *Nature* **339**:389–392.

[40] Huet, T., R. Cheynier, A. Meyerhans, G. Roelants, and S. Wain-Hobson. 1990. Genetic organization of a chimpanzee lentivirus related to HIV-1. *Nature* **345**:356–359.

[41] Hunt, R. D., B. J. Blake, L. V. Chalifoux, P. K. Sehgal, N. W. King, and N. L. Letvin. 1983. Transmission of naturally occurring lymphoma in macaque monkeys. *Proc. Natl. Acad. Sci. U S A* **80**:5085–5089.

[42] Janssens, W., K. Fransen, M. Peeters, L. Heyndrickx, J. Motte, L. Bedjabaga, E. Delaporte, P. Piot, and G. van der Groen. 1994. Phylogenetic analysis of a new chimpanzee lentivirus SIVcpz-gab2 from a wild-captured chimpanzee from Gabon. *AIDS Res. Hum. Retroviruses* **10**:1191–1192.

[43] Jin, M. J., H. Hui, D. L. Robertson, M. C. Müller, F. Barré-Sinoussi, V. M. Hirsch, J. S. Allan, G. M. Shaw, P. M. Sharp, and B. H. Hahn. 1994. Mosaic genome structure of simian immunodeficiency virus from west African green monkeys. *EMBO J.* **13**:2935–2947.

[44] Jin, M. J., J. Rogers, J. E. Phillips-Conroy, J. S. Allan, R. C. Desrosiers, G. M. Shaw, P. M. Sharp, and B. H. Hahn. 1994. Infection of a yellow baboon with simian immunodeficiency virus from African green monkeys: evidence for cross-species transmission in the wild. *J. Virol.* **68**:8454–8460.

[45] Johnson, P. R., A. Fomsgaard, J. S. Allan, M. Gravell, W. T. London, R. A. Olmsted, and V. M. Hirsch. 1990. Simian immunodeficiency viruses from African green monkeys display unusual genetic diversity. *J. Virol.* **64**:1086–1092.

[46] Kannagi, M., J. M. Yetz, and N. L. Letvin. 1985. In vitro growth characteristics of simian T-lymphotropic virus type III. *Proc. Natl. Acad. Sci. U S A* **82**:7053–7057.

[47] Kappes, J. C., C. D. Morrow, S. W. Lee, B. A. Jameson, S. B. Kent, L. E. Hood, G. M. Shaw, and B. H. Hahn. 1988. Identification of a novel retroviral gene unique to human immunodeficiency virus type 2 and simian immunodeficiency virus SIVmac. *J. Virol.* **62**:3501–3505.

[48] Khabbaz, R. F., W. Heneine, J. R. George, B. Parekh, T. Rowe, T. Woods, W. M. Switzer, H. M. McClure, M. Murphey-Corb, and T. M. Folks. 1994. Brief report: infection of a laboratory worker with simian immunodeficiency virus. *N. Engl. J. Med.* **330**:172–177.

[49] Khan, A. S., T. A. Galvin, L. J. Lowenstine, M. B. Jennings, M. B. Gardner, and C. E. Buckler. 1991. A highly divergent simian immunodeficiency virus (SIVstm) recovered from stored stump-tailed macaque tissues. *J. Virol.* **65**:7061–7065.

[50] Kodama, T., D. P. Silva, M. D. Daniel, J. E. Phillips-Conroy, C. J. Jolly, J. Rogers, and R. C. Desrosiers. 1989. Prevalence of antibodies to SIV in baboons in their native habitat. *AIDS Res. Hum. Retroviruses* **5**:337–343.

[51] Kurth, R., and S. Norley. 1994. Simian immunodeficiency viruses of African green monkeys. *Curr. Top. Microbiol. Immunol*. **188**:21–33.

[52] Lernould, J.-M. 1988. Classification and geographical distribution of guenons: a review, p. 78–103. In A. Gautier-Hion, F. Bourlière, and J.-P. Gautier (eds.): A primate radiation: evolutionary biology of the African guenons. Cambridge University Press, United Kingdom, Cambridge.

[53] Letvin, N. L., W. R. Aldrich, N. W. King, B. J. Blake, M. D. Daniel, and R. D. Hunt. 1983. Experimental transmission of macaque AIDS by means of inoculation of macaque lymphoma tissue. *Lancet* **2**:599–602.

[54] Letvin, N. L., K. A. Eaton, W. R. Aldrich, P. K. Sehgal, B. J. Blake, S. F. Schlossman, N. W. King, and R. D. Hunt. 1983. Acquired immunodeficiency syndrome in a colony of macaque monkeys. *Proc. Natl. Acad. Sci. U S A* **80**:2718–2722.

[55] Lowenstine, L. J., N. C. Pedersen, J. Higgins, K. C. Pallis, A. Uyeda, P. Marx, N. W. Lerche, R. J. Munn, and M. B. Gardner. 1986. Seroepidemiologic survey of captive Old-World primates for antibodies to human and simian retroviruses, and isolation of a lentivirus from sooty mangabeys (*Cercocebus atys*). *Int. J. Cancer* **38**:563–574.

[56] Marx, P. A., Y. Li, N. W. Lerche, S. Sutjipto, A. Gettie, J. A. Yee, B. H. Brotman, A. M. Prince, A. Hanson, R. G. Webster, et. al. 1991. Isolation of a simian immunodeficiency virus related to human immunodeficiency virus type 2 from a west African pet sooty mangabey. *J. Virol*. **65**:4480–4485.

[57] Morin, P. A., J. J. Moore, R. Chakraborty, L. Jin, J. Goodall, and D. S. Woodruff. 1994. Kin selection, social structure, gene flow, and the evolution of chimpanzees. *Science* **265**:1193–1201.

[58] Müller, M. C., N. K. Saksena, E. Nerrienet, C. Chappey, V. M. Hervé, J. P. Durand, P. Legal-Campodonico, M. C. Lang, J. P. Digoutte, A. J. Georges, et al. 1993. Simian immunodeficiency viruses from central and western Africa: evidence for a new species-specific lentivirus in tantalus monkeys. *J. Virol*. **67**:1227–1235.

[59] Murphey-Corb, M., L. N. Martin, S. R. Rangan, G. B. Baskin, B. J. Gormus, R. H. Wolf, W. A. Andes, M. West, and R. C. Montelaro. 1986. Isolation of an HTLV-III-related retrovirus from macaques with simian AIDS and its possible origin in asymptomatic mangabeys. *Nature* **321**:435–437.

[60] Ohta, Y., T. Masuda, H. Tsujimoto, K. Ishikawa, T. Kodama, S. Morikawa, M. Nakai, S. Honjo, and M. Hayami. 1988. Isolation of simian immunodeficiency virus from African green monkeys and seroepidemiologic survey of the virus in various non-human primates. *Int. J. Cancer* **41**:115–122.

[61] Olmsted, R. A., V. M. Hirsch, R. H. Purcell, and P. R. Johnson. 1989. Nucleotide sequence analysis of feline immunodeficiency virus: genome organization and relationship to other lentiviruses. *Proc. Natl. Acad. Sci. U S A* **86**:8088–8092.

[62] Osterhaus, A. D., N. Pedersen, G. van Amerongen, M. T. Frankenhuis, M. Marthas, E. Reay, T. M. Rose, J. Pamungkas, and M. L. Bosch. 1999. Isolation and partial characterization of a lentivirus from talapoin monkeys (*Myopithecus talapoin*). *Virology* **260**:116–124.

[63] Peeters, M., K. Fransen, E. Delaporte, M. Vanden Haesevelde, G. M. Gershy-Damet, L. Kestens, G. van der Groen, and P. Piot. 1992. Isolation and characterization of a new chimpanzee lentivirus (simian immunodeficiency virus isolate cpz-ant) from a wild-captured chimpanzee. *AIDS* **6**:447–451.

[64] Peeters, M., C. Honore, T. Huet, L. Bedjabaga, S. Ossari, P. Bussi, R. W. Cooper, and E. Delaporte. 1989. Isolation and partial characterization of an HIV-related virus occurring naturally in chimpanzees in Gabon. *AIDS* **3**:625–630.

[65] Peeters, M., W. Janssens, K. Fransen, J. Brandful, L. Heyndrickx, K. Koffi, E. Delaporte, P. Piot, G. M. Gershy-Damet, and G. van der Groen. 1994. Isolation of simian immunodeficiency viruses from two sooty mangabeys in Cote d'Ivoire: virological and genetic characterization and relationship to other HIV type 2 and SIVsm/mac strains. *AIDS Res. Hum. Retroviruses* **10**:1289–1294.

[66] Rey-Cuillé, M. A., J. L. Berthier, M. C. Bomsel-Demontoy, Y. Chaduc, L. Montagnier, A. G. Hovanessian, and L. A. Chakrabarti. 1998. Simian immunodeficiency virus replicates to high levels in sooty mangabeys without inducing disease. *J. Virol*. **72**:3872–3886.

[67] Saltarelli, M., G. Querat, D. A. Konings, R. Vigne, and J. E. Clements. 1990. Nucleotide sequence and transcriptional analysis of molecular clones of CAEV which generate infectious virus. *Virology* **179**:347–364.

[68] Sharp, P. M., E. Bailes, D. L. Robertson, F. Gao, and B. H. Hahn. 1999. Origins and evolution of AIDS viruses. *Biol. Bull*. **196**:338–342.

[69] Sharp, P. M., E. Bailes, M. Stevenson, M. Emerman, and B. H. Hahn. 1996. Gene acquisition in HIV and SIV. *Nature* **383**:586–587.

[70] Sharp, P. M., D. L. Robertson, and B. H. Hahn. 1995. Cross-species transmission and recombination of 'AIDS' viruses. *Philos. Trans. R. Soc. Lond. B. Biol. Sci*. **349**:41–47.

[71] Simon, F., P. Mauclère, P. Roques, I. Loussert-Ajaka, M. C. Müller-Trutwin, S. Saragosti, M. C. Georges-Courbot, F. Barré-Sinoussi, and F. Brun-Vézinet. 1998. Identification of a new human immunodeficiency virus type 1 distinct from group M and group O. *Nat. Med*. **4**:1032–1037.

[72] Simon, F., D. Robertson, A. Ayouba, C. Apetrei, S. Souquière, J. Lewis, and P. Mauclère. 1999. The characterization of four novel SIV strains from Cameroon: implications for primate lentivirus diversity. 6th Conference on Retroviruses and Opportunistic Infections. Abstract 76.

[73] Soares, M. A., D. L. Robertson, H. Hui, J. S. Allan, G. M. Shaw, and B. H. Hahn. 1997. A full-length and replication-competent proviral clone of SIVAGM from tantalus monkeys. *Virology* **228**:394–399.

[74] Sonigo, P., M. Alizon, K. Staskus, D. Klatzmann, S. Cole, O. Danos, E. Retzel, P. Tiollais, A. Haase, and S. Wain-Hobson. 1985. Nucleotide sequence of the visna lentivirus: relationship to the AIDS virus. *Cell* **42**:369–382.

[75] Stephens, R. M., J. W. Casey, and N. R. Rice. 1986. Equine infectious anemia virus *gag* and *pol* genes: relatedness to visna and AIDS virus. *Science* **231**:589–594.

[76] Strebel, K., T. Klimkait, and M. A. Martin. 1988. A novel gene of HIV-1, *vpu*, and its 16-kilodalton product. *Science* **241**:1221–1223.

[77] Tomonaga, K., J. Katahira, M. Fukasawa, M. A. Hassan, M. Kawamura, H. Akari, T. Miura, T. Goto, M. Nakai, M. Suleman, et al. 1993. Isolation and characterization of simian immunodeficiency virus from African white-crowned mangabey monkeys (*Cercocebus torquatus lunulatus*). *Arch. Virol*. **129**:77–92.

[78] Tristem, M., C. Marshall, A. Karpas, and F. Hill. 1992. Evolution of the primate lentiviruses: evidence from *vpx* and *vpr*. *EMBO J*. **11**:3405–3412.

[79] Tsujimoto, H., R. W. Cooper, T. Kodama, M. Fukasawa, T. Miura, Y. Ohta, K. Ishikawa, M. Nakai, E. Frost, G. E. Roelants, et al. 1988. Isolation and characterization of simian immunodeficiency virus from mandrills in Africa and its relationship to other human and simian immunodeficiency viruses. *J. Virol*. **62**:4044–4050.

[80] Tsujimoto, H., A. Hasegawa, N. Maki, M. Fukasawa, T. Miura, S. Speidel, R. W. Cooper, E. N. Moriyama, T. Gojobori, and M. Hayami. 1989. Sequence of a novel simian immunodeficiency virus from a wild-caught African mandrill. *Nature* **341**:539–541.

[81] Van der Kuyl, A. C., C. L. Kuiken, J. T. Dekker, and J. Goudsmit. 1995. Phylogeny of African monkeys based upon mitochondrial 12S rRNA sequences. *J. Mol. Evol*. **40**:173–180.

[82] Van Rensburg, E. J., S. Engelbrecht, J. Mwenda, J. D. Laten, B. A. Robson, T. Stander, and G. K. Chege. 1998. Simian immunodeficiency viruses (SIVs) from eastern and southern Africa: detection of a SIVagm variant from a chacma baboon. *J. Gen. Virol*. **79**:1809–1814.

[83] Vanden Haesevelde, M. M., M. Peeters, G. Jannes, W. Janssens, G. van der Groen, P. M. Sharp, and E. Saman. 1996. Sequence analysis of a highly divergent HIV-1-related lentivirus isolated from a wild captured chimpanzee. *Virology* **221**:346–350.

[84] Wu, X. X., X. M. Tu, F. Q. He, H. J. Shi, C. Z. W., Q. Wei, H. Jiang, and J. D. Shi. 1991. Studies on the monitoring of viruses in Chinese rhesus monkeys (*Macaca mulatta*). *Chin J Lab. Anim. Sci*. **1**:179–183.