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THE HISTORY OF SIVs AND AIDS: EPIDEMIOLOGY, PHYLOGENY AND BIOLOGY OF ISOLATES FROM NATURALLY SIV INFECTED NON-HUMAN PRIMATES (NHP) IN AFRICA

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1. ABSTRACT

Simian immunodeficiency virus (SIV) naturally infects non-human primates in Africa. To date, 40 SIVs have been described both in natural hosts and in heterologous species. These viruses are highly diverse and the majority cluster in 6 relatively equidistant phylogenetic lineages. At least 8 SIVs are currently considered as recombinant viruses, based on different clustering patterns in different genomic regions. Only three types of genomes are known, based on the number of accessory genes: *vpr*-containing genomes, *vpr*-*vpx* containing genomes and *vpr*-*vpu*-containing genomes. vpx resulted by a duplication of the vpr gene following non-homologous recombination and is characteristic of SIVs infecting the Papionini tribe of monkeys and HIV-2 in humans. *vpu* is characteristic of SIVcpz and HIV-1 and may have originated from a recombination involving SIVs from cercopitecini monkeys. SIV seems to be non-pathogenic in the vast majority of natural hosts in spite of a high levels of viral replication. This is probably a consequence of virus-host adaptation, in which the incubation period of the disease generally exceeds the life span of the African primate host. SIVs also have a high propensity for cross-species transmission. In the new host, the outcome may vary from inapparent infection to highly pathogenic, the former being reported for African monkeys, whereas the latter being observed in macaques and humans. The high diversity of SIVs was

generated by a high mutation rate due to a low fidelity of the reverse-transcriptase and active viral and host cell turnover, host-dependent evolution and recombination. Cross-species transmission is not rare, however preferential host switching may drive the majority of cross-species transmissions. Numerous SIVs tested so far are able to grow *in vitro* on human PBMC, therefore it has been postulated that SIV represents a threat for infection of humans in Central Africa and that AIDS is a zoonosis. However, although the simian origin of the two HIV types is broadly acknowledged, there are no data that AIDS is acquired like a zoonosis. SIV may undergo adaptation in the new human host in order to emerge in the general population. The study of SIV in their natural hosts should provide important clues to the real threat to human populations and also elucidate the mechanisms associated with a long-term persistent viral infection without clinical consequences for the host.

2. INTRODUCTION

Non-human primate lentiviruses were discovered only 17 years ago. Yet intensive studies have resulted in the description and complete or at least partial characterization of more than 30 different types of simian immunodeficiency viruses (SIVs) which infect different species of African monkeys and apes. At least two of these viral types infect humans. Most of the SIVs grow *in vitro* within human peripheral blood mononuclear cells (PBMCs), thus having the potential to emerge in the human population. These findings pose the major question of whether or not new cross-transmission event (s) will result in new human lentiviruses. The answer to this question needs to be addressed to avoid new threats to human health.

3. DISCOVERY OF SIVs IN AFRICAN NON-HUMAN PRIMATE SPECIES: THE PATH FROM THE DISCOVERY OF SIMIAN ORIGIN OF HIVs TO THE CHARACTERIZATION OF THE LARGEST AND MOST DIVERSE GROUP OF VIRUSES KNOWN IN WILD MAMMALS

The modern history of non-human primate lentiviruses and their pathogenic potential began 12 years before the emergence of AIDS, with an outbreak of lymphomas in captive rhesus macaques (*Macaca mulatta*) at the California National Primate Research Center (CNPRC) in Davis, CA (1,2). A second outbreak occurred in the mid 1970s in stump-tailed macaques (*Macaca arctoides*) in the same setting (3). At that time, these two epizootics were not recognized as having an infectious origin, even though immune suppression and opportunistic infections were found. Before the occurence of these outbreaks these macaques had been in contact with healthy sooty mangabeys (SMs) from which they had been infected. These SMs have been retrospectively shown to be SIV seropositive (1). Ironically, some of the healthy SIV carriers surviving these two outbreaks were sent to other Primate Centers and they served as sources for SIV infections in macaques (SIVmac) several years later (4). Subsequently, sooty mangabeys were recognized as the possible source of SIV in macaques (1, 5).

At that time, AIDS was already recognized as a major infectious disease in humans, affecting patients from 5 continents. The scientific community was perplexed by the dynamics of this pandemic. HIV-1 as the cause of AIDS had already been identified in 1983 (6). Even in these early days, establishing the origin of the viruses responsible for AIDS pandemic received high priority. However, SIVmac, although related to HIV-1, did not share all the structural features of the latter virus (7). Moreover, macaques were even more susceptible to the disease than humans, which suggested that macaques may not be the natural host of SIV. Indeed, extensive studies in Asian species fail to reveal any evidence of SIV in wild-caught macaques (8,9,10). Conversely, within a very short period of time, significant evidence of lentivirus circulation in African monkeys and apes pointed to a simian origin of AIDS (11,12). Following the discovery in 1986 of HIV-2 (13), a virus which was shown to be closely related to the SIVsm (14), it was rapidly established that this human AIDS virus had a simian origin (14,15). The discovery of SIVcpz in the area of HIV-1 epidemic emergence pointed to a simian source of HIV-1 (12,16). Finally, in 1998, HIV-1 group N was discovered in a Cameroonian patient with AIDS. This virus clearly clusters with SIVcpz from Cameroon in parts of the genome, which reinforced the hypothesis that SIVcpz was the ancestor of HIV-1 (16,17,18). Altogether these seminal studies have solved the origin of HIV-1 and HIV-2.

Another major accomplishment of the study of HIV simian counterparts is the description of a large group of lentiviruses in their African non-human primate hosts (table 1) showing high genetic diversity, a complex evolutionary history and a threat for cross-species transmission and emergence in the human population. Also, these viruses may have a different biology in their natural hosts, thus providing essential clues for our understanding of HIV pathogenesis and for designing effective approaches to control the disease.

4. AIDS AS A ZOONOSIS? CONFUSION OVER THE ORIGIN OF THE VIRUS AND THE ORIGIN OF THE EPIDEMICS

Based on results showing the simian origin of HIV, AIDS was postulated as a zoonosis (reviewed in 19). This hypothesis was based on data showing cross-species transmission (16), such as: (i) similarities in viral genome organization; (ii) phylogenetic relatedness; (iii) prevalence in the natural host; (iv) geographic coincidence and (v) plausible routes of transmission. Both SIVsm/HIV-2 and SIVcpz/HIV-1 fulfill these criteria (14,16,19), however, although the hypothesis of simian origin of AIDS is nowadays largely acknowledged, the idea that AIDS is a zoonosis has never been proven and must be questioned.

The strict definition of a zoonosis is "a disease of animals that may be transmitted to man under natural conditions (e.g., brucellosis, rabies)" (20) or "a disease communicated from one kind of animal to another or to a human being; usually restricted to diseases transmitted naturally to man from animals" [Medical Dictionary Online,

Table 1. African non-human primates infected with SIV

		Viral type	Full-length genome availability	Partial sequence	Serological evidence[7]	Pathogenic in host species[8]	Pathogenic in heterologous hosts
Humans	Homo sapiens	HIV-1 group M	M62320, K03455, U21135[3]	Yes		Y	N
		HIV-1 group O	L20587, L20571	Yes		Y	NA
		HIV-1 group N	AJ271370, AJ006022	Yes		Y	NA
		HIV-2 group A	X05291, NC001722	Yes		Y	Y
		HIV-2 group B	U27200, X61240	Yes		Y	Y
Non-human primates							
Chimpanzees	Pan troglodytes troglodytes (Central African chimp)	SIVcpzGAB/ CAM/US	X52154, AF103818, AF115393, AJ271369	U11495[6]		N	Y
	P. t. schweinfurthii (Eastern chimp)	SIVcpzANT/TAN	U42720, AF447763	Yes		N	NA
	P. t. vellorosus	SIVcpzCAM4[1]		AF115394		N	NA
Cercopithecoidea							
Cercopithecinae							
Papionini							
Mangabeys	Cerccebus atys (sooty mangabey)	SIVsm	X14307, U72748, M80194, AF077017, AF334679	X78505-11, AY158968-84		N	Y
	Cercocebus torquatus (red-capped mangabey)	SIVrcm	AF349680	AF349681, AF028607, AF028608		N	N
	Cercocebus agilis (agile mangabey)			Yes		N	NA
	Cercocebus torquatus lunulatus (white-crowned mangabey)	SIVagm.Ver[1]	NA[4]	D10702			
	Lophocebus albigena (gray-crested mangabey)				Yes		
Mandrills	Mandrillus sphinx (mandrill)	SIVmnd-1	M27470	AF328282, AF328283		Y	NA
		SIVmnd-2	AF328295, AY159322			Y	N
	M. leucophaeus (drill)	SIVdrl	AY159321	AJ011017		N	NA
Baboons	Papio cynocephalus (yellow baboon)	SIVagm.Ver[2]	NA	Yes	Yes	NR[9]	
	Papio ursinus (chacma baboon)	SIVagm.Ver[2]	NA	Yes	Yes	NR	
Macaques	Macacca mulatta (rhesus macaque)	SIVmac[1]	M19499, D01065, M76764, M16403			Y	
	M. nemestrina (pig-tailed macaque)	SIVmne[1]	M32741, U79412			Y	
	M. arctoides (stump-tailed macaque)	SIVstm[1]	M83293			Y	
Cercopithecini							
Allenopithecus	A. nigroviridis (Allen's monkey)				Yes		
Talapoins	Miopithecus talapoin (talapoin)	SIVtal	NA	AF119357-58		N	NA
	M. ougouensis (Gabon talapoin)	SIVtal	NA	AF478594-95			
Patas	Erythrocebus patas	SIVagm.Sab[2]	NA				NA
African greens	Chlorocebus aethiops (grivet)	SIVagm.Gri	M66437	Yes		N	NA
	C. pygerythrus (vervet)	SIVagm.Ver	X07805, M29975 M30931	Yes		Y	Y
	C. tantalus (tantalus)	SIVagm.Tan	U58991	Yes		N	NA
	C. sabaeus (sabaeus)	SIVagm.Sab	U04005	Yes		N	N
Cercopithecus genus							
Diana group	C. diana (diana monkey)		NA	NA			
Mitis group	C. nictitans (greater spot-nosed monkey)	SIVgsn	AF468658, AF468659	AF478588-90		NR	NA
	C. mitis (blue monkey)	SIVblu	NA	Yes		NR	NA
	C. albogularis (Syke's monkey)	SIVsyk	L06042			NR	NA
Mona group	C. mona (mona monkey)	SIVmon	AJ549283	AF478591		NR	NA
	C. denti (Dent's mona)	SIVden	Yes[5]	Yes		NR	NA
	C. pogonias (crested mona)				Yes		
	C. lowei (Lowe's mona)				Yes		
Cephus group	C. cephus (mustached guenon)	SIVmus	Yes	AF478592-93		NR	NA
	C. ascanius (red-tailed monkey)	SIVasc	Yes			NR	NA
Lhoesti group	C. lhoesti (L'Hoest's monkey)	SIVlhoest	AF075269, AF188114, AF188115, AF188116			NR	Y
	C. solatus (sun-tailed monkey)	SIVsun	AF131870			NR	NA
Neglectus group	C. neglectus (De Brazza's monkey)	SIVdeb	Yes	AJ549756, AF478600-05		NR	NA
Hamlyni group	C. hamlyni (Owl-faced monkey)				Yes		
Colobinae	Colobus guereza (C. guereza)	SIVcol	AF301156	AF301154, AF301155		NR	NA
	Piliocolobus badius (western red colobus)	SIVwrc	NA	AY138265-68		NR	NA
	Procolobus verus (olive colobus)	SIVolc	NA	AY138269		NR	NA

[1]Accidentally transmitted in captivity [2] Naturally occurring in the wild [3] GeneBank accession numbers of the full-length sequences. For HIVs, only some reference strains out of more than 150full-length genomic sequences available [4] NA-not available [5] Some full-length sequences are not yet released [6] For some SIVs, only partial genomic sequences are available. In those instances in which full-length sequences are available for a given virus, some partial sequences of interest are also listed in this column [7] Only serological evidence reported for these viruses [8] Although most reports suggest that SIVs are not pathogenic in their natural non-human primate hosts, cases of immunesuppression have been reported [9]Not reported

http://cancerweb.ncl.ac.uk/cgi-bin/omd]. Interestingly, in the Dictionary of Virology it is emphasized that the term zoonosis is frequently misused: "a zoonosis is a disease or an infection naturally transmitted between vertebrate animals and humans. However, the term has been frequently misunderstood" (21).

All these definitions show that the use of this term is questionable in the case of the emergence of AIDS pandemic. Several arguments are provided to support this objection:

1. In spite of the large exposure to SIV-infected monkeys in Central and West Africa (22), extensive molecular epidemiologic studies documented only 10 cross-species transmission events during the last century. Only four of these cross-over events resulted in epidemic strains: HIV-1 group M, the major group of viruses of the pandemic, group O, which is responsible for perhaps 5% of cases in Cameroon (23) and groups A and B of HIV-2, which are the epidemic forms of HIV-2 (24, 25). One should note that some of the closest relatives of SIVcpz (HIV-1 group N) and of SIVsm (HIV-2 groups C through G) are extremely rare in humans, with only 6 HIV-1 group N-infected patients known (26) and only single individuals infected by HIV-2 groups C-G (25, 27, 28). This suggests that cross-species transmitted viruses are not sufficiently adapted for spread into the new host population to generate an epidemic. This situation is not unique in virology: direct transmission of influenza from its avian host seems to have a lower pandemic potential than the transmission of recombinant influenza viruses originated from the pig's "mixing vessel": only 18 cases of H5N1 influenza infection have been recorded during the epidemic in Hong Kong (29). These cases were severe, with a mortality rate of more than 30%. However, no evidence of human-to-human transmission of H5N1 virus was found (30). Moreover, serological screening of poultry workers directly exposed to the avian virus has shown that about 10% were seropositive, and that the infection was asymptomatic or mildly symptomatic, with no secondary cases reported (31). These findings suggest the need for animal transmitted viruses to adapt to the new host before initiating significant epidemics or pandemics.

2. Experimental cross-species transmission of SIVs in different species of monkeys has shown that in many cases the virus is harmless or cleared by the new host (32). Similarly, some of the HIV-2 groups show low pathogenic potential in the human host (25). These findings lead to the conclusion that only the zoonotic origin of HIV-1 is known, whereas the disease is a pure human nosological entity. Again, these data shows that in order to induce the disease, the virus must undergo adaptation and selection processes in the new host. There are no data to support AIDS as a zoonosis.

3. SIVs infections in their natural host are generally asymptomatic (33-38) and immunodeficiency is extremely rare (39-41). This finding reinforces the assumption that a change in the pathological potential of the virus is needed for SIV to become pathogenic in the new primate host (42). In zoonotic infections such as rabies or West Nile encephalitis, the animal source is also susceptible to the disease (43, 44). However, at least for rabies, it had been shown that the animal reservoir might be resistant to the disease (43).

4. Finally, in Central Africa, humans have been exposed for centuries to SIVs and the epidemic has apparently only emerged in the second half of the last century, which suggests the intervention of some favoring factor (s) in the emergence of HIV. These factors might be represented by the deforestation, increase of urbanization and travel in the 20th century (45). Also it was postulated that the main factor behind the emergence of HIV in human population might be represented by an increase of the use of injections with unsterile needles and syringes. This factor might significantly promote viral adaptation through serial passages (46, 47) or favor adaptation by other mechanisms such as recombination.

One should note that most of the SIVs reported so far have not been grown *in vitro*, thus, the statement that with very few exceptions all SIVs infect human PBMCs might not be true. In fact, most of the cercopithecine SIVs do not grow in human PBMCs (48-50).

These arguments indicate that viral cross-species transmission is in itself not the only requirement for the generation of epidemics, and that the origin of HIV should not be confused with the origins of AIDS. Other factors must be required for HIV adaptation and epidemic spread in the new human host. All these aspects being considered, AIDS is not a zoonosis in the strict definition (47), but a human infectious disease of simian origin, similar to hepatitis B (51, 52) and HTLV infections (53, 54).

In conclusion, the study of SIV has identified only the simian origin of HIV. Questions still remain: which factor (s) has driven the cross-species transmission, virus adaptation and how can new cross-species transmissions be avoided?

5. STUDY OF PRIMATE LENTIVIRUS DIVERSITY

5.1. Sampling

Wild non-human primates are difficult to be approached or captured in the forest or savannah, therefore sampling is very difficult. Several other approaches have been used to estimate SIVs prevalence in African non-human primate hosts: (i) testing of monkeys in zoos and colonies (8, 38); (ii) testing of pet monkeys within their natural range (11, 22, 55); (iii) testing bush meat in African markets (22) and (iv) use of non-invasive samples, such as urine and feces, for serological and molecular diagnostic in wild or captive primates (56, 57).

All of these methods have limitations and therefore generate bias in prevalence estimates.

5.1.1. Captive monkeys as a model for the study of SIV prevalence

The study of monkeys in zoos or colonies may not reflect the true prevalence because most were captured

as juveniles or bred in captivity. There is a significant increase in SIV prevalence in adult wild monkeys as compared to juveniles (14,58-60). Also, close contact between captive monkeys in zoos and colonies provides opportunities for cross-species transmission: examples of monkeys infected in captivity are a chimpanzee in Cameroon (61), a white crowned mangabey in Kenya (62) and numerous macaques in the United States(63).

To overcome these problems it was proposed that the study of pet monkeys sampled within their natural range could provide significant information concerning the diversity of SIVs (11). Although most of the pet monkeys are captured when young, and the prevalence levels might be lower than those in wild animals, pet monkey testing is a relevant approach for the study of SIV prevalence. They are wild-captured, thus reflecting the situation of feral animals. Pets have been shown to be infected with SIV, and at least 2 new representative SIV strains have been obtained by this approach: the closest simian counterpart of HIV-2, in a sooty mangabey from Sierra Leone (14, 64) and SIVrcm, a virus which naturally infects the red-capped mangabeys (55). Testing of pet samples has confirmed previously obtained results with monkeys in zoos and colonies (40). Although mortality rates are high for pet monkeys in Africa, they may sometimes be resampled if subsequent analysis of the infecting virus is required.

A recent extensive serological and molecular epidemiology study conducted in Cameroon included testing of 215 pet monkeys belonging to 16 different indigenous species (22). Serological testing identified SIV infection in 10 species, 6 of which were not yet known to carry a specific SIV. Five new SIVs have been amplified in this study and their genetic characterization is in progress (22). Most of the monkeys included in this study were juveniles or infants. However, the overall prevalence of SIVs in this group was estimated to be 11.6% and infection rates varied from species to species (22).

5.1.2. Study of the bush meat: advantages and limitations

Reports have suggested that zoonotic transfers of primate lentiviruses to humans is due to bush meat consumption and exposure to monkey blood during hunting and food preparation (11, 16, 19, 65). If this hypothesis is proven, humans in Central Africa, especially in rural regions, are at high risk for cross-species transmission of primate lentiviruses. An extensive study was conducted in Cameroon between 1999 and 2001 to evaluate the magnitude of this exposure (22). This study included systematic sampling of non-human primates used as bush meat in markets. Blood was collected by cardiac puncture, with lymph nodes and spleen tissues collected whenever possible. The overall seroprevalence of SIV infection in 11 tested species has been 18.4%, and ranged between 5 to 40% for different species (22), being approximately within the same range as previous estimates of SIV prevalence in the wild. Some of the viruses obtained were amplified and phylogenetically characterized. This study provided strong evidence of human exposure to SIV infection, however, the major limitation is that post-mortem samples are in poor condition, thus not allowing virus isolation and further biological characterization. Its main advantage is that it offers large numbers of samples in a short period of time and provides estimations of prevalence in the wild.

5.1.3. Alternative sampling

Most of the natural hosts of SIV are highly endangered species and therefore sampling blood from these animals is not usually feasible. Alternative non-invasive diagnostic strategies have been developed for testing SIV prevalence in wild non-human primates. These strategies use urine and feces for serological diagnosis and viral RNA amplification. Initial evaluation has shown that urine is highly sensitive (100%) and specific for the detection of anti-SIVcpz antibodies, whereas feces, which had a lower sensitivity for antibody detection (65%) were useful for PCR amplification of viral RNA (positive result in 66% of cases) (66). We had used this strategy for virus detection and characterization in sooty mangabeys and confirmed that urine was highly sensitive for antibody detection (96%), while fecal antibody detection was significantly less sensitive compared to urine (16%). We have also found that feces were useful for amplification of viral RNA (50%). Moreover we were able to establish a correlation between the plasma viral load and virus amplification from feces (56).

Beside its obvious advantages, the limitations are: (i) the nature of sample precludes standardization: thus, in spite of previous reports, feces from SIVmnd-1-infected mandrills in Central Gabon have been negative thus far, in spite of a very high prevalence of SIVmnd infection in that area [Clifford, personal communication]; (ii) a positive animal cannot be tracked, so the virus cannot be isolated nor can its *in vivo* pathogenesis be investigated.

5.2. Diagnostic and identification strategies for SIVs

5.2.1. Serological testing

Serology is the gold standard for studying the prevalence of SIVs in non-human primates, for the discovery of new SIVs and for documenting cross-transmission to humans.

Most laboratories screen for anti-lentiviral antibodies using commercial ELISA and Western blot kits. These tests are based on antigens consisting of viral lysates or recombinant proteins or synthetic peptides corresponding to immunodominant epitopes of the two subtype B variants (strains LAI and MN) and HIV-2 group A (ROD strain). These "mixed" tests are therefore able to detect anti-HIV-1 and anti-HIV-2 antibodies. Cross-reactivities with other lentiviral lineages enable the use of these tests for screening non-human primate samples. However, the screening tests lack sensitivity for the diagnosis of divergent strains, such as HIV-1 group O samples or HIV-1 group M non-subtype B samples during seroconversion (67,68). In humans, sensitivity problems had been solved by adding specific group O peptides in the test design and by the use of 4th generation tests which allow detection of p24 antigen and anti-HIV antibodies. For a more sensitive detection of SIVs in non-human primates, two strategies have been developed: the first one is based

Table 2. Primer sets used for "diagnostic" PCR to identify divergent SIVs

Primer name	Position	Primer sequence	Reference
UNIPOL 1	2420	AGTGGATTCATAGAAGCAGAAGT	83
UNIPOL 2	2700	CCCCTATTCCTCCCCTTCTTTTAAAA	83
UNIPOL 3	1940	TGTCAACATAGTAACAGATTCACAATA	83
UNIPOL 4	2900	ACTACTGCCCCTTCACCTTTCCA	83
HPOL4538	2900	TACTGCCCCTTCACCTTTCCA	84
HPOL4235	2570	CCCTACAATCCCCAAAGTCAAGG	84
HPOL4327	2650	TAAGACAGCAGTACAAATGGCAG	84
HPOL4481	2800	GCTGTCCCTGTAATAAACCCG	84
DR1	235	TRCAYACAGGRGCWGAYGA	77
DR2	1020	AIADRTCATCCATRTAYTG	77
DR4	710	GGIATWCCICAYCCDGCAGG	77
DR5	930	GGIGAYCCYTTCCAYCCYTGHGG	77
Polis4	2090	CCAGCNCACAAAGGNATAGGAGG	69
PolOR	2902	ACBACYGCNCCTTCHCCTTTC	69

Different primer combinations see Figure 1 may be used

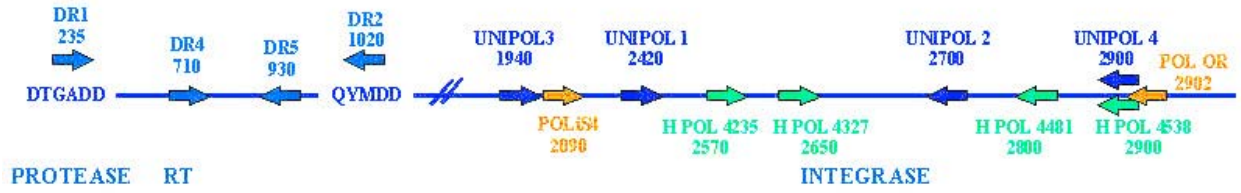

Figure 1. PCR "diagnostic" strategies for identification of new SIVs (Fragment lengths are: DR1/DR2=789 bp; DR4/DR5=194 bp; DR1/PolOR=2667 bp; Polis4/PolOr=812 bp; Hpol4235/Hpol4538=303 bp; Hpol4327/Hpol4481=154 bp; UNIPOL1/UNIPOL2=280 bp).

on the use of a highly sensitive line assay (INNO-LIA HIV, Innogenetics, Ghent, Belgium) as a screening test. Using this strategy, more than 10 different new virus types have been identified in non-human primates (22, 69-71). The second strategy uses synthetic peptides which are unique to representative strains belonging to different SIV lineages (72). Both Gp41/36 and V3 peptides are used. Gp41/36 peptides enable extensive cross-reactivities thus rendering the test highly sensitive; conversely, the V3 peptides reactivities are very specific, therefore, their use allows differentiation between viruses belonging to different lineages (72). This test has been used for the discovery of several SIVs (40, 73, 74) and it was also used to identify a Cameroonian man who had an indeterminate HIV serology but reacted strongly (and exclusively) with a SIVmnd V3 loop peptide (40). Although viral sequences were not obtained in this man, the finding suggests that SIVs other than SIVcpz and SIVsm have the potential to cross into the human population and calls for monitoring in Central Africa.

5.2.2. Molecular characterization

Full length sequences are required to fully describe a new SIV. The database is increasing each year and presently 36 full-length SIV genomes are available [http://hiv-web.lanl.gov] and their number is expected to rapidly increase, as significant advances have been recently reported in characterizing SIV diversity (22, 40, 48, 57, 75, 69-71, 73, 75-82). The requirement of full-length sequencing of the newly identified viruses is necessary to characterize their phylogenetic relationships and to identify recombinant structures. Also, full genome analysis will place new SIVs into one of three genomic groups (see below). By this analysis SIVs containing *vpx* or *vpu* have been recently identified (40, 55, 70, 76-78, 80, 81). Altogether, these analyses will clarify the molecular evolutionary history of primate lentiviruses as well as the threat to human population.

In order to "diagnose" a new virus, most invetigators use PCR (or RT-PCR) for the amplification of the integrase region, which is the most conserved region between different SIV types. Several sets of primers have been evaluated for this purpose: Unipol (83), Hpol (84), DR (77) or Or/Is4 (69) (Figure 1; table 2).

Once the diagnostic fragment is characterized, specific primers can be designed to target the circular genomic forms in a "walk on genome" approach (69, 70, 81, 82).

5.2.3. Virological approaches

The efficiency of the isolation of SIVs varies widely. Their ability to replicate in human PBMC or T cell lines has been evoked as a major argument in favor of these viruses infecting the human population exposed. This ability has been documented for SIVcpz (12), SIVsm/SIVmac (80, 85), SIVagm (79, 85), SIVlhoest (79, 80), SIVmnd-1 (80, 86), SIVrcm (55, 80), SIVmnd-2 and SIVdrl (40, 82, 87) (table 3). Altogether, these data confirm that SIV may have an intrinsic capacity to enter the human population through $CD4^+$ T lymphocytes. SIVs ability to infect human macrophages have been also reported for SIVagm and SIVmnd (33, 86). For HIV-1 it was shown that the macrophage tropism was linked to the use of

Table 3. Host range of SIVs in different cell lines

Growth support	Cell description	SIVcpz	SIVsm	SIVmac	SIVagm	SIVlhoest	SIVsun	SIVmnd-1	SIVsyk	SIVtal	SIVrcm	SIVmnd-2	SIVdrl
		+	+	+	±	+	-	+	-	-	+	+	+
human MDM[2]		-	+	+	±	+	-	-	-		±		
macaque PBMC			+	+					-	-		+	+
chimpanzee PBMC		+	-			+		+	-	-	-	-	-
MT2	T cell line				+	-	-			-	-	-	-
C8166	T cell line				+	+	+			-		-	-
H9	Cloned from Hut78		+	+	-	-	-				+	-	-
MT4	T cell line			+	+	+	+				-	-	+
U937	Promonocytic cell line			-	-	-	-		-		-	-	-
SupT1	T cell line			-	+	+	+		+	-	-	+	+
PM1					-	-	-				+	-	-
Hut78	T cell line		+	+	-	-	-					-	-
Molt 4 Clone 8	T cell line	+	-	-	+	+	+		-	-	-	+	+
CEMss	T cell line	+			+	+	+				-	-	+
CEMx174	T cell - B cell hybrid line		+	+	-	+	-		++	+	-	+	+

[1] PBMC-peripheral blood mononuclear cells [2]MDM-monocyte-derived macrophages

chemokine receptor CCR5, which is the major co-receptor *in vivo* for viral entry for most SIVs (88, 89). In a recent study, it was shown that 75% of the tested SIV isolates infect human macrophages (49). The exceptions are SIVsun and SIVsyk, which cannot replicate in human PBMC or macrophages. SIVagm also presents discordant patterns with low or absent replication in human PBMCs (49). This study also provided evidence that SIVmac239 can replicate in some cases in human macrophages, which is remarkable, since this virus is considered T tropic and unable to replicate in human (90) or rhesus macaque (91) macrophages. Also SIVmnd-1 GB1 was reported to replicate in human PBMCs but not in macrophages (49). These data are consistent with previous studies reporting exclusive use of CXCR-4 as a co-receptor by this virus (92). However, one should note that the SIVmnd-1 GB1 from the NIAID repository had been previously adapted on SupT1 cells, which may have affected tropism.

Some SIVs might require special culture conditions. The *in vitro* SIVsyk tropism is very restricted. This virus grows in Syke's monkey PBMC, but only after CD8 cell depletion (93). Data on *in vivo* viral replication showed that only one (SIVlhoest) out of four cercopithecini SIVs have the ability to grow on human PBMCs and macrophages (table 3) suggesting that extensive *in vitro* studies on SIVs properties are needed in order to correctly evaluate the threat for human population following exposure to these viruses.

6. EPIDEMIOLOGY

6.1. Natural host species and taxonomy

SIV infection has been described in 40 simian species and subspecies (table 1). Partial or complete viral sequences are available for 28 species and 5 additional species have been found to harbor SIV-specific antibodies. In the vast majority of cases, the infected species represent the reservoir of that virus type, which is designated by an abbreviation of the host primate species, although numerous exceptions exist. Therefore, the SIV isolated from chimpanzees is SIVcpz. When different subspecies of the same species are infected, the name of the subspecies is included in virus designation. The four subspecies of African green monkeys (vervet, grivet, tantalus and sabaeus) are infected by SIVagm.Ver, SIVagm.Gri, SIVagm.Tan and SIVagm.Sab, respectively. For the chimpanzee subspecies infected by SIVs, there is an exception to this rule: each SIVcpz isolate is named from the known or last known country of origin of the chimpanzee, probably as a consequence of the low prevalence of SIVcpz and the reduced number of viral isolates. Thus, the *Pan troglodytes troglodytes* subspecies is infected by SIVcpzGAB (Gabon), SIVcpzCAM (Cameroon) and SIVcpzUS (Hollowman Air Force base, New Mexico), whereas *P. t. schwenfurthii* is infected by SIVcpzANT (Democratic Republic of Congo via Antwerpen) and SIVcpzTAN (Tanzania) (12, 16, 61, 66, 94).

For the individual isolates of different SIV types, the current agreement is to include in the name of the isolate the country of origin: thus SIVmnd-1 GB1 and SIVrcm GAB1 are viruses isolated from Gabon (55), whereas SIVrcm NG409 originates from Nigeria (80). Some authors also include the year of sample. Thus, SIVsmSL92 is a sooty mangabey virus isolated from sample collected in Sierra Leone in 1992 (14). This is a useful feature to trace the origin of viruses allowing for a better understanding of their evolution.

6.2. Prevalence in the wild

Data are limited on SIV prevalence in different species of primates. However, some patterns have emerged from studies carried out thus far.

Numerous species of African non-human primates undoubtedly have high levels of SIV prevalence. Of these, African green monkeys (AGM) seems to be

particularly interesting: they not only are the most numerous non-human primates in Sub-Saharan Africa, but clear evidence of the simian cross-transmission potential of SIVagm has been observed in the wild, where this virus has been isolated from two species of baboons and the patas monkey (95-97). In captivity, in Kenya, SIVagm.Ver was transmitted to white crowned mangabeys housed at the same primate center (62). Also, SIVagm has been experimentally shown to be a pathogenic virus, being able to induce AIDS in pig-tailed macaques (98). Studies on hundreds of wild-born AGMs belonging to different subspecies revealed a prevalence of SIVagm infection of 40-50% (8, 9, 99). These prevalence levels are similar in all AGM subspecies (100), vervet (*Chlorocebus pygerythrus*), grivet (*C. aethiops*), tantalus (*C. tantalus*) and sabaeus (*C. sabaeus*) and are independent of their geographic origin (101). AGMs are the most geographically dispersed monkeys in inter-tropical Africa, thus representing a significant SIV reservoir. There is a correlation between the age of AGMs and the prevalence of SIVagm infection (60,102). Thus, in a retrospective analysis conducted at the Pasteur Institute of Dakar, Senegal on sera collected between 1967 and 2000 it was shown that SIVagm prevalence correlates with age (102). Prevalence in adult AGMs was 80%, fourfold higher than in juveniles aged 1 to 3 years. In another study of vervet monkeys in Awash National Park in Ethiopia, East Africa, no infections were identified in very young monkeys (with deciduous dentition only) (60). Interestingly, seroepidemiological studies showed that AGMs from the Caribbean Islands were not infected by SIV (99,103). AGMs were extensively transported from Africa to the Caribbean in the 17th and 18th centuries (104) and their lack of infection has been explained by their capture as juveniles. The alternative explanation that SIVagm was not yet present in the AGM population two centuries ago, is highly improbable. However, this hypothesis cannot be discharged if considering that HIV-1 prevalence in East Africa already reached levels of 25-30% after only 50 years of epidemic evolution.

A study of SIVsm prevalence in feral sooty mangabeys in Sierra Leone revealed that 4 out of 16 tested wild mangabeys were infected with SIVsm. Out of the infected monkeys, three were adults, the SIVsm prevalence being higher in adult monkeys as compared to juveniles (14). This study had produced compelling evidence that sooty mangabeys are infected at high prevalence in the wild (25%) and also suggested that the major route of transmission in this species is sexual (14). This explained why the prevalence in pet mangabeys in Sierra Leone and Liberia was significantly lower (4-8%) than in wild monkeys (11,14): pet monkeys had been captured while juvenile, before being sexually active and thus not at great risk for SIVsm.

SIV prevalence in other feral monkeys may be as high as that reported for African green monkeys. Eight out of the 14 (57%) tested l'Hoest monkeys (*Cercopithecus lhoesti*) originating from Haut-Congo and Kiwu regions of the Democratic Republic of Congo were infected with SIVlhoest (105). The prevalence of SIVmnd-1 infection in wild mandrills originating from the Lope Reserve in Gabon was 76% (16 out the 21 tested) [Marx et al., unpublished data]. In this case, significant age-related differences in prevalence levels have been reported for SIVmnd-1-infected mandrills (40). Moreover, a lower prevalence has been reported in juvenile mandrills in an earlier study which found that only 2 out of the 23 founders of a mandrill colony in Franceville, Gabon had been positive when captured (58, 106). SIVmnd prevalence in mandrills in US zoos revealed an overall prevalence of 17% (8). One should note that at the time of this testing, the second mandrill virus was not yet discovered, there fore this prevalence included both SIVmnd-1 and SIVmnd-2 infections.

Prevalence rates of SIV infection in Syke's monkeys (*Cercopithecus albogularis*) might be elevated, as suggested by testing serum from 100 wild-caught or colony-born monkeys, which gave a prevalence rate of 59% (93, 107). Another study showed that 23 out of 73 (32%) tested monkeys were seropositive (62). Only one virus has been isolated from all these monkeys. More recently, 17 out of 60 (28%) Syke's originating from different regions of Kenya tested positive and new virus strains were characterized. In the same study 9 out of 14 (64%) blue monkeys (*Cercopithecus mitis*) have tested positive and a SIVblu has been characterized (75).

Testing of 9 red-capped mangabeys (*Cercocebus torquatus*) in Gabon revealed that only one of these was infected with SIVrcm (55). A more recent report established higher SIVrcm prevalence levels of 22% (4/18) (72).

The prevalence of SIVs in different *Colobinae* species has also been investigated (69, 71). Seven of the 25 (28%) wild born guereza colobus (*Colobus guereza*) monkeys from Cameroon were infected with a SIVcol (69). In the West African species of colobus six out of 13 (46%) monkeys tested positive. Colobines belonging to three species have been included in this study and viruses have been characterized from two of these species: SIVolc from olive colobus (*Procolobus verus*) and SIVwrc from western red colobus (*Piliocolobus badius*) (71). No information concerning SIV presence in Asian species of colobus is available.

Apes have also been reported to carry SIVs, although the prevalence rates seem to be significantly lower. Thus, the common chimpanzee (*Pan troglodytes*) is infected by SIVcpz. At least two chimpanzee subspecies (*P. t. troglodytes* and *P. t. schweinfurthii*) are naturally infected (12, 16, 61, 66, 94). Studies on hundreds of captive wild-born chimpanzees (*P. t. troglodytes*) originating from Democratic Republic of Congo, Gabon, Cameroon and Ivory Coast resulted in the isolation of 6 SIVcpz strains (named SIVcpzGAB-1, SIVcpzGAB-2, SIVcpzCAM-3, SIVcpzCAM-4, SIVcpzCAM-5, SIVcpzCAM13) (12, 17, 61, Nerrienet, personal communication]. Only one case of SIVcpz infection has been identified in captive chimpanzees in the US (SIVcpzUS) (16). One should note that these rates might represent an underestimate, in

keeping with the capture of these chimps as juveniles. Intriguingly, serological testing of infant chimpanzees (aged less than 1 year) in Gabon and Cameroon has shown seropositivities without any virus being isolated or amplified. Such a clinical figure is highly suggestive of a passive transplacental transfer of antibodies from the infected mother. This may imply that SIVcpz prevalence in wild chimpanzees might be higher than expected in West-Central Africa [F. Simon, personal communication; P. A. Marx, C. Apetrei, unpublished observation].

Until recently, only one isolate had been available originating from *P. t. schweinfurthii*: SIVcpzANT (94). A recent study revealed three more cases of SIVcpz infection have been identified by testing *P. t. schweinfurthii* from, National Kibale Park (Uganda) and Gombe National Park (Tanzania). All these three SIVcpz-infected chimpanzees belonged to the same group in Gombe National Park (57, 66).

For the remaining two chimpanzees subspecies the situation is different: no case of infection has been detected by testing 387 West African chimpanzees (*P. t. verus*) caught in the wild or bred in captivity (108). Also, the only case of SIVcpz infection in the last subspecies of chimpanzees (SIVcpzCAM-4 infection in *P. t. vellorosus*) resulted in captivity by transmission from an infected *P. t. troglodytes* (SIVcpzCAM-3) (61). Altogether, epidemiological data revealed that the prevalence rates of SIVcpz infection in wild animals are significantly lower than those reported for other species of non-human primates. Whether SIV is extinct in some chimpanzee sub-species or it is a recent occurrence in the others, is not yet known.

Sero-epidemiological surveys of African monkeys identified seroprevalence in some primate species without any virus being yet isolated from these monkeys. These are *Cercopithecus hamlyni*, *Allenopithecus nigroviridis*, *Lophocebus albigena, C. pogonias* and *C. lowei* (8,19,22). Also, baboons showed relatively frequent serological reactivities by both ELISA and Western blot (72, 109, 110), whereas no virus could be recovered from these species. However, two baboon species (*Papio anubis* and *P. hamadryas*) have been shown to carry SIVagms from sympatric green monkeys (97, 98).

Sero-epidemiological studies failed to produce evidence of SIV infection in two major ape species in Africa: gorillas (8, 72) and bonobos (111). As these two species are closely related to humans, it is possible that the presumptive viruses infecting bonobos and gorillas might provide significant clues concerning SIV zoonotic potential. Another important negative result for the evaluation of lentivirus evolution and distribution on the African continent is that no evidence of SIV infection could be obtained for the Barbary macaques in the Gibraltar region (*Macaca sylvanus*) and in baboons in Saudi Arabia. This might eventually suggest that the emergence and cross-species transmission of SIVs in African non-human primates occurred after the separation of these two species from sub-Saharan species.

6.3. Routes of transmission

As already mentioned, sero-epidemiological surveys in AGMs, sooty mangabeys and mandrills revealed higher prevalence levels in adult monkeys than in juveniles, indicating a horizontal route of transmission. In AGMs, two routes of transmission have been described: sexual contact and bites (60, 102).

A different situation was observed in the semi-free colony of mandrills at International Medical Research Center of Franceville, Gabon. In this colony, no sexual transmission was found after 16 years of follow-up (40, 58, 112, 113). Two of the founders had been infected with two different viral types (SIVmnd-1 and SIVmnd-2) (40). Interestingly, two of the dominant males became SIVmnd-2-infected with no evidence of sexual transmission of this virus being observed. SIVmnd-1 had been transmitted to 4 offspring (males and females) of the SIVmnd-1 GB1-infected female founder. SIVmnd-2 had been transmitted from the infected male founder to 4 other males, following aggressive contacts for dominance (40, 114). In wild mandrills from the Lope Reserve in Central Gabon cases of SIVmnd-1 infection could be diagnosed in both sexes (40). More recent data have suggested that the Ougoue River in Central Gabon separated two distinct populations of mandrills. These two mandrill subspecies are infected with different SIVmnd types: all the SIVmnd-1-infected mandrills originated south of the Ougoue River, whereas mandrills infected with SIVmnd-2 originated from Northern Gabon and Cameroon (115). Viral segregation in the wild seems to be following biogeographical factors and has been interpreted as sub-species specific evolution of the two SIVmnd viruses.

Several cases of horizontal transmission occurring by biting have been described in captive monkeys. Thus, SIVsm has been transmitted between two sooty mangabey females (38) and SIVcpz has been transmitted between two chimpanzees belonging to two different subspecies (61). Also, SIVsm has been reported to be transmitted among macaques by biting (3).

Vertical transmission from mother to infant seems less frequent than horizontal transmission. The vertical transmission cases in captive mandrills in Gabon were already mentioned. One should note that in these cases no mechanism (s) of transmission (*in utero*, perinatally or by breast feeding) could be identified. In a recent prospective study, experimental mother-to-offspring transmission by breast feeding was not found (116). During another study, we failed to detect vertical transmission in AGMs (117).

7. SIV GENETICS AND CLASSIFICATION AND AN OVERVIEW OF PRIMATE LENTIVIRUS BIOLOGY

7.1. Position within the lentivirus genus

SIVs belong to the *Lentivirus* genus of the *Retroviridae*. These viruses are morphologically distinct from other retroviruses in that they have a bar or cone-shaped core (nucleoid). They have a complex structure with numerous accessory genes in addition to *gag*, *pol* and *env*

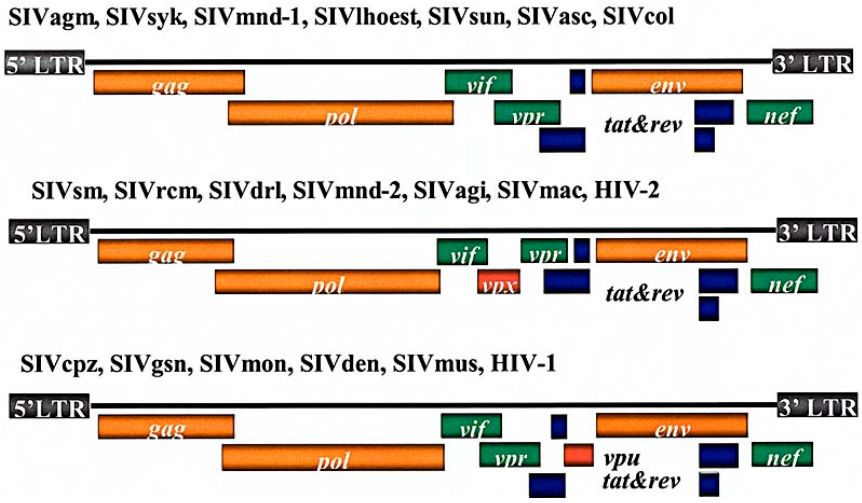

Figure 2. Three genomic types of simian immunodeficiency viruses.

genes. The number of accessory genes varies according to the type of virus. All known lentiviruses are exogenous and are transmitted horizontally and vertically. Lentiviruses are associated with a variety of diseases in cats, horses, goats, cattle and primates. Diseases include immunodeficiencies, neurological disorders, arthritis and others (118). Genomic organization and virus-host information data is available for lentiviruses infecting different mammalian hosts: feline immunodeficiency virus (FIV), caprine arthritis-encephalitis virus (CAEV), equine infectious anemia virus (EIAV) and bovine immunodeficiency virus (BIV). The non-lymphotropic lentiviruses (EIAV, CAEV and visna) do not cause immunodeficiency, whereas BIV may be non-pathogenic in cattle (119). FIVs have been described in wild cats and may be non-pathogenic in these natural hosts (120). The presence of accessory genes is variable: *rev, vif* and *A* for FIV, *tat*, *rev* and *S2* for EIAV, *rev*, *tat* and *vif* for CAEV, visna and BIV (119). Three accessory genes are specific only for primate lentiviruses: *vpr*, *vpx* and *vpu*.

7.2. Only three genomic types of SIVs

Primate lentiviruses genomes have the most complex retroviral structure. They contain the three retroviral structural genes (*gag*, *pol* and *env*) and the long terminal repeats (LTR) at the two genome extremities. The accessory genes are located in the central part of the genome and in the 3' region and they codify regulatory proteins. All primate lentiviruses harbor 5 regulatory genes (*vif*, *rev*, *tat*, *vpr* and *nef*) which generally overlap over genome. Genes for Tat and Rev consists of two exons (exon 2 lies in the *env* ORF). The presence of two other regulatory genes (*vpx* and *vpu*) is variable. Three patterns of genomic organization have been described for primate lentiviruses (Figure 2).

- SIVagm, SIVmnd-1, SIVlhoest, SIVsun, SIVsyk, SIVcol, SIVasc and SIVdeb contain only 5 accessory genes (*tat*, *rev*, *nef*, *vif* and *vpr*) (48, 69, 79, 121, 122, Saragosti, personal communication). This group now also includes SIVagm. Initial studies described SIVagm as having a peculiar structure characterized by the presence of a *vpx* and the absence of *vpr* or *vpu* (123). Subsequently, given the homology between *vpx* and *vpr*, it was suggested that SIVagm *vpx* should be reconsidered to be a *vpr* (124).

- HIV-1, SIVcpz, SIVgsn, SIVmon, SIVden and SIVmus share the same genomic organization with the three structural genes and the 5 common regulatory genes. However, their genomes also include a supplementary gene, *vpu* (125, 126). Until recently, this gene has been detected only in HIV-1 and SIVcpz and it was assumed that *vpu* is a recent acquisition of lentiviruses being specific only to apes (125, 127). However, the recent description of SIVgsn, the virus naturally infecting the greater white-spotted guenon (*Cercopithecus nictitans*), which also contains a *vpu*, suggests that apes acquired their lentiviruses following cross-species transmission from *Cercopithecus* monkeys (70). It is not clear how the *vpu* have been acquired by *C. nictitans*. One of the SIVs infecting another species in the same group of monkeys, SIVsyk from the Sykes' monkey (*C. albogularis*) does not have *vpu*. However, recent data have shown that SIVgsn is not an exception. At least two monkeys in the *C. mona* group of monkeys are naturally infected with *vpu*-containing SIVs: mona monkey (SIVmon) (78, Peeters, personal communication] and Dent's mona (*C. mona denti*) (SIVden) (81). Finally, SIVmus from cephus monkeys (*C. cephus*) have been recently reported to carry a *vpu* (77).

This genomic group can be further divided in two groups based on the overlapping of the *env* and *nef* genes. This overlapping is observed for SIVgsn and SIVden but not SIVcpz/HIV-1 (81).

- HIV-2, SIVsm, SIVmac, SIVrcm, SIVmnd-2 and SIVdrl form the third genomic group, which is characterized by the presence of the *vpx* gene (7, 128, 129). Similar to the *vpu* case, until recently *vpx* has been found only in HIV-2, SIVsm and SIVmac. Recently discovered SIVs isolated from Papionini monkeys (which includes

mangabeys, mandrills and drills) also contains this gene. These are SIVrcm (from red-capped mangabeys), SIVdrl (from drills), SIVmnd-2 (from mandrills) and SIVagi (from agile mangabey) (40, 55, 74, 77, 80, 82, 87). Thus far, *vpx* is a specific gene for SIVs infecting the Papionini group of monkeys. The *vpx* gene was acquired following a non-homologous recombination which resulted in a duplication of the *vpr* (130). For the remaining viruses (SIVtal, SIVblu, SIVdeb, SIVolc, SIVwrc, SIVasc), complete genome information is not as yet available.

To resume the discussion, apes-infecting SIVs carry a *vpu*, whereas papionini-infecting SIVs carry a *vpx*. The situation is less clear for *Cercopithecinae* monkeys, in which *vpu* may be present or absent. Thus far only 3 groups (out of 8) of the *Cercopithecus* genus carry *vpu*-containing viruses (*Cercopithecus mona, C. mitis* and *C. cephus* groups). *Chlorocebus* and *C. lhoesti* supergroup monkeys have an 8 gene organization, *Miopithecus* SIV is not yet fully characterized, whereas *Allenopithecus* and *Erythrocebus* have no specific SIV. Although specific SIVs have not yet been described for all guenons, the high prevalence in the wild corroborated the high diversity of viruses infecting these species. This points to the Cercopithecini as the origin of SIVs or at least as the major reservoir of virus. Also, recent studies suggest that *vpu* first appeared in cercopithecines which therefore appear to be a significant reservoir for viruses in the SIVcpz/HIV-1 lineage (70). These differences between genomic structures of SIVs infecting different cercopithecine species might be better explained (although not always consistent) when superimposing SIV diversity over host relationships. Recent studies based on genetic analysis of both mitocondrial and chromosomal DNA of different species of guenons revealed a significant clustering in two divergent groups. The first one is represented by l'hoest monkeys (l'hoesti and solatus), AGMs and patas. One should note that SIVs infecting these monkeys always contain an 8 gene genomic structure. The second genetic group of cercopithecini is formed by *C. ascanius*, *C. cephus*, *C. nictitans*, *C. mitis*, *C. pogonias*, *C. mona*, *C. hamlyni*, *C. diana* and *C. neglectus* monkeys. As for the host relationships, which are less clear than for the first group, viruses infecting these monkeys consist of 8 or 9 genes. Within this group of monkeys, *C. ascanius*, *C. cephus*, *C. nictitans* and *C. mitis* are sister taxa and might have a more recent common ancestor. Viruses infecting these monkeys are also more closely related to each other. Two of them are carrying a *vpu* (SIVgsn and SIVmus).

Humans are infected by two different lentiviral types, HIV-1 and HIV-2, belonging to two of the genomic types which have a simian origin (SIVcpz and SIVsm, respectively). Of note, none of the *Cercopithecinae* viruses have been identified in humans. It is interesting to note that both human types have a structure which includes 6 accessory genes. The significance of this fact is not clear. A recent report of a new cross-species transmission of SIV to humans, documented only based on serological data, involved an SIVmnd-like virus; although in the envelope gene the two viruses infecting mandrills share antigenic properties, this human case occurred in the area of SIVmnd-2 (a virus carrying a *vpx* gene) circulation (40).

7.3. Phylogenetic clusters

SIV infections have so far been described in 40 African non-human primates. Partial or full-length nucleic acid sequences are available for 34 types, whereas 23 types have at least one complete genome sequence. Phylogenetic analyses of the available strains have shown a high variability and different patterns of clustering (Figure 3). Phylogenetic analysis of the available SIV strains is complicated due to high sequence diversity and recombination between divergent lineages resulting in different patterns of clustering. To simplify this presentation, we will refer to six "classical" SIV lineages: SIVcpz/HIV-1, SIVsm/HIV-2, SIVagm, SIVlhoest, SIVsyk and SIVcol. However, the relationship between these SIV lineages, and newly characterized SIVs, is highly complex such that the characterization of recombinants is limited to the identification of the most obvious mosaic genomes. Also, to explain the relationships between viruses infecting different species of monkeys and apes it has been suggested that, at least in some instances, there is evidence for "host-dependent" evolution or co-divergence, the bifurcation or split of a viral lineage arising as the result of the split/speciation of the host lineage (19, 25, 48, 101). However, host dependent evolution implies that the divergence of the SIV lineage will have taken place at the same time as the primate speciation (or sub-speciation), which in all cases occurred hundreds of thousands to millions of years ago. The best attempts to date SIV divergence using molecular clocks have estimated timings of hundreds to thousands of years in the past (131). If this discrepancy is not an artefact of the methods currently used then an alternative hypothesis, "preferential host-switching", is required to explain the similarities between the virus and host phylogenies (132). This hypothesis relies on the fact that cross-species transmission between sub-species or closely related species can result in a significant match between the primate and SIV bifurcations. Thus, preferential host-switching, a tendency for closely related species to exchange viruses more frequently, can account for the observed similarities between the SIV and primate phylogeny (132).

The 6 "classic" phylogenetic lineages are:

- SIVcpz isolated from chimpanzees (*Pan troglodytes*) (12,16, 57, 61, 66, 94, 125, 133).
- SIVsm from sooty mangabeys (*Cercocebus atys*) (11, 14, 38, 56, 129, 134, 135).
- SIVagm from the four species of African green monkeys (genus *Chlorocebus*) (102, 104, 122, 123, 136-140).
- SIVsyk from Syke's monkey (*Cercopithecus albogularis*) (93, 107).
- SIVlhoest, which includes viruses isolated from the L'Hoesti supergroup (*C. lhoesti* and *C. solatus*) (48, 79, 105) and from mandrills (*Mandrillus sphinx*) (106,121).
- SIVcol isolated from *Colobus guereza* (69).

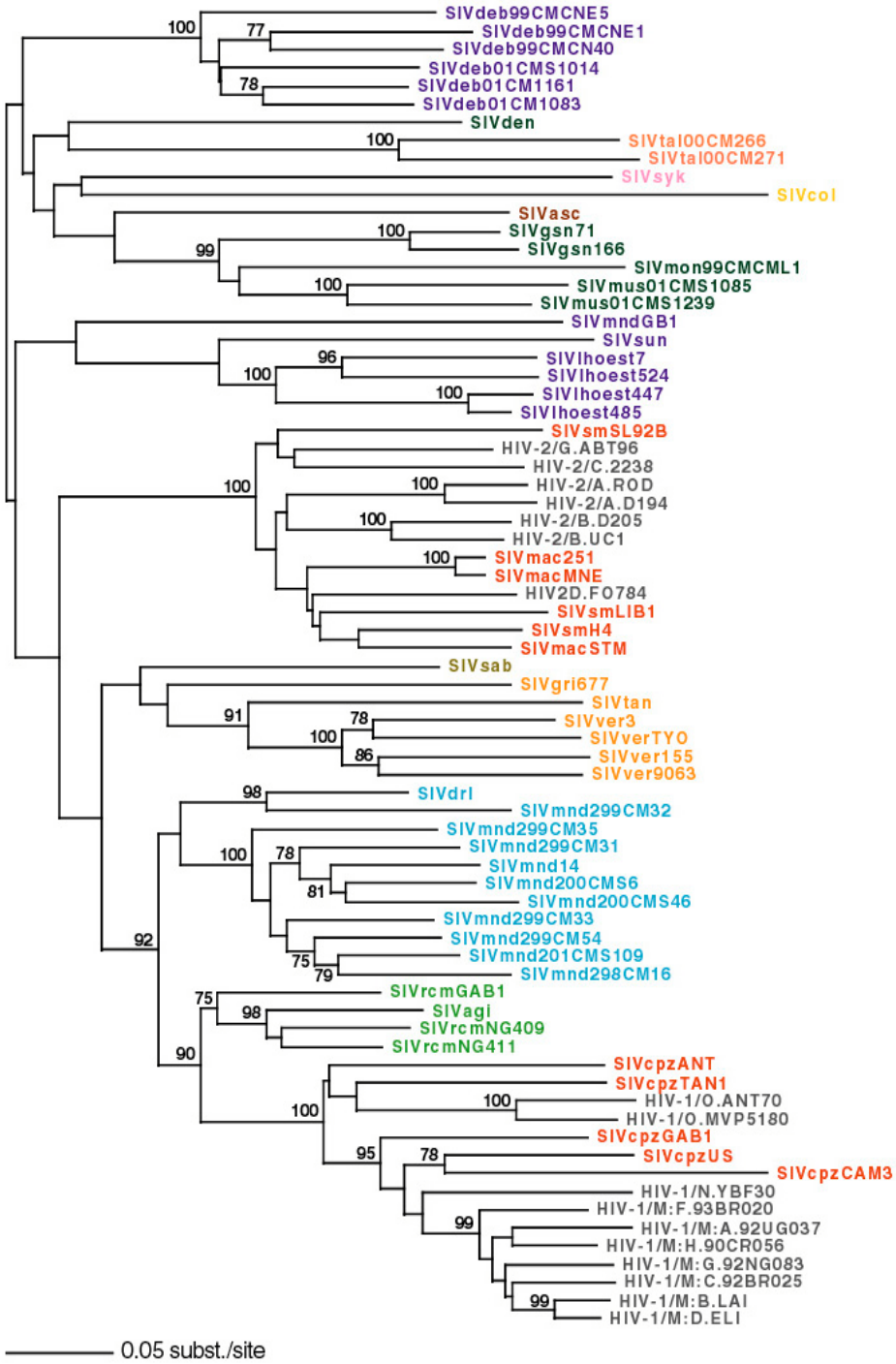

Figure 3. Phylogenetic relationships among SIV types and HIV strains inferred from *pol* by neighbor-joining using the HKY model of nucletotide substitution; 522 sites remained after removing gaps. The numbers to the left of nodes indicate percentage bootstrap replicates supporting the clade to the right; bootstraps results of 75% or greater are shown. The phylogeny is mid-point rooted. The scale indicates substitutions per site and refers to the horizontal branch lengths. The vertical branch lengths are for clarity only.

These six phylogenetic lineages are approximately equidistant, with genetic distances of up to 40% in the Pol proteins. Five of the 6 lineages have two or more strains. The l'hoesti lineage is unique in being formed by SIVs circulating in distantly related species.

In phylogenetic trees, HIV-1 and HIV-2 are dispersed among related SIVs and show no species-specific pattern. HIV-1 is part of the SIVcpz lineage, at least in *gag-pol* trees, whereas HIV-2 is part of the SIVsm lineage (Figure 3). Thus, primate lentivirus phylogenetic trees

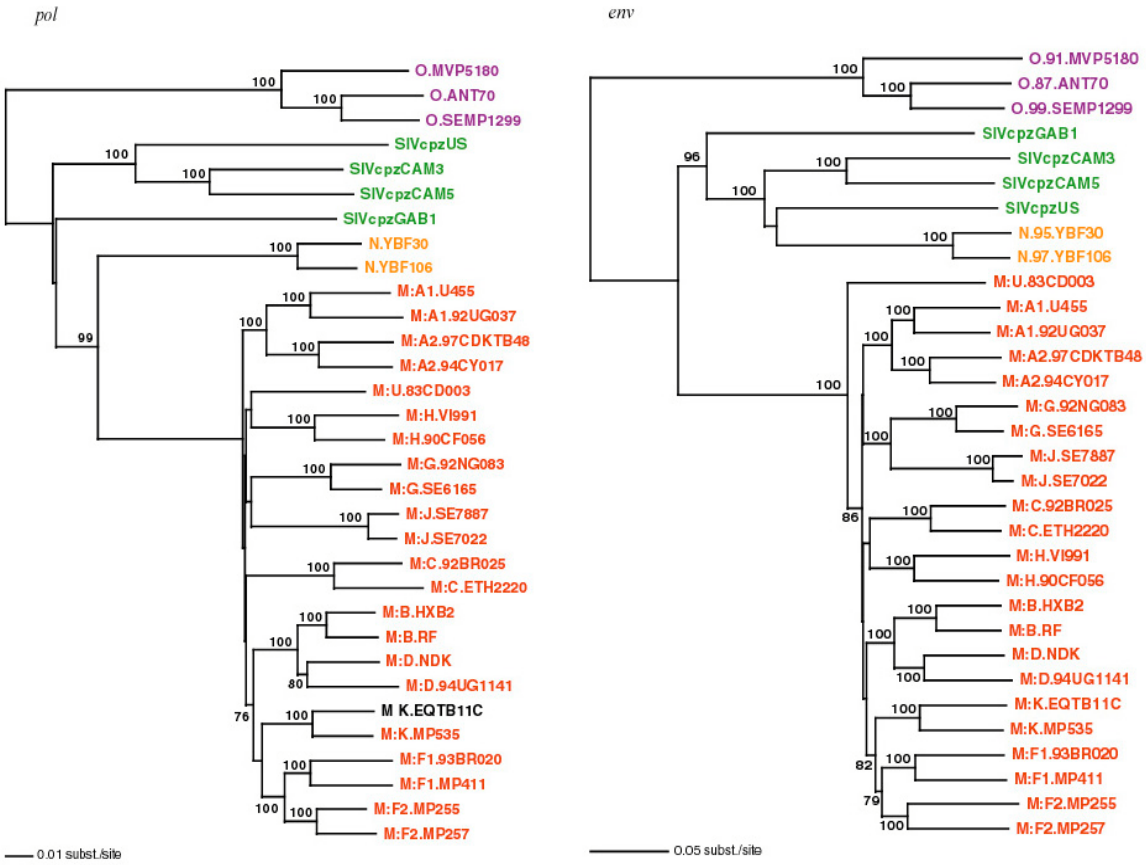

Figure 4. Phylogenetic relationships among SIVcpz from *Pan troglodytes troglodytes* and HIV-1 strains. The trees are inferred from *pol* (a) and *env* (b) by neighbor-joining using the HKY model of nucletotide substitution; 2723 and 1756 sites respectively remained after gaps were removed. See the legend to Figure 3 for further details.

show that, from a phylogenetic point of view, the differentiation between HIVs and SIVs is irrelevant, the two human types being not grouped together and thus not being close relatives, thus providing the argument of the simian origin of HIVs. Phylogenetic analyses corroborate epidemiological studies showing that the AIDS pandemic arose in the second half of the 20th century by interspecies transmission from non-human primate hosts (19, 141, 142).

Phylogenetic lineages are not superimposable on genomic types. As the phylogenetic relationships are continuously and rapidly changing with the addition of new strains, it is probably more effective to consider 3 types of primate lentiviruses, as a function of the genomic organization. This simplifies their classification and our perceptions of SIV origin and evolution.

7.3.1. SIVcpz/HIV-1 lineage

This lineage contains HIV-1 which is the major cause of the AIDS pandemic and its closest simian counterpart, which has been isolated from chimpanzees (Figure 4). It is the best defined lineage because more than 200 HIV-1 strains have been completely sequenced and characterized. However, relatively few SIVcpz isolates are known.

Chimpanzees can be split in four subspecies based on mitochondrial DNA analysis (143, 144): *Pan troglodytes troglodytes*, *P. t. schwenfurthii*, *P. t. vellorosus* and *P. t. verus*. These subspecies have different geographical distribution, with *P. t. troglodytes* living in Central Africa, *P. t. schwenfurthii* in East Africa, *P. t. verus* in West Africa and *P. t. vellorosus* in West-Central Africa, being separated from *P. t. troglodytes* by the Sanaga River in the southern Cameroon (145). SIVs have been detected in only two of these sub-species and a clear host-dependent evolution can be described for SIVcpz. Thus, viruses isolated from Central African chimpanzees cluster together in a *P. t. troglodytes* subcluster (16, 61). Until recently a single highly divergent SIVcpz isolate was available from *P. schweinfurthii* (94). However, recently three new strains have been reported to cluster with the SIVcpzANT strain (57, 66, 75). Finally, a study in Cameroon has reported a case of infection in a *P. t. vellorosus* (SIVcpzCam-4), but sequence analyses strongly suggested that this infection occurred in captivity from a *P. t. troglodytes* (SIVcpzCam-3) (61). Subspecies characterization for SIVcpz infected non-human primates proved to be of importance for our understanding of the orgin of HIV-1, pointing to SIVcpz as the source of HIV-1 infection (16, 61).

Sequence analyses of HIV-1 isolates obtained from all over the world have shown that they fall in three distinct phylogenetic clusters defined as groups, M, N and O (18, 146) (Figure 4a, b). Group M viruses are the most numerous and the most geographically dispersed. Group O is comprised of viruses isolated from individuals originating from Cameroon. A few cases have been reported to occur in Europe and the United States (147-150). Only 6 cases of group N infection are known to date and they occur exclusively in Cameroon (18, 26). If HIV-1 phylogenetic trees are constructed including SIVcpz sequences, the three HIV-1 groups are not clearly separated from SIVcpz; instead, HIV-1 group N viruses are more closely related to SIVcpz than to other HIV-1 groups (Figure 4). This indicates that HIV-1 has arisen by cross-species transmission from chimpanzees (16, 18) and also points to the three HIV-1 groups originated from three different cross-species transmission events. This hypothesis is also supported by the observation that HIV-1 groups clearly show differences in their biological properties (151, 152). All three HIV-1 groups are more closely related to SIVcpz isolates from *P. t. troglodytes* than to isolates from *P. t. schweinfurthii* (Figure 4), which shows that the former chimpanzee subspecies and not the latter represents the source of HIV-1 (16,61). Finally, one should note that HIV-1 group N viruses are recombinants, being more closely related to SIVcpz in *gag-pol* and to HIV-1 group M in *env* trees (16, 61) (Figure 4a, 4b). It was suggested that the recombination event which generated this virus probably occurred in chimpanzees shortly before its cross-species transmission to humans (153). However, a recent study on HIV-1 group N diversity established that the alternative hypothesis of a HIV-SIV recombinant being generated in a human superinfected with a group M ancestor and a SIVcpz strain cannot be discounted (154). Phylogenetic data also have an epidemiological and historical support: the origin of HIV-1 occurred in Central Africa (155-157). The chimpanzee subspecies *P. t. troglodytes* is distributed in Cameroon, Gabon and neighboring countries from Equatorial Africa, and the HIV-1 group N have been only identified in patients from this region (17, 18, 26), the majority of group O cases originate from patients in this region (147) and although the group M has an universal distribution, the greatest strain diversity is also observed in Central Africa (155-158). Finally, the oldest HIV-1 strain was sampled in Kinshasa in 1959 (159), whereas the oldest HIV-1 isolate (Z321) was obtained from a specimen collected in the Democratic Republic of Congo in 1976 (160).

In the few naturally infected chimpanzees, SIVcpz appears to be nonpathogenic (161-163), recapitulating the virus-host relationships observed in other lentiviral infections in their natural non-human primate hosts. SIVcpzANT was passed to one chimpanzee, without strong evidence of immune dysfunction (164). One of these animals showed a slow decline in $CD4^+$ cell numbers (163). In the SIVcpzANT-naturally infected chimpanzee, viral loads were higher than those observed in HIV-1-infected chimpanzees, comparable to viral loads observed during the chronic phase of HIV-1 infection in humans (164). Recent studies of primary infection of chimpanzees with HIV-1 strains of different phenotype have shown different patterns of viral replication. Thus, R5-dependent non-syncytium-inducing HIV-1 isolates and SIVcpz-ANT were found to have relatively higher viral loads than the syncitia inducing, X4-dependent or X4/R5 primary HIV-1 isolates (165).

Of the more than 150 chimpanzees experimentally infected with HIV-1, only 1 has developed AIDS (166-168) and three more showed signs of progressive HIV infection (169). Although chimpanzees are susceptible to HIV-1 infection (170, 171) most infected chimpanzees mount vigorous humoral and cell-mediated immune response, maintain normal counts of $CD4^+$ T lymphocytes, harbor low plasma viral loads and remain healthy (169). The apparent lack of disease progression in HIV-infected chimpanzees is possibly due to the absence of chronic immune activation, with a normal response to recall antigens, resistance of chimpanzee macrophages to infection with primary HIV isolates, preservation of regenerative capacity of $CD4^+$ cells, no increase in expression of activation markers or apoptosis and absence of cytotoxic $CD8^+$ T cell infiltration and degenerative changes in lymph nodes (164, 167, 172-174). Interestingly, *in vitro* studies have shown that chimpanzee PBMCs have a lower capacity to support viral replication when compared to human PBMCs. This difference is not due to a lower availability of target cells for viral infection or to a different susceptibility to apoptosis, but to a post-entry barrier to virus replication (175). *In vitro*, SIVcpz replication is suppressed by beta-chemokines and $CD8^+$ cells, but not by natural killer cells from infected chimpanzees (176). In contrast to humans, HIV- and SIVcpz-infected chimpanzees do not have increased intracellular levels of beta-chemokines (177).

7.3.2. SIVsm/SIVmac/HIV-2 lineage

SIVsm naturally infects sooty mangabeys (*Cercocebus atys*) and is closely related to HIV-2 and to SIVmac (5, 129, 178). Phylogenetic analyses, as well as geographic coincidence, support the idea that multiple cross-species transmissions from sooty mangabeys to humans gave rise to HIV-2 A-G groups (formerly referred as "subtypes") (11, 14, 15, 19, 25). Similarly, experimental transmission of SIVsm to macaques is at the origin of SIVmac (63). Full-length SIVmac sequences form a tight cluster in the HIV-2/SIVsm/SIVmac phylogenetic trees, and can be traced to a virus that infected captive sooty mangabeys at the California National Primate Research Center (Davis, CA) (5, 129, 179, 180). We have recently shown (56) that at least 5 of the founders of the Yerkes colony were SIV-infected when imported to the United States. This observation is supported by our results showing the co-circulation of at least five SIVsm lineages in the SM colony of the Tulane National Primate Research Center (transferred from the Yerkes National Primate Research Center). At least two other sooty mangabeys have been infected with two divergent viruses which gave rise to the SIVmac and SIVstm, which are grouped separately in the SIVsm/SIVmac/HIV-2 phylogenetic trees.

Partial SIVsm sequences from naturally infected sooty mangabeys from Liberia, Sierra Leone and Ivory

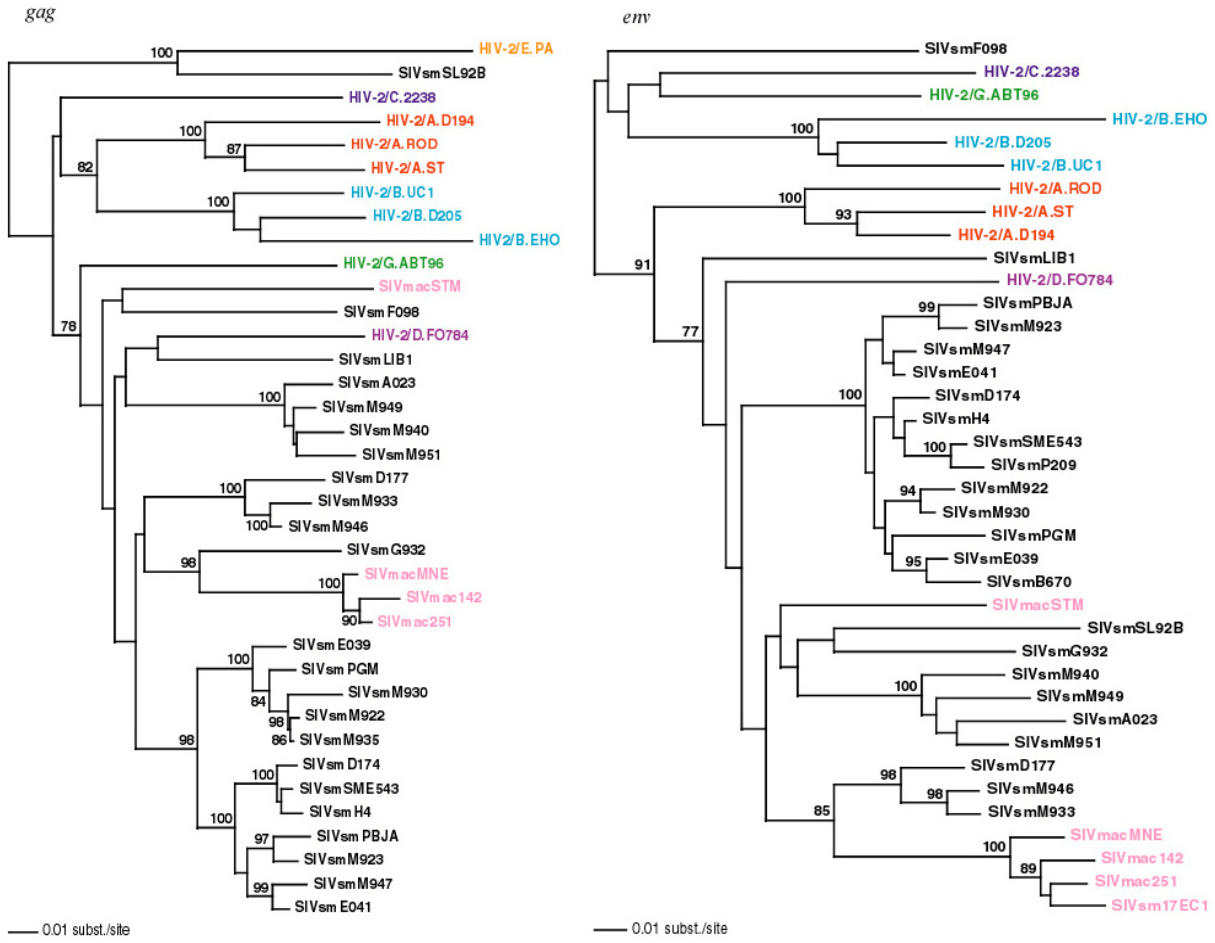

Figure 5. Phylogenetic relationships among SIVsm, SIVmac and HIV-2 strains inferred from *gag* and *env* by neighbor-joining using the HKY model of nucletotide substitution; 718 and 393 sites respectively remained after gaps were removed. See the legend to Figure 3 for further details.

Coast have revealed wide genetic diversity (11, 14, 39, 134), with the SIVsm strains originating from Sierra Leone forming a subcluster in the SIVsm lineage [P. A. Marx, B. Ling, C. Apetrei, unpublished data]. Two of the viruses identified in our survey of sooty mangabeys from Sierra Leone, SIVsmSL92b and SIVsmSL92c, were found to cluster closely with the *gag* sequence of HIV-2 PA, the sole representative of the non-epidemic HIV-2 group E (14). SIVsmSL92b and SIVsm92c were isolated from two sooty mangabey kept as pets in the village of Panguma, in central Sierra Leone. HIV-2 PA was amplified from a Los Angeles dialysis patient who was born in Sierra Leone near Panguma (25, 181). This remarkable geographic coincidence, associated with the homology of the *gag* sequences, provided the most conclusive evidence that interspecies transmission was at the origin of HIV-2 (14).

However, the striking feature of HIV-2 trees (Figure 5) is the discordance in the prevalence of different HIV-2 genetic variants. Of seven HIV-2 groups, only A and B are epidemic (24, 25, 28). The rest, groups C-G (25, 27, 28) are non-epidemic strains that are weakly pathogenic, replicate poorly in infected humans and are found only within the range of sooty-mangabeys or in persons who emigrated from Western Africa (25, 182). Recently, one of the strains clustering in these groups has been found to produce immune suppression [F. Simon, personal communication]. Moreover, SIVsm has been accidentally transmitted to humans in laboratories in the United States but in one case the infection was cleared (182) whereas in the second case (a human infection with SIVsm670), a persistent non-symptomatic infection had been observed (183).

SIVsm infection in sooty mangabeys has been extensively investigated to understand the factor (s) responsible for the non-pathogenicity. SIVsm clearly maintains its pathogenic potential, demonstrated by the accidental or experimental transmission of the virus to the rhesus, pig-tailed or stump-tailed macaques [1, 3, 4]. However, in sooty mangabeys, chronic infection with SIVsm is not associated with a chronic activation of immune responses. T-cell cytotoxic activity is weak and infected peripheral blood mononuclear cells are not highly susceptible to apoptosis (184, 185). Study of the lymph nodes of the infected sooty mangabeys showed no evidence

of morphologic changes, follicular hyperplasia or trapping of virus particles by follicular dendritic cells (38).

In sooty mangabeys naturally infected with SIVsm, several interesting features have been described: a weak humoral response against the p27 core antigen (38) weak or undetectable neutralizing antibodies (186) and secretion by $CD8^+$ cells of soluble factors inhibiting SIVsm replication *in vitro* (187).

Viral loads in SIVsm chronically-infected sooty mangabeys vary from relatively low to particularly high (38, 56), sometime higher than the threshold values associated with disease progression in macaques (188). In spite of these high viral load levels, sooty mangabeys maintain a normal T-cell turnover rate (34, 189). Also, age-dependent changes in T cell homeostasis and SIVsm viral load was observed in sooty mangabeys (189). A decreased CCR5 expression on $CD4^+$ T cells of the SIVsm infected mangabeys has been recently reported and suggested to be play a role in the diminished immune responses and the lack of disease progression in this natural host species (190). Of note, the only experimental primary infection of sooty mangabeys reported to date was done using the cloned SIVmac239 (184) and experimental study of primary SIVsm infection in mangabeys remains to be done.

7.3.3. SIVagm lineage

SIVagm is formed by a very diverse group of viruses which was postulated to have co-evolved with their natural host species in a host-dependent fashion. Originally, SIVagm was described as a single group of very divergent viruses (136, 139). Subsequent studies have shown that the four species of AGM are infected with distinct viral forms. Thus, genetic divergence between SIVagmVer isolates is up to 20% in the Pol amino acid sequences (179), whereas genetic distances in the Gag protein sequences vary to 30% between SIVagmGri-1 and SIVagmVer-155 (140, 191). SIVagmSab isolated from sabaeus monkey is a recombinant virus, with a *gag-pol* insert with a SIVrcm structure, and a SIVagm structure in the rest of the genome (80, 139, P.A. Marx, unpublished data]. The recombination event appears to be ancient, as current studies only detected the recombinant thus far (127, 139, 192).

Numerous studies have investigated the dynamics of SIVagm infection in different AGM subspecies and have shown that SIVagm is nonpathogenic in both experimental and natural infections (33, 35, 36,193-199). However, macaques experimentally infected with SIVagm have been shown to develop AIDS (98). Also, a case of immunodeficiency in an AGM with SIVagm and STLV has been reported (41).

The early phase of SIVagm infection is associated with a high viral load in both peripheral blood and lymph nodes, with a peak of viral replication of up to 10^8-10^9 occurring by day 10 post-infection (35, 198). The viral load then decrease significantly to a set point, by 30 to 60 days post-infection (35). During the chronic phase of infection, viral loads remain high (33, 35, 36, 198). This replicative capacity of SIVagm is correlated with its genetic evolution which indicates a rapid, continuous replication, similar to those observed in pathogenic HIV/SIV infections (200). This shows that the non-pathogenic nature of SIVagm infection in AGMs is determined by the rapidly induced equilibrium between virus and host rather than by the poorly replicating virus or the genetic host resistance to virus replication. During the chronic phase of the SIVagm infection there is no dichotomy between the cell-associated viral loads in lymph nodes and in peripheral blood. Virus-producing cells are found only in T cell areas of the lymph nodes and the spleen and no trapping of virus particles by follicular dendritic cells has been found in the germinal centers of the lymph nodes or spleen (195). These replication patterns differentiate SIVagm infection from pathogenic lentiviral infections. Studies are needed to investigate the factors controlling viral replication in lymph nodes.

The hypothesis of a lower susceptibility of AGM to lentiviral infections has also been investigated. A high polymorphism has been reported for CD4 and CCR-5 in AGMs (201-204), but no deletion was observed in the coding regions. Both CD4 and CCR5 from AGM have been shown to be fully functional (202, 203, 205), similar to other species of African monkeys (90, 205). Other authors suggested that the resistance to SIVagm infection is due to virus-induced down-regulation of the expression of $CD4^+$ (206, 207). The hallmark of SIVagm pathogenesis in AGMs is the low activation of immune cells which corroborate the absence of $CD4^+$ T cell depletion from chronically infected AGMs undergoing apoptosis following *ex-vivo* stimulation (208) and the absence of follicular hyperplasia and $CD8^+$ T cell infiltration in lymph node germinal centers in early and late phases of SIVagm infection (35, 102).

During SIVagm primary infection, seroconversion occurs within five weeks postinfection (35, 209). It is unlikely that neutralizing antibodies play a major role in AGM resistance to AIDS: they are difficult to detect, especially against homologous isolates (193, 210). However, neutralization patterns are strain-dependent and high neutralizing antibody titers can be observed in some AGMs (213). Moreover, SIVagm is more sensitive to neutralization after prior exposure to soluble CD4 (103). The most relevant difference in humoral immune response between SIVagm infection and pathogenic lentiviral infections is the low anti-p27 titer observed in naturally infected AGMs (103, 212). No explanation has been offered for this phenomenon, but it seems to be common in African simian hosts (38, 79, 106).

During the chronic phase of infection the cytotoxic T-cell responses are weak (193) but CTL detection methods applicable to AGM model are not yet available. A series of soluble factors which inhibit viral replication *in vitro* are secreted by African green monkey $CD8^+$ cells: interleukin-16, $CD8^+$ T-cell antiviral factor (CAF) or beta-chemokines (102).

Altogether, these factors contribute, at least in part, to a low chronic activation of the immune system

which prevents major distruction of the $CD4^+$ T cell population and favours the renewal capacity of the immune system. Several studies of the SIVagm infection in AGMs model are in progress.

7.3.4. SIVsyk lineage

Although SIV prevalence seems to be elevated in the Syke's monkey (*Cercopithecus albogularis*), only one strain has been completely characterized in this lineage (107). Recently new isolates have been reported (75). Partial sequences of these isolates cluster in a SIVsyk lineage, although they are divergent (22). A partial genomic sequence of the SIVtal from a talapoin monkey (*Miopithecus talapoin*) in a zoo has been reported to be most closely related to SIVsyk (50). However, SIVtal from Gabonese talapoins (*Miopithecus ougouensis*) are highly divergent from SIVsyk (22).

The main characteristic of SIVsyk is its restrictive cellular tropism *in vitro*. SIVtal replicates only in $CD4^+$ enriched PBMCs from the Syke's monkey and does not grow in human, mangabey or macaque PBMCs (93). The virus has been experimentally transmitted to macaques, which remain clinically healthy, in spite of a persistent infection (107). SIVtal-infected talapoins were reported to have lower $CD4^+$ counts compared to uninfected monkeys (50). SIVtal infections of rhesus and cynomolgous macaques are in progress. No sign of immunesuppression have been observed after two years of follow-up (50).

7.3.5. SIVlhoest lineage

This lineage is formed by viruses belonging to three different species, l'Hoest monkey (*Cercopithecus l'hoesti*), sun-tailed monkey (*Cercopithecus solatus*) and mandrill (*Mandrillus sphinx*). The mandrill virus (SIVmnd-1 GB1) was isolated from a captive mandrill in Gabon more than 12 years ago (106, 121) and was the only representative of this lentiviral lineage, "SIVmnd". The new viral types recently associated with this lineage (48, 79, 105) are more closely related to each other than to SIVmnd-1 (48). However, the sun-tailed monkey and l'hoesti monkey do not share the same geographical area, being separated by more than 1000 miles: sun-tailed is endemic in Gabon, in West-central Africa, whereas l'Hoest monkey is common in East Africa, in Kenya and Democratic Republic of Congo. The two monkey species are closely related and belong to the *Cercopithecus lhoesti* group of cercopithecine together with *C. preussi* (145, 213). This is why the phylogenetic relationships between the two viruses have been considered significant for host-dependent evolution and the lineage name was changed to SIVlhoest (48, 79). The SIVlhoest prevalence in wild monkeys was investigated, and the rates of infection are comparable to those observed in AGMs (105). Altogether, these observations show that l'Hoest monkeys represent a reservoir of SIV and that these viruses infected these two monkey species for a long time, the separation occurring before the host species speciation or before they became geographically isolated (127). Neither of the two viruses seem to be the direct ancestor of SIVmnd-1. Mandrills share the same range with *C. solatus* in Gabon and it was considered that SIVmnd-1 emerged following a cross-species transmission event occurring in the past. It is also possible that the cross-species transmission event involved another as yet unidentified SIV that has infected both l'hoesti group monkeys and mandrills [David Robertson, unpublished observation]. The recent isolation of a second mandrill lentivirus which has a structure related to those of the other viruses infecting Papionini monkeys (40, 87) supports the hypothesis of a cross-transmission event from solatus to mandrills. The emergence of SIVmnd-1 seems to be quite ancient, since the virus is largely present in wild animals (40) and pathogenesis studies have shown that SIVmnd-1 seems to be non-pathogenic in the mandrill host in spite of an active replication during both primary and chronic infection (37, 214). However, viruses forming this lineage seem to have retained the pathological potential, as shown by the capacity of SIVlhoest and SIVsun to induce immune suppression in pig-tailed macaques (79, 215) and by a case of immunodeficiency in a mandrill naturally infected by SIVmnd-1 (39).

In vitro studies done with viruses in this lineage revealed some interesting features: SIVmnd-1GB1 and SIVlhoest, but not SIVsun replicate efficiently in human PBMC, which suggests that the ability to infect the human host can vary within one lineage (80, 86). Moreover, SIVmnd-1 and SIVlhoest also grow in chimpanzee PBMCs (80). The co-receptor usage was also reported to be different for the viruses from this lineage: thus, SIVlhoest and SIVsun have a similar co-receptor usage, using CCR5 and Bonzo, whereas SIVmnd-1 GB1 was reported to use CXCR4 (80, 92). However, one should note that the reference SIVmnd-1 GB1 strain was adapted to cell culture, which may explain the differences in co-receptor usage. Using primary SIVmnd-1 GB1 isolates we have observed that the major co-receptor used by this virus is CCR5 (39, R. Onanga, personal communication).

As mandrills are infected with two different lentiviral types, there are opportunities to perform comparative pathogenetic studies *in vivo*. Experimental infection of mandrills with SIVmnd-1 have shown that the virus replicates at high levels during the primary infection and that this viral replication contrasts with only transient changes in $CD4^+$ and $CD8^+$ cell numbers during this early phase of infection (37, 116). Cell activation occurs only during the primary infection, with no significant differences between chronically infected and uninfected mandrills (116). During the chronic phase, viral loads are maintained at high levels (10^5-$5x10^5$ Eq/ml), similar to other lentiviral infections in African non-human primates (214). In wild mandrills, the same pattern of viral replication can be observed (214). Altogether, these data suggest an equilibrated viral-host dynamics in mandrills. This equilibrium might be interpreted as a viral adaptation, SIVmnd-1 generating a persistent infection, with an incubation period exceeding the normal life span of the host species. We had recently shown, after 18 years of follow-up, that SIVmnd-1 is ultimately pathogenic in some individuals. In a chronically infected mandrill, the viral load increased (>0.5 logs) and was associated with a depletion of $CD4^+$ cells and a significant increase in $CD20^+$ cells (39).

Experimental infections of pig-tailed macaques with SIVlhoest and SIVsun have demonstrated their pathogenic potential in the heterologous species (215). Dramatic loss of $CD4^+$ cells have been observed within 100 weeks post-infection. This depletion was more profound in SIVsun-infected animals. More than 50% of pig-tailed macaques died in 90 to 200 weeks post-infection. The cause of death was generally secondary to opportunistic infections, but one SIVsun-infected pig-tailed macaque died of lymphosarcoma. During the primary infection, a high viral replication has been noted, with peaks of viral load of 10^8-10^9 copies/ml. One of the most astonishing aspect of these evolutive SIV infections was that the set points were remarkably low (of 10^2-10^3 copies/ml). With the onset of AIDS, a small increase of viral loads (to 10^4 copies/ml) has been documented (215).

7.3.6. SIVcol lineage

This lineage has been described only recently and it contains several strains originating from black and white colobus (*Colobus guereza*) (69). The prevalence of SIVcol infection seems to be significant, 28% (69). Diversity of SIVcol is similar to those observed with viruses forming the other lineages. Two strains have been completely sequenced and they differ in up to 20% of amino acid sequences. These differences suggest that colobus guereza is a natural host for SIV. Also, the description of SIVcol might have general significance relative to the timing of SIV emergence in African primate populations. Old World monkeys are divided in two subfamilies: *Colobinae* and *Cercopithecinae* (145). Until recently, SIVs have not been isolated from non-human primates other than the *Cercopithecinae*, the only exception being SIVcpz. As will be discussed later, SIVcpz may have originated from *Cercopithecinae* (216). SIVcol is the first virus from monkeys belonging to the *Colobinae* sub-family. Phylogenetic clustering of SIVcol shows it as a highly divergent SIV with no evidence of cross-species transmission, which corroborates evolutionary theories suggesting that lentivirus emergence in simian populations occurred from a single ancestor and the hypothesis that virus divergence occurred with host species differentiation. It is estimated that *Colobinae* separation from other species of Old World monkeys occurred more than 11 million years ago (217). For these reasons it has been assumed that the emergence of primate lentiviruses occurred 11-20 million years ago (69). But SIVcol could have a cercopithecini source not yet found. If SIVs diverged 10 million years ago, Asian colobus should have SIVs.

This idea is supported by subsequent studies on viruses originating form two other *Colobinae* species, SIVolc from olive colobus (Procolobus verus) amd SIVwrc from Western red colobus (Pilocolobus badius), both from West Africa. These two viruses cluster together, but on a different branch than SIVcol, being closer to SIVlhoesti cluster than to other lineages (71) (Figure 3). This finding suggests that SIVs from colobes in the Ivory Coast and from Cameroon did not derive from a common ancestor infecting these monkeys before their speciation. Also, the phylogenetic clustering for the two Western Africa subspecies suggests cross-species transmission events (71).

7.4. Recombinant viruses

7.4.1. SIVagm.Sab

Initial studies of SIVagm diversity based on *env* analyses showed that these viruses evolved in a host-dependent fashion, with four phylogenetic subclusters coinciding with the 4 subspecies of AGMs (139). However, supplementary analyses of the LTR of the SIVagm.Sab, which naturally infects sabaeus monkeys (*Chlorocebus sabaeus*) in West Africa, revealed a TAR duplication which is characteristic of the LTRs of the sooty mangabey group of SIVs. Full length genome phylogenetic analyses confirmed that SIVagm.Sab is a recombinant virus which contains SIVsm-like fragments in the 3' half of the *gag* gene and the 5' half of *pol*. This recombinant virus has displaced the non-recombinant form, as all the SIVagm.Sab viruses characterized so far share the same structure. Also, the high divergence of the SIVagm.sab and the strain diversity within the SIVagm.Sab subcluster (139, 192, 218) suggest that the introduction of the virus in the AGM population is ancient. Comparative pathogenetic studies shown that SIVagm.Sab replicates better than SIVagm.Ver during the primary infection (209) in both sabeus and vervets.

7.4.2. SIVrcm

This virus has been discovered in 1998, being isolated from a household pet red-capped mangabey (*Cercocebus torquatus torquatus*) naturally infected in Gabon (55). Phylogenetic analyses of the complete genomic sequences demonstrated that SIVrcm has the same genomic structure as SIVsm/SIVmac/HIV-2 group but also has some remarkable features (80). Based on these virological features and the close relationship between red-capped mangabeys and sooty mangabeys (some authors consider the two monkeys to be the same species) one would predict that the two viruses originating from related mangabey species should form a mangabey cluster, similar to that observed in African green monkeys. However, phylogenetic analyses failed to establish a clear relationship between SIVrcm and SIVsm. Moreover, clustering patterns of SIVrcm are different for different fragments, being highly suggestive of a recombinant nature of SIVrcm. SIVrcm is close to SIVagm.Sab in *gag*, with SIVcpz in *pol-vif* (Figure 3) and with SIVsm in *env-nef*) (80). The SIVcpz-like insert in *pol-vif* which confers a naturally-occuring SHIV profile to SIVrcm was considered as particularly important and changed concepts concerning the gene flow dynamics and direction in primate lentiviruses. The most important question was whether the SIVcpz-like insert was transmitted from the chimpanzee lentivirus or if the genetic exchange had an opposite direction in that SIVcpz was generated by an ancient recombination with an ancestral 'SIVrcm'-like virus. The latter hypothesis is favored by the recent description of the SIVmnd-2 and SIVdrl, two viruses which infect mandrills and drills respectively and have a *pol-vif* structure which is close to the SIVrcm (40, 77, 82, 87). This finding suggest that the so-called "SIVcpz insert" in the SIVrcm genome is in fact a genetic fragment characteristic for SIVs infecting *Papionini* monkeys and would be consistent with a host-dependent evolution within the *Cercocebus* monkeys. Moreover, the recently described SIVagi isolated from the agile mangabey

in Cameroon (74) has SIVrcm as its closest relative. This further suggests a host dependent evolutionary pathway of SIVs infecting Papionini or a new cross-transmission event involving these two subspecies (74). Finally, the recently described SIVgsn from greater spot-nosed monkey (*Cercopithecus nictitans*) [see below] has shown that this virus contains a *vpu* and has an *env* gene sequence which is very close to SIVcpz (70). Altogether, these findings suggest that SIVcpz might have originated from a recombination event involving SIVrcm-like and SIVgsn-like viruses (216).

However, in spite of these close phylogenetic relationships, neither SIVgsn nor SIVden are the direct ancestors of SIVcpz. SIVden *vpu* coding sequence is shorter than its HIV-1/SIVcpz and SIVgsn counterparts (81). The differences between the *vpu* of SIVden and that of SIVgsn indicate that they do not have a recent common origin. The difference between both *vpu* from SIVden and SIVgsn and that of HIV-1/SIVcpz suggests that another SIV not yet discovered is likely to be the reservoir for the HIV-1/SIVcpz lineage (81).

SIVrcm strains have been obtained from RCMs in Gabon, Cameroon and Nigeria (55, 73, 80). Phylogenetic comparisons of these isolates have revealed that these sequences are more closely related (Figure 3). Thus, the extent of the protein identity between SIV rcm isolates GB1 and NG1 was similar to that observed between divergent isolates (GAB1 and US) of SIVcpz from *Pan troglodytes troglodytes*, but lower than that seen between different SIVagm.ver from vervets or between different SIVlhoest from l'hoesti monkeys. Phylogenetic analyses also show that, consistent with their geographic origin, the two viruses from Nigeria are closer to each other than to the SIVrcm from Gabon (80). Altogether, these features show that the red-capped mangabey is a natural host of this lentivirus.

SIVrcm uses the CCR2b as the coreceptor for viral entry (219). This unique property occurs as a consequence of a high frequency of homozygosity for a 24 bp deletion (delta 24-bp) in the CCR5 co-receptor encoding gene of RCMs. Eleven out of the 15 RCMs originating from Africa and an American zoo were homozygous for delta 24-bp, whereas the remaining 4 RCM were heterozygous. These results yielded a very high (86.6%) allelic frequency for the gene defect. The homozygous delta 24-bp CCR5 genotype did not support R5-tropic lentivirus infections and failed in signal transduction assays mediated by beta-chemokines (219). These results showed for the first time that a natural and persistent simian lentivirus infection can occur in the presence of CCR5 gene deletions and that the mangabey deletion is ancient in comparison to the reported age of the CCR5 deletion in humans (219). Subsequently, another group (219) found an allelic frequency of 76.9% for the deleted allele of CCR5. One of the heterozygous monkeys (RCM411) was naturally infected with the SIVrcm. A second infected mangabey (RCM409) was homozygous for the delta 24-bp deletion in CCR5. In another study, chemokine ligands were used to test their ability to inhibit SIVrcm replication in human PBMC (220) and it was shown that SIVrcm makes truly exclusive use of CCR2 as a coreceptor in primary human PBMC.

SIVrcmGB1 was experimentally transmitted from the naturally-infected RCM to an uninfected RCM and to 2 cynomolgus macaques by inoculating 10 ml of whole heparinized blood (55). By day 70 post-infection, the experimentally-infected RCM seroconverted, WB reactivities being similar to those observed in naturally infected RCM. The two inoculated cynomolgus macaques seroconverted by 11 days postinoculation. SIVrcm was recovered from macaques PBMCs as late as day 150. No significant changes in the $CD4^+$ counts were observed in the two macaques. After a 4 year follow-up, both SIVrcm-infected RCM are free of disease [P. Marx, unpublished observation].

Two rhesus macaques were serially inoculated with SIVrcm (32). The virus was readily isolated from both macaques during the primary infection and then, from day 21 on, cultures were negative. Both animals seroconverted by day 28. Each animal showed an initial loss of $CD4^+$ cells and an associated $CD8^+$ cell expansion. However, after four weeks, the $CD4^+$ and $CD8^+$ counts in each animal returned to pre-infection levels. Proviral DNA load in rhesus macaques was measured by a quantitative PCR assay. On Day 8 p.i. one rhesus macaque presented the peak of proviral load (1,000 infected cells per 100,000 PBMC) which quickly dropped to low levels after the acute infection, and by day 129 p.i. proviral level was 16 per 100,000 cells. The peak of proviral load for the second rhesus macaque was lower than for the first one and was reached later, by day 14 p.i. (160 copies per 100,000 cells). By day 121, the proviral load level was 14 copies per 100,000 cells. To date, both rhesus macaques are healthy after three years. In conclusion, SIVrcm can be transmitted to both cynomolgous and rhesus macaques. The virus infection is limited in both species. After 3 years of follow-up, no clinical or biological signs of immune suppression was recorded in macaques. A moderate increase in viral pathogenicity was observed after serial passages of SIVrcm in rhesus macaques (221).

7.4.3. SIVmnd-2/SIVdrl

SIVmnd-2 and SIVdrl are two highly related viruses which have been recently isolated and characterized from mandrills (*Mandrillus sphinx*) and drills (*M. leucophaeus*), respectively (40, 77, 82, 87). Ironically, SIVmnd-2 was isolated by two different groups in 1988, together with SIVmnd-1 (106), and 1989 (N. Lerche, unpublished data) but it was not sequenced because it was assumed to be identical with the first lentiviral type infecting mandrills, which belongs to the l'hoesti lineage (121). Both SIVmnd-2 and SIVdrl have a mosaic structure, with a different branching pattern across the genome. Thus, across *gag*, *pol*, *vif*, *vpx*, and *tat*, they are more closely related to SIVrcm, whereas across *env* and *nef*, they are more closely related to SIVmnd-1 (40, 82). One should note that both viruses have similarities with SIVcpz/HIV-1 in the *pol* gene, the "SIVcpz"-like pol insert appearing as a Papionini virus signature. SIVmnd-2 contains a *vpx*. They

also have a peculiar LTR structure, with a trans-activation response element (TAR) different from other SIVs. Three stem-loop elements can be predicted for SIVmnd-2, the first one similar to that found in SIVrcm, with a 2-base UU bulge, but with a distinct feature represented by a 7-base loop. The other two TAR elements found in SIVmnd-2 are more similar to the first stem-loop structure found in SIVmnd-1, both presenting the characteristic 4-base bulge (40).

SIVmnd-2 is highly prevalent in wild mandrills located in Cameroon and Gabon, North of the Ougoue river (22, 40, 87), in the area in which drill and mandrills are sympatric, which might explain the close relationship between the two viruses. Moreover, in Cameroon, a human infection with SIVmnd was serologically identified, showing that SIVmnd-2 or SIVdrl may represent a threat for new cross-species transmissions to humans (40). There is some evidence that SIVmnd-2 is pathogenic in mandrills. A female mandrill born in 1971 and housed in the San Diego Wild Animal Park since 1984 have been found to be seropositive and the virus was isolated. This mandrill died at the age of 18 years from persistent diarrhea, weight loss, invasive *Balantidium coli* infection unresponsive to standard therapies and disseminated atypical mycobacteriosis. These are typical clinical signs indicative of immunodeficiency, however no data are available on SIVmnd-2 viral load or $CD4^+$ cell number (40).

7.4.4. SIVgsn

This virus was discovered recently (70) following an extensive screening of SIV seroprevalence in greater spot-nosed monkeys (*Cercopithecus nictitans*) in Cameroon. In this study, 165 wild-born greater spot-nosed monkeys were tested and 27 (16.4%) had antibodies that cross-reacted strongly with at least one HIV protein. Four of these samples specifically reacted with the SIVcpzANT V3 peptide and virus could be amplified and characterized for two of them (70). Sequence analyses of these two full-length genomes revealed an interesting structure, with the presence of a *vpu* gene (the first *vpu* gene described for a virus not belonging to the HIV-1/SIVcpz lineage) and a discordant branching pattern in phylogenetic trees. Thus, SIVgsn is more closely related, although distant, to SIVsyk in the 5' end of the genome and to SIVcpzANT in the envelope, with the latter similarity being higher than the one with SIVsyk in *gag-pol*.

These findings suggest that SIVgsn genome is a mosaic structure resulting from a recombination event. The pattern of clustering with SIVsyk revealed that this relationship is not significant and it is more likely that, at least in the central part of the genome, SIVgsn forms its own lineage. The relationship with SIVsyk in the *gag* region might be relevant for host-dependent evolution, as the two monkeys are closely related, although not geographically overlapping. The acquisition of *vpu* during the evolution of SIVgsn may have conferred a selective advantage to this virus. Recent reports suggest that SIVgsn is not an exception in the *Cercopithecus* genus, and that at least three other viruses originating from monkeys in the *C. mona* and *C. cephus* groups have this gene (76, 78, 81). Whether or not SIVgsn is a recombinant virus or a pure lineage, it might represent a source of SIVcpz (216).
SIVgsn have not been isolated in culture, so no information on its pathogenic potential is available. The study of the biological properties of the *vpu* gene from the SIVgsn should offer significant information concerning the significance of this viral product for both viral biology and for its role in cross-species transmission.

8. CONCLUSION

Non-human primate lentiviruses form a large group of viruses which circulate in their primate hosts and are highly adapted. SIVs have a long history, of thousands of years and have undergone frequent cross-species transmission and host-dependent evolution. The picture is completed by recombination events which are probably related to cross-species transmission and adaptation. Altogether these point to a huge pool of genomic sequences which are widely distributed in Central Africa and represent a potential threat for human infection.

Lentiviral classification as pure lineages or recombinant viruses is mainly a matter of the chronology of the discoveries. Our knowledge of SIV will undoubtedly undergo significant changes as new viruses are characterized in their natural hosts. The risk of cross-species transmission and the factors driving these events should be characterized in order to prevent the emergence of new viruses and to control the AIDS pandemic. Characterization of viral biology in non-human primate populations is essential to understanding the mechanisms of viral adaptation and the role of immune system to control the disease.

This presentation might have some inconsistencies mainly generated by the rapid accumulation of new data on both SIV diversity and its pathogenesis. A synthesis of currently available data on SIV diversity, classification and biology is still premature, as most of the data are incomplete. This classic adagio is apropo to the ever changing nature of SIV research: "*We can see the Linnaenan obsession with classifying and naming now as a foredoomed attempt to stabilize and fix what is in reality a continuous flux, and it seems highly appropriate that Linnaeus himself finally went mad; he knew he was in a labyrinth, but not that it was one whose walls and passages were eternally changing*" (222).

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