The Call of the Wild: What Can Be Learned from Studies of SIV Infection of Natural Hosts?

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1. Introduction

The HIV/AIDS pandemic, with an estimated 40 million people infected worldwide and several million AIDS-related deaths per year, represents one of the worst tragedies of the twentieth century. A series of pivotal studies established that HIV infection and AIDS in humans originated from multiple episodes of zoonotic transmission of CD4+ T cell-tropic lentiviruses infecting African monkey species and collectively defined as Simian Immunodeficiency Viruses (SIV) [1]. HIV-1, which is responsible for the overwhelming majority of AIDS cases in humans, derives from the chimpanzee (*Pan troglodytes*) virus SIVcpz [2, 3], while HIV-2 derives from SIVsmm, which naturally infects the sooty mangabey (SM, *Cercocebus atys*) [4–6]. Among the natural hosts for SIV, SMs are particularly relevant as SIVsmm was used to generate the various rhesus macaque (*Macaca mulatta*, RM)-adapted SIVmac viruses (e.g., SIVmac239, SIVmac251) that are often used for studies of AIDS pathogenesis and vaccines [6–9]. As shown in Table 1, more than 30 additional African monkey species are known to be naturally infected with SIV in the wild and in captivity, including mandrills, African green monkeys (AGMs), baboons, l'hoest monkeys, and numerous others (reviewed in [1]). SIV infection of natural hosts is common in the wild and in captivity, and appears to be acquired at the time of sexual maturity (*i.e.*, between 2–4 years of age, see [10]). All primate lentiviruses identified thus far fall within a single phylogenetic lineage distinct from lentiviruses from other species of mammals [11]. Within this primate lentivirus radiation, each primate species is generally infected with a specific subtype of SIV, such that multiple strains from any host species form a monophyletic clade. An exception is the mandrill (*Mandrillus sphinx*) that harbors two phylogenetically divergent types of SIV [12, 13]. The key virological features of SIV infection of natural hosts will be discussed in the section "Virological features" of this Review.

A puzzling feature of SIV infection in natural host monkey species is an observed general lack of pathogenicity. In most natural host animals, transmission of virus is not followed by profound CD4+ T cell depletion or AIDS-defining illness even after many years of infection [1, 14–20]. In marked contrast, without antiretroviral treatment, most HIV-infected individuals become severely immunocompromised and develop AIDS within 2–10 years. In addition, experimental SIV infection of non-natural host Asian monkey species, such as RMs, pigtail macaques (PTM, *Macaca nemestrina*), stump-tailed macaques (STM, *Macaca arctoides*), and cynomolgus monkeys (CYM, *Macaca fascicularis*), results in the development of symptoms similar to those described in AIDS patients (simian AIDS), including the progressive loss of CD4+ T cells and infection with opportunistic pathogens (reviewed in [21]).

Table 1 African non-human primates infected with SIV and some characteristics of the infecting virus

Family/Subfamily/ Tribe/Group	Species (common name)	Viral type	Seq avail[3]	Serological evidence[5]	SIV isolated in vitro	Viral tropism	Pathol in host	Pathol in heterolo hosts	Ref
Pan	*P. troglodytes troglodytes* (Central African chimp)	SIVcpzGAB/ CAM/US	FS&PS		SIVcpzGab1/ Cam3/Cam5	CCR5	NR	hu, HIV-1	2, 3, 57, 58
	P. t. schweinfurthii (Eastern chimp)	SIVcpzANT/TAN	FS&PS		SIVcpzANT	CCR5	NR	NA	53-56
	P. t. vellorosus	SIVcpzCAM41	PS		SIVcpzCam4	NR[6]	NR	NA	57
Superfamily Cercopithecoidea, Family Cercopithecidae, Subfamily Cercopithecinae, Tribe Papionini									
Cercocebus	*C. atys* (sooty mangabey)	SIVsm	FS&PS		SIVsmH4/SL92b	CCR5	Yes[7]	hu, HIV-2; Rh[8] , PTM, STM; Black Mangabey	5, 7, 40, 41, 42, 112
	C. torquatus (red-capped mangabey)	SIVrcm	FS&PS		SIVrcmGB1/NG411	CCR2	NR	No (CYM, Rh)	44, 102
	C. agilis (agile mangabey)	SIVagi	PS	Yes	SIVagi703	CCR2	NR	NA	107
	C. t. lunulatus (white-crowned mangabey)	SIVagm.Ver[1]	PS	No	No	NA	NA		48
Lophocebus	*Lophocebus albigena* (gray-crested mangabey)		NA[4]	Yes	No	NA	NA	NA	68
	L. aterrimus (black crested mangabey)		NA	Yes	No	NA	NA		177, 210
Mandrillus	*Mandrillus sphinx* (mandrill)	SIVmnd-1	FS&PS		SIVmnd-1GB1	CXCR4	Yes	NA	12, 62, 97, 128
		SIVmnd-2	FS&PS		SIVVmnd14/5440	CCR5	Yes	No (Rh)	12, 13, 68, 75
	M. leucophaeus (drill)	SIVdrl	FS&PS		SIVdrlFAO	CCR5	NR	NA	75
Papio	*Papio cynocephalus* (yellow baboon)	SIVagm.Ver[2]	PS	Yes		NA	NR		78
	P. ursinus (chacma baboon)	SIVagm.Ver[2]	PS	Yes		NA	NR		79
Superfamily Cercopithecoidea, Family Cercopithecidae, Subfamily Cercopithecinae, Tribe Cercopithecini									
Allenopithecus	*A. nigroviridis* (Allen's monkey)		NA	Yes	No	NA	NR	NA	33
Miopithecus	*M. talapoin* (talapoin)	SIVtal	PS		SIVtal	NR	No	No (CYM, Rh)	106
	M. ougouensis (Gabon talapoin)	SIVtal	PS		No	NA	NA		211
Erythrocebus	*E. patas* (patas monkey)	SIVagm.Sab[2]	PS		No	NA	NR		77
Chlorocebus	*C. aethiops* (grivet)	SIVagm.Gri	FS&PS		SIVagm.gri677	CCR5	NR	NA	24, 34, 123
	C. pygerythrus (vervet)	SIVagm.Ver	FS&PS		SIVagm.ver9063	CCR5	Yes	Yes (PTM)	119
	C. tantalus (tantalus)	SIVagm.Tan	FS&PS		SIVagm.tan27	CCR5	NR	No (patas)	36, 120
	C. sabaeus (sabaeus)	SIVagm.Sab	FS&PS		SIVagm.sab2/92018	CCR5, CXCR4	NR	No (Rh)	24, 73

[1] Accidentally transmitted in captivity; [2] Naturally occurring in the wild; [3] FS-full sequence; PS-partial sequence; [4] NA-not available; [5] Only serological evidence reported for these viruses; [6] Not reported; [7] Although most reports suggest that SIVs are not pathogenic in their natural non-human primate hosts, cases of immunesuppression have been reported; [8] Rh-rhesus macaque (*Macaca mulatta*); PTM-pig-tailed macaque (*M. nemestrina*); STM-stump-tailed macaque (*M. arctoides*); CYM-cynomolgous macaque (*M. fascicularis*)

Table 1 cont.

Family/Subfamily/ Tribe/Group	Species (common name)	Viral type	Seq avail[3]	Serological evidence[5]	SIV isolated in vitro	Viral tropism	Pathol in host	Pathol in heterolo hosts	Ref
Cercopithecus									
Diana group	*C. diana* (diana monkey)		NA	Yes	No	NA	NA	NA	33
Mitis group	*C. nictitans* (greater spot-nosed monkey)	SIVgsn	FS&PS		No	NA	NR	NA	76
	C. mitis (blue monkey)	SIVblu	PS		No	NA	NR	NA	49
	C. albogularis (Syke's monkey)	SIVsyk	FS&PS		SIVsyk173	CCR5	NR	NA	46, 47
Mona group	*C. mona* (mona monkey)	SIVmon	FS&PS		No	NA	NR	NA	212
	C. denti (Dent's mona)	SIVden	FS		No	NA	NR	NA	34
	C. pogonias (crested mona)		NA	Yes	No	NA	NA		33
	C. campbelli (Campbell's mona)		NA	Yes	No	NA	NA		33
	C. lowei (Lowe's mona)		NA	Yes	No	NA	NA		34
Cephus group	*C. cephus* (mustached guenon)	SIVmus	FS&PS		No	NA	NR	NA	76
	C. ascanius (red-tailed monkey)	SIVasc	FS&PS		No	NA	NR	NA	98
	C. erythrotis (red-eared guenon)	SIVery	PS		No	NA	NR		213
	C. neglectus (De Brazza's monkey)	SIVdeb	FS&PS		No	NA	NR	NA	99
L'hoest supergroup	*C. lhoesti* (L'Hoest's monkey)	SIVlhoest	FS&PS		SIVlhoest524	CCR5	NR	Yes (PTM)	45, 96, 127
(*Allochrocebus* genus?)	*C. solatus* (sun-tailed monkey)	SIVsun	FS&PS		SIVsun	CCR5	NR	Yes (PTM)	126
	C. preussi	SIVpre	PS		No	NA	NR		213
Hamlyni group	*C. hamlyni* (Owl-faced monkey)		NA	Yes	No	NA	NA		34
Superfamily Cercopithecoidea, Family Cercopithecidae, Subfamily Colobinae									
	Colobus guereza (C. guereza)	SIVcol	FS&PS		No	NA	NR	NA	51
	Piliocolobus badius (western red colobus)	SIVwrc	PS		No	NA	NR	NA	50
	Procolobus verus (olive colobus)	SIVolc	PS		No	NA	NR	NA	50

[3] FS-full sequence; PS-partial sequence;; [5] Only serological evidence reported for these viruses;

An additional consistent and intriguing feature of natural SIV infection is the presence of high levels of plasma viremia that in many cases actually exceed the levels typically observed in pathogenic HIV and SIV infections [15–20]. This unexpected finding contrasts with the well-known observation that, in both HIV-infected individuals and experimentally SIV-infected macaques, higher levels of virus replication predict faster disease progression [22–25]. At present, it is still unclear why SIV infection is non-pathogenic in natural host monkey species while inducing immunodeficiency in non-natural hosts (included in this definition are humans, who have only recently become a host species). In addition, it is not known whether SIV infection of natural hosts has always been non-pathogenic or mildly pathogenic, or whether present-day animals may derive from the survivors of an ancient retroviral pandemic. As such, the lack of disease progression in naturally SIV-infected monkeys may represent the favorable outcome of many thousands of years of parallel co-evolution between SIVs and their various natural host species. It is now widely recognized that a better understanding of the mechanisms underlying the lack of disease in natural hosts for SIV infection will likely provide important clues as to the pathogenesis of AIDS in HIV-infected individuals [26, 27]. The significance of this line of research for future efforts to halt the AIDS pandemic cannot be overstated.

In this review we will discuss the main virological, immunological, and clinical features of SIV infection of natural hosts, and will conclude by reviewing a series of pathogenic hypotheses that may explain the absence of disease progression in these animal species.

2. Epidemiology of natural SIV infection

2.1 Phylogeny of Old World monkeys.

The Old World monkeys (family *Cercopithecidae*) are divided into two subfamilies (*Cercopithecinae* and *Colobinae*) [28]. The *Cercopithecinae* subfamily is further divided into two tribes: *Papionini* and *Cercopithecini*. The *Papionini* tribe includes the two mangabey genera (*Chlorocebus* and *Lophocebus*), the baboons (*Papio*), mandrills and drills (*Mandrillus*), and gelada monkeys (*Theropithecus*), all from Africa, and the Asian genus, *Macaca* [29]. The *Cercopitecini* tribe comprises over 25 species, including three arboreal genera: *Allenopithecus*, *Miopithecus*, and *Cercopithecus* and three terrestrial genera: *Erythrocebus*, *Chlorocebus* and *Cercopithecus lhoesti* supergroup [28]. Altogether, there are over 25 species in the *Cercopithecini* tribe. Although a taxonomic consensus has not been reached yet, this primate classification is in agreement with the classification of SIVs in which specific genera (e.g., *Cercopithecus*, *Miopithecus*, *Chlorocebus* and *C. l'hoesti*) harbor a unique SIV lineage [30]. Monkey from the *Colobinae* subfamily (Colobus monkeys) are common in both Africa and Asia, in which SIVs have been isolated in the central African colobus-guereza and from the west African red colobus and olive colobus (genera *Colobus*, *Piliocolobus*, and *Procolobus*). It is interesting to note that the approximate equidistance among the major SIV lineages does not match the phylogenetic relationships of their hosts (Figure 1). Asian species of Old World monkeys (colobine and macaques), as well as some African species (such as baboons), do not carry a species-specific SIV, suggesting that the last common ancestor of the Old World monkeys was not infected by SIV 25 million years ago [31], and that the emergence of SIVs followed the infection, at a later time point, of one of the derived African species with a lentivirus from a non-primate source [32].

2.2 Prevalence of SIV infection in the wild.

SIV prevalence appears to be relatively high in African non-human primate species. Studies of hundreds of wild-born AGMs, the most numerous and geographically dispersed monkeys in Sub-Saharan Africa, indicate that animals belonging to different subspecies [*i.e.*, vervet (*Chlorocebus pygerythrus*), grivet (*C. aethiops*), tantalus (*C. tantalus*) and sabaeus (*C. sabaeus*)] all demonstrate a prevalence of SIVagm infection of 40–50% [33–35], independent of their geographic origin [36]. SIVagm prevalence correlates with age [37] and, consistent with a pattern of sexual transmission, no infections were identified in very young monkeys [38]. Interestingly, AGMs from the Caribbean islands are not infected with SIV, and this lack of infection has been attributed to the importation, in the 17th and 18th centuries [39], of juvenile animals from Africa. The alternative explanation that SIVagm was not yet

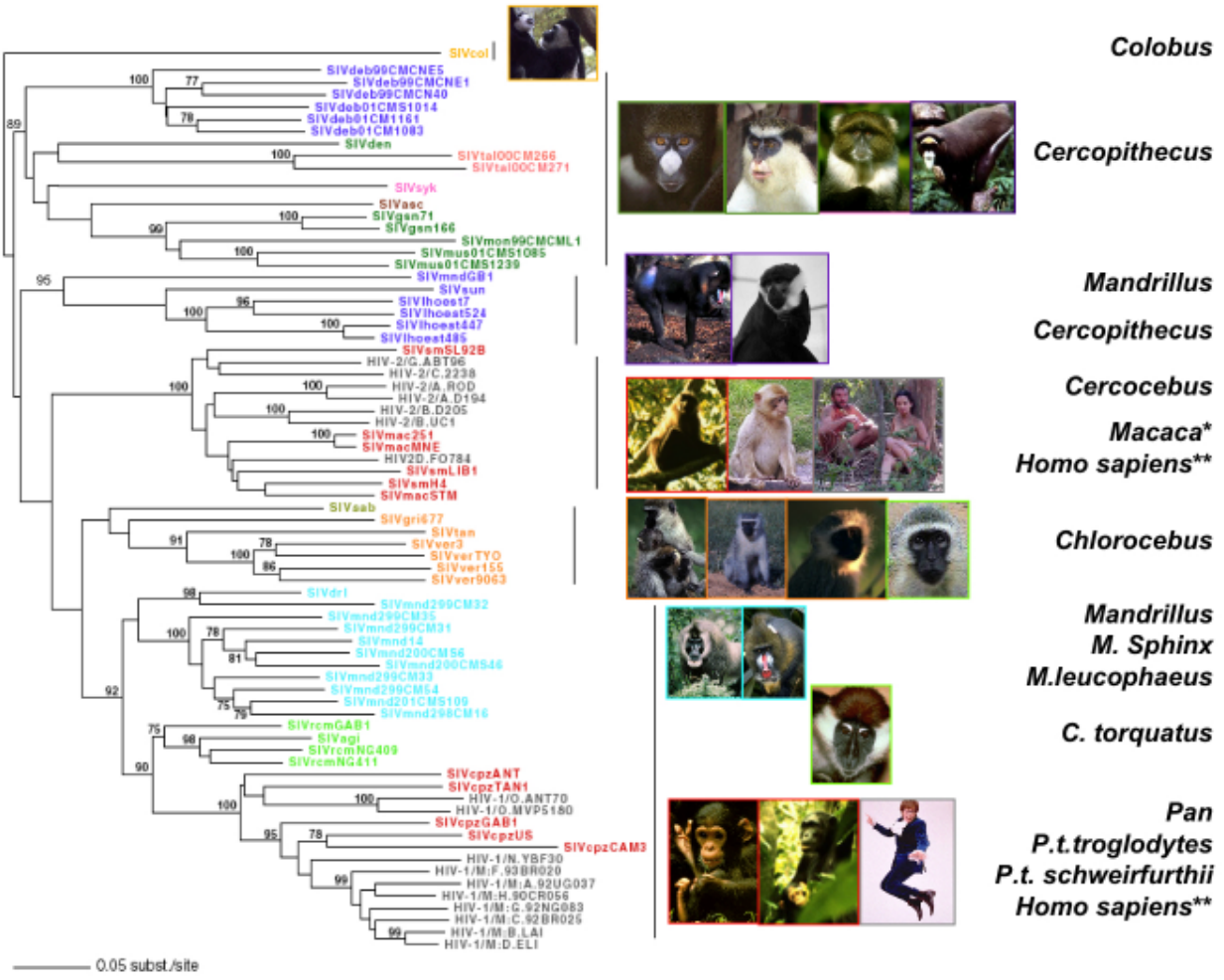


Figure 1. Phylogenetic relationships among SIV types and HIV strains inferred from pol *by neighbor-joining using the HKY model of nucleotide substitution. Numerous viral strains are known only based on small* pol *integrase fragments. This tree was designed to include the maximum number of strains, therefore is based on a relatively short fragment (522 sites after removing gaps). Phylogenetic clusters are groups of related viruses and are defined by high bootstrap values. 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.*

present in the African AGM population two centuries ago is highly improbable, although cannot be dismissed if considering that HIV-1 prevalence in East Africa already reached levels of 25–30% after only 50 years of epidemic evolution. Similarly high prevalence (25–60%) of SIV infection is found in feral SMs in Sierra Leone, with evidence that the major route of transmission in this species is also sexual [40–42]. The fact that the prevalence of SIVsmm infection is higher in adult monkeys than in juveniles [40] may explain why initial evaluations found a lower prevalence (4–8%) in mangabeys kept as pets, as they are known to be captured as juveniles [5, 40]. In the red-capped mangabeys, prevalence may be close to 22% [43, 44]. In wild mandrills from Gabon the prevalence of SIVmnd-1 infection was reported to be 76% [12], with the same age-dependence as observed in AGMs and mangabeys [12]. In *Cercopitecini* the prevalence is similar to that of AGMs, with 57% of l'Hoest monkeys (*Cercopithecus lhoesti*) [45], 28–59% of Syke's monkeys (*Cercopithecus albogularis*) [46–49], and 64% of blue mon-

keys (*Cercopithecus mitis*) infected [49]. Finally, in different *Colobinae* species the prevalence of SIV infection was found to be 28–46% [50, 51]. SIV infection is absent in Barbary macaques of the Gibraltar region (*Macaca sylvanus*) and Saudi Arabian baboons (*Papio hamadrayas*), suggesting that the emergence and cross-species transmission of SIVs in African non-human primates occurred after the separation of these two species from their sub-Saharan counterparts [52].

Of the anthropomorphic primates or pongids (*i.e.*, great apes) only two subspecies of Central African chimpanzees (*Pan troglodytes*) are known to carry specific SIVcpz strains: *P. t. troglodytes* and *P. t. schweinfurthii* [3, 42, 53–59]. Although the prevalence rates seem to be significantly lower than AGMs, mangabeys, and mandrills, foci of SIVcpz infections have been identified within the endemic geographic area [54]. Infection has not been detected in *P. t. verus* (a west African subspecies) caught in the wild or bred in captivity [60] and only one case of SIVcpz infection was documented in *P. t. vellorosus* (SIVcpzCAM-4), but this occurred in captivity by transmission from an infected *P. t. troglodytes* (SIVcpzCAM-3) [57]. Whether SIV has become extinct or was never a pathogen in certain chimpanzee sub-species is not yet known. Sero-epidemiological studies have failed to produce evidence of SIV infection in gorillas (*Gorilla gorilla*) [33, 43] or bonobos (*Pan paniscus*) [61]. As these two species of apes are closely related to humans, knowledge of the potential effects of SIV infection in bonobos and gorillas might provide valuable clues concerning SIV zoonotic potential.

2.3 Routes of transmission.

The higher prevalence of SIV infection in adult animals described in AGMs, SMs, and mandrills suggests that the main transmission route in the wild is horizontal transmission through sexual contact as well as bites and scratches [37, 38] [10]. However, twenty-years of observation of the semi-free colony of mandrills at the Centre Internationale de Recherche Medicale (CIRM), in Franceville, Gabon did not reveal any sexual transmission [12, 62–64]. Two of the founder males infected with two different viral types (SIVmnd-1 and SIVmnd-2) [12] transmitted the infection to four offspring and four other males, respectively, following aggressive contacts for dominance [12, 65]. In captive monkeys, several cases of horizontal transmission resulting from bites have been described [15], in some instances resulting in cross-species transmission of SIV [57, 66].

Interestingly, transmission from mother to infant seems less frequent than transmission between adult animals, and no case of perinatal transmission has ever been detected in AGMs [67]. It should be noted, however, that mother-to-infant transmission can occur, as SIV infection has been observed, albeit rarely, in pet monkeys captured at very early ages [68]. In addition, mother-to-infant transmission was reported in captive mandrills in Gabon [62]. However, the mechanism(s) of SIVmnd mother-to-infant transmission (in utero, perinatally or via breast-milk) are unclear, and a prospective study failed to produce experimental mother-to-offspring transmission by breast-feeding [69].

2.4 Cross-species transmission: frequency, restriction factors, and clinical outcome.

An important but still unanswered question is whether other members of the SIV group of viruses, in addition to SIVcpz and SIVsmm, could cross the species barrier to humans, potentially causing new pandemic waves [1, 70]. Some authors have suggested that massive human exposure to SIV through bushmeat consumption could fuel the emergence of new HIV types [1]. Other authors propose that simple exposure to these viruses is necessary but not sufficient for the selection of a new HIV type with the capacity for sustained transmission in human populations [71, 72]. Cross-species transmission of SIVs between different species of non-human primates has clearly occurred, as demonstrated by the emergence of recombinant SIVs [12, 44, 73–76] which could only have been generated as a consequence of such cross-species transmission events. Also, clear evidence of SIV cross-transmission between different species of African non-human primates was observed in the wild [77–79] and in captivity [48]. Importantly, experimental cross-species transmission of SIVsmm to different macaque species resulted in the development of the macaque model for AIDS [7]. SIVagm, SIVlhoest and SIVsun have also been successfully transmitted and were each shown to be pathogenic in PTMs [80]. In other instances, experimentally transmitted SIVmnd-2, SIVrcm or SIVagm to RMs only resulted in acute replication that was promptly cleared by the macaque host [13, 81, 82].

The mechanism(s) governing cross-species transmission of SIVs are largely unknown, but certain host factors have recently been identified that confer resistance or susceptibility to infection. Although this field is in its early stages, data are rapidly accumulating that show that cross-species transmission of retroviruses can be effectively blocked by specific host factors and that viral adaptation may be needed for successful transmission in a new host. The role of *vif* in species-specificity of SIVs was understood after the identification of the *vif* cellular target, the cellular protein APOBEC3G, that is incorporated into the virion during the reverse transcription to deaminate the minus strand of viral DNA [83], resulting in inactivation [84–87] and/or degradation of the viral genome [88]. This *vif* activity is species-specific, with human APOBEC3G being inhibited by HIV-1 Vif but not by SIVagm Vif, whereas AGM APOBEC3G is inhibited by SIVagm Vif, but not by HIV-1 Vif [89]. The mechanism of this species-specificity is a single amino acid change in APOBEC3G, *i.e.*, a aspartate to lysine in position 128 [89–91]. Interestingly, the functional interactions between APOBEC3G and Vif can be reversed; mutation D128K generates a human APOBEC3G that is no longer inhibited by HIV-1 Vif but is now inhibited by SIVagm Vif and vice versa [89–91]. Another host-restriction factor that has been described recently is based on the TRIM5alpha gene product, a member of the tripartite motif (TRIM) family of proteins that is present in the cytoplasmic bodies and whose function is still poorly understood. TRIM5alpha mediates the restriction to HIV replication in non-human primate species, most notably the rhesus macaques, by blocking infection after HIV-1 entry but before reverse-transcription, more specifically by modulating the uncoating of a retroviral capsid [92, 93].

3. Virology of SIVs

3.1 Primate lentiviruses.

SIVs belong to the Lentivirus genus of the Retroviridae, and are distinct from other retroviruses due to their complex structure with several accessory genes in addition to *gag*, *pol* and *env*. In particular, three accessory genes are specific for primate lentiviruses: *vpr*, *vpx* and *vpu*. All known lentiviruses are exogenous and can be found in many mammals, including cats, horses, goats, cattle and primates, where they may induce immunodeficiency, neurological disorders, arthritis and other diseases [94]. Some data exist regarding the genomic organization and virus-host interaction 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). It is interesting to note that both BIV and FIV also appear to be non-pathogenic in natural hosts [94, 95].

3.2 Genomic organization of SIVs.

All primate lentiviruses contain the three structural retroviral genes (*gag*, *pol*, *env*), the long terminal repeats (LTRs) at each end of the genome, and five accessory genes (*vif*, *vpr*, *nef*, *tat*, *rev*). 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): (i) SIVagm, SIVmnd-1, SIVlhoest, SIVsun, SIVsyk, SIVcol, SIVasc and SIVdeb contain only 5 accessory genes (*tat*, *rev*, *nef*, *vif* and *vpr*) [31, 47, 51, 96–99]; (ii) SIVcpz, SIVgsn, SIVmon, SIVmus and SIVden share this genomic organization with the addition of a supplementary gene, *vpu* [100, 101]; (iii) SIVsmm, SIVrcm, SIVmnd-2 and SIVdrl genomes are characterized by the presence of the *vpx* gene [6, 12, 75, 102]. SIVmac and HIV-2, which originated from cross-species transmission from SMs, also carry *vpx* [103, 104]. HIV-1, which originated following cross-species transmission from chimpanzees [2, 105], is similar to group (ii) in that it also carries a *vpu*. For the remaining known viruses (SIVtal, SIVblu, SIVolc, SIVwrc, SIVasc, SIVagi), complete genomes are not available [49, 50, 98, 106, 107].

3.3 Phylogenetic clusters of SIV.

Within phylogenetic trees of mammalian lentiviruses, all SIVs cluster as a single group, suggesting that all derive from a common ancestor virus that existed more than 1 million years ago [32, 108]. Phylogenetic analysis of the available SIV strains is complicated by the high sequence diversity and the frequency of recombination events. While phylogenetic trees of SIVs are traditionally presented with

six clusters, recent studies have shown that the definition of "pure" versus "recombinant" lineages is primarily a matter of chronology [109]. The first clear cluster of SIV includes viruses from guenons (*Cerchopitecus*). These viruses share a number of important structural features, indicating that their clustering resulted from an ancient lineage that infected *Cercopithecus* monkeys in the distant past [99]. The second cluster includes the SIVsmm from SMs [5, 6, 15, 40–42, 110–112] as well as its derivative viruses HIV-2 and SIVmac [6, 7, 113]. Multiple cross-species transmissions from SMs to humans gave rise to HIV-2 groups A through H [1, 4, 5, 40, 114, 115], while experimental transmission of SIVsmm to macaques resulted in the SIVmac viruses [116]. SIVmac sequences can be traced to viruses that infected captive SMs at the California National Primate Research Center (Davis, CA) [117, 118]. Interestingly, SIVsmm sequences from naturally infected SMs from Liberia, Sierra Leone and the Cote d'Ivoire have revealed wide genetic diversity [5, 40–42, 112]. The third cluster includes SIVagm from the four species of AGMs (genus *Chlorocebus*) [24, 36, 73, 119–123]. Since the four species of AGM are infected with distinct viruses, it is believed that SIVagm has evolved in a host-dependent fashion [73, 124, 125]. The fourth cluster (SIVlhoest group) includes viruses isolated from the *L'Hoesti* supergroup (*C. lhoesti* and *C. solatus*) [45, 96, 126, 127] and mandrills (*M. sphinx*) [12, 97, 128]. The fifth cluster includes SIVcol from the mantled colobus (*C. guereza*) [51], which is the first SIV isolated from monkeys belonging to the *Colobinae* sub-family. Finally, the sixth cluster was initially defined by SIVcpz and HIV-1. When *pol* trees are constructed, this cluster also includes two other divergent viruses, SIVrcm from red-capped mangabeys and SIVmnd-2/SIVdrl from mandrills and drills north of the Ougoue river. It was originally considered that SIVrcm carries a SIVcpz insert in the *pol-vif* genes. However, more recently, with the discovery of the SIVgsn/SIVmon/SIVmus group of viruses, all of them carrying a *vpu*, it was postulated that SIVcpz is in fact a recombinant virus (see below). Partial sequences from newly discovered SIVs (SIVblu, SIVolc, SIVwrc, SIVasc, SIVagi) are not yet assigned to a lineage. We wish to emphasize that phylogenetic lineages are not superimposable on genomic types; as our under-

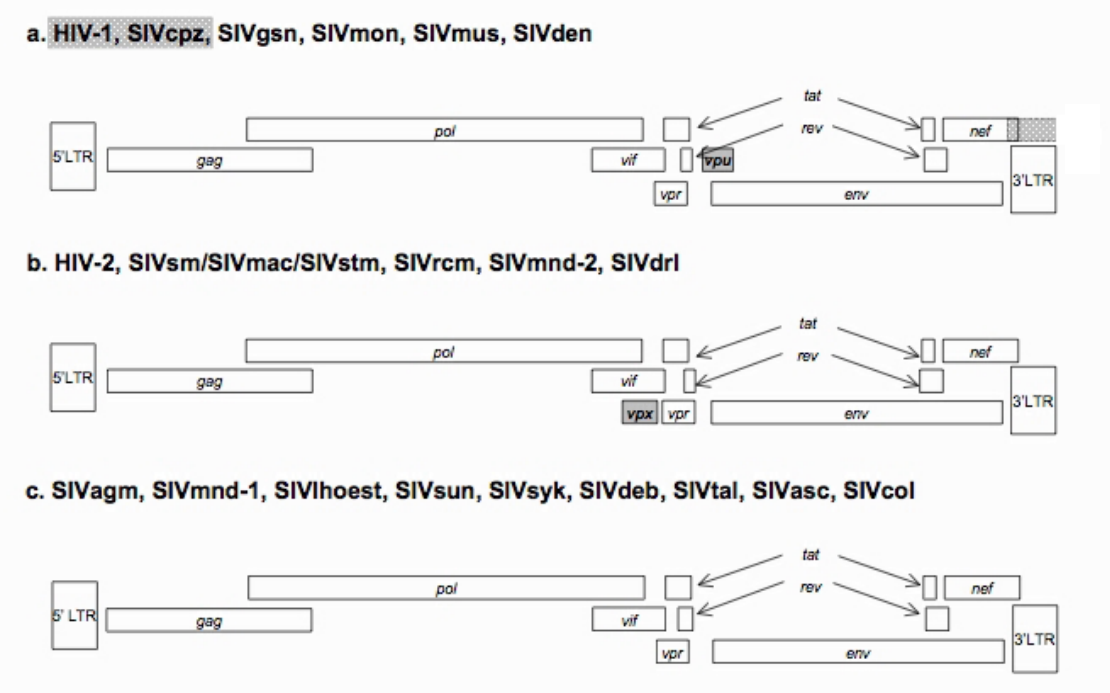


Figure 2. Genomic types of simian immunodeficiency viruses (SIV). Each gene is represented by a rectangular box with the name inside. Arrows point to genes spread over 2 locations. The genomic group including HIV-1 and SIVcpz can be further divided in two groups based on the overlapping of the env *and* nef *genes. This overlapping is observed for SIVgsn/SIVmon/SIVmus and SIVden but not SIVcpz/HIV-1 (boxed in grey).*

standing of the phylogenetic relationships continues to be modified with the addition of new strains. It may, in fact, be more effective to consider the three types of primate lentiviruses based on the genomic organization, as described above.

3.4 Recombinant viruses.

Recombination events may occur between different SIVs, as a result of cross-species transmission, as well as between different viral subtypes within the same species. The most critical recombination of SIVs appears to be that involving ancestors of the SIVrcm with the SIVgsn/SIVmus/SIVmon lineages, resulting in the origin of the chimpanzee SIVcpz [59, 74], whose cross-species transmission to humans created the HIV/AIDS pandemic [2, 3, 53–57, 100, 129–131]. Other SIVs originating from recombination events include SIVagm.sab (that contains SIVrcm-like fragments) and SIVmnd-2/SIVdrl (that has a mosaic structure partly related to SIVrcm and partly to SIVmnd-1 [12, 75]). Some recent studies suggest that SIVrcm (that has the genomic structure of SIVsmm/SIVmac/HIV-2 group [102], but contains fragments similar to SIVagm.Sab and SIVcpz [102] and therefore was initially considered a recombinant virus) might be a "pure" virus [74], meaning that other viruses showing similarities with SIVrcm sequences are likely recombinants [132]. As serological evidence of human infection with SIVmnd-2 was recently reported in Cameroon, it appears that SIVmnd-2/SIVdrl may be a threat for new cross-species transmissions to humans [12].

3.5 Co-receptor usage by SIVs.

In all studied instances, SIVs bind and infect cells using the same system of receptors used by HIV-1 consisting of CD4 and a chemokine co-receptors. The most relevant co-receptors for HIV-1 replication *in vivo* are CCR5 and CXCR4 [133], with about 50% of cases of progression to AIDS temporally associated with a switch in viral tropism from R5 ("macrophage" tropic) to X4 ("lymphocyte" tropic) viruses [133]. Most of the SIVs naturally infecting non-human primates in Africa use CCR5 as the main co-receptor [134, 135]. However, SIVmnd-1, SIVagm.sab and some of the SIVsmm may also use CXCR4, although no pathologic correlation has been described in the infected animals [136–138]. In the two cases of simian AIDS in a natural host of SIV infection (one SM and one mandrill) for which co-receptor usage has been tested, we failed to detect a switch in co-receptor usage associated with disease progression [139, 140]. Interestingly, an exception to the use of CCR5 or CXCR4 by natural hosts is represented by SIVrcm from the red-capped mangabey that uses CCR2b as the coreceptor for viral entry [141]. An intriguing explanation for this finding is that the CCR5 gene of red-capped mangabeys contains a 24 bp deletion making recognition of *env* by CCR5 impossible [141]. As such, this finding may constitute an example of convergent evolution with humans who possess the delta-32 mutation in the CCR5 gene. A virus related to SIVrcm, the SIVagi from the agile mangabey (*Cercocebus agilis*) also uses CCR2, despite the fact that all agile mangabeys tested thus far do not show any CCR5 gene deletion [107]. The close phylogenetic relationships between SIVrcm and SIVagi, corroborated by these biological properties, suggest that SIVagi derives from cross-transmission of SIVrcm [107, 132].

3.6 Dynamics of viral replication in natural hosts of SIVs.

In HIV-infected patients, levels of plasma viral load are an important indicator of disease progression [22, 142, 143]. In marked contrast, all studied examples of SIV infection in natural hosts (*i.e.*, SIVsmm, SIVagm and SIVmnd-1) very rarely progress to AIDS, despite levels of viral replication during the chronic phase of infection that are as high, or even higher, than those observed in chronically HIV-1-infected individuals [15, 17–20, 111, 144–146]. While most studies of this nature were performed using captive animals, the only investigation of SIV viral load in wild animals showed similarly high levels of viral replication [20]. Longitudinal analyses of the dynamics of plasma viremia in naturally SIV-infected animals suggest that the level of viral replication is relatively constant over time [20, 140]. Interestingly, in the one naturally SIV-infected SM that progressed to AIDS the set point level of viral replication was higher than average [132, 139]. However, naturally SIV-infected AGMs display a range of viral replication, in both peripheral blood and lymph nodes, that is considerably wider than that

observed in SMs or mandrills [17, 18, 20, 146, 147].

A series of recent studies investigated the early dynamics of SIV replication in experimentally SIV-infected natural hosts including SMs, AGMs, and mandrills [138, 145]. While these studies were based on a mode of infection that is clearly "non-natural", they are still of interest because they allowed the investigation of the early events of SIV infection in natural hosts, which are otherwise virtually impossible to study. Experimental SIV infection of natural hosts is characterized by a peak in viremia (10^6–10^9 copies/ml of plasma) occurring between 9–11 days post-infection [138, 145], followed by a sharp decline (1–2 logs) and attainment (in all tested models of infection- SIVsmm, SIVagm.sab92018, SIVagm.ver644, SIVmnd-1, and SIVmnd-2), of a chronically high level of viral replication that is similar to that observed in naturally infected animals [12, 18, 145, 146]. Interestingly, when two species of AGMs (*Chlorocebus sabaeus* and *C. pygerythrus* or vervets) are experimentally infected with their respective SIVagm viruses (SIVagm.sab92018 and SIVagm.ver644), SIVagm.ver644 infection of vervets consistently results in a lower peak viremia than SIVagm.sab92018 infection of *C. sabaeus*. The further observation of lower viremia in SIVagm.ver644-infected *C. sabaeus* than in SIVagm.sab92018-infected vervets suggests that, in AGMs, the profile of viral replication during primary infection may be dependent on the viral strain used for the infection, and not on the host species. [138]

The observation of high viremia during the usually non-pathogenic SIV infection of natural hosts is certainly puzzling, but is likely to represent the result of an evolutionary virus-host adaptation that allows maximal survival of the host in the presence of maximal virus replication. The exact mechanisms underlying this host-virus adaptation and, in general, the lack of disease progression in African monkeys that are naturally infected with SIV are not yet fully understood, and the available data and remaining questions will be discussed below. One clear finding, however, is that natural SIV infections, in contrast to pathogenic HIV infection of humans and SIV infection of non-natural hosts, are not associated with chronic high levels of immune activation, T cell turnover, and bystander T cell apoptosis [16, 18, 148].

4. Immunological features of natural SIV infection

4.1 Primary SIV infection of AGMs and mandrills.

To better understand the immunological features of the acute SIV infection of natural hosts, we have performed a series of experimental SIV infections of AGMs and mandrills [138, 145–147, 149, 150]. SIVagm.ver644 infection of vervets does not induce any change in CD4+ T cell count, while experimental SIVagm.sab92018 infection of *C. sabaeus* induces a significant CD4+ T cell decline during the first two weeks of infection [138]. In mandrills, experimental SIVmnd-1-infection induced a transient, moderate depletion of CD4+ T cells in both blood and lymph nodes at the peak of plasma viremia, while SIVmnd-2 infection resulted in only a slight reduction of CD4+ T cell percentages in the lymph nodes and not in the peripheral blood [146, 147]. Importantly, experimental SIV infection of both AGMs and mandrills sharply contrasts with the pathogenic SIVmac infection of macaques in that the CD4+ T cell counts in the natural hosts rebounded to pre-infection values soon after acute infection and remained stable throughout the chronic phase [138, 146].

An important component of the interaction between primate lentiviruses and the host immune system is the generation of a state of a chronic immune activation that is particularly evident in HIV-infected individuals and is thought to be a determinant of the AIDS-associated CD4+ T cell depletion. We investigated the kinetics of immune cell activation during experimental SIVagm-infection of AGMs and SIVmnd-2-infection of mandrills, and found that, in both species, an early increase in the fraction of activated CD4+ and CD8+ T cells is followed by the return to baseline levels of immune activation despite continuously high viremia in the chronic phase of SIV infection (10^3–10^6 RNA copies/ml plasma) [147, 149].

In a more recent study of the early immunological events following experimental SIVagm infection of AGMs, we focused our investigation on the cytokine production and FOXP3 expression. We observed a strong induction of TGF-β1 and FOXP3, followed by a significant increase in IL-10 expression in these AGMs. In sharp contrast to pathogenic lentiviral infections, we observed only a transient

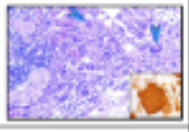
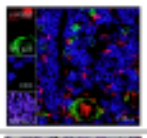
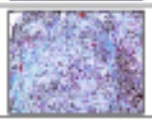
increase of IFN-γ expression and no changes in the levels of TNF-α and MIP-1α/β expression following infection. These results, combined with the finding of an early increase in the levels of CD4+CD25+ T cells suggest that SIVagm infection of AGMs is associated with the rapid establishment of an anti-inflammatory environment which may prevent the host from developing the aberrant chronic T cell hyperactivation that is correlated with progression to AIDS during HIV-1 infection [149]. Taken together, these data further support the hypothesis of a protective role for the downregulation of T cell activation in natural hosts infected with species-specific SIVs. In particular, it is becoming clear that the establishment of anti-inflammatory profiles of gene expression early on in the immune response to SIV antigens is associated with protection against AIDS [149].

4.2 Immunology of natural SIV infection of SMs.

Immunological studies of the non-pathogenic SIV infection in natural host monkey species have been difficult to perform due to limited access to the animals and a lack of well-characterized immunological reagents. One of the best available resources to study non-pathogenic SIV infection in a natural host species is the large colony of naturally SIV-infected SMs of the Yerkes National Primate Research Center of Emory University (Atlanta). SIV-infected SMs from Yerkes colony, as well as animals from other smaller colonies, have been the object of several virological and immunological studies over the past few years [15, 16, 18, 139, 150–155], see Table 2.

Similar to other natural hosts, SIVsmm-infected SMs usually maintain normal CD4+ T cell counts and very rarely develop AIDS despite high levels of virus replication [15, 18, 144]. In a recent report of a study undertaken to investigate the effects of SIVsmm infection on the SM immune system, we described a cross-sectional analysis of the lymphocyte phenotype and function in 29 SIV-infected and 19 uninfected SMs [18]. This analysis showed that the SIVsmm-infected SMs maintain near normal CD4+

Table 2. Cases of AIDS reported in African non-human primate hosts

				
Virus type	SIVagm	SIVmnd-1	SIVsm	SIVsm
Clinical disease	Diarrhea Cryptosporidiosis MAC	Weight loss	Lymphoma	Weight loss, Diarrhea
Viral load increase	ND	>0.5 log	>2 log	>0.5 log (serum)
CD4 loss	ND	Yes	Yes	Yes
WB Ab loss	ND	Yes	Yes	No
Anti V3 loss	ND	Yes	ND	No
Giant cell disease		ND		
LN structure	Severe disruption	ND		
Natural infection	Yes	Yes	Yes	No (SIVsm)

T cell counts in both blood and lymph nodes, and are characterized by preserved function of their T lymphocytes [18]. Analysis of the expression of markers of T cell activation, proliferation, and apoptosis indicated that the SIVsmm-infected SMs show limited immune activation and T cell apoptosis when compared to HIV-infected individuals [18]. In particular, SIVsmm-infected SMs showed: (i) only mild increases in the fraction of proliferating CD4+ T cells in the blood, with normal levels of proliferating CD8+ T cells; (ii) normal levels of proliferating CD4+ and CD8+ T cells in the lymph nodes; (iii) normal production of pro-inflammatory cytokines by T cells; (iv) a low frequency of apoptotic T cells in the lymph nodes; and (v) normal *in vitro* susceptibility to apoptosis [18]. In addition, we found that SIVsmm-infected SMs seem to maintain a preserved T cell regenerative capacity, with normal bone marrow morphology and function, normal levels of T-cell Receptor Excision Circle (TREC)-expressing T cells, and preserved lymph node architecture [18]. As we observed significant differences in CD4+ T cell count between individual SIVsmm-infected SMs, we investigated a potential correlation between increased T cell activation and a trend towards CD4+ T cell depletion. By performing a series of linear regression analyses, we discovered a significant inverse correlation between CD4+ T cell count and the level of T cell activation [18]. Taken together, these results support the hypothesis that the absence of generalized immune activation in SIVsmm-infected SMs is a mechanism that favors the preservation of CD4+ T cell homeostasis. Consistent with this hypothesis are the results of another study in which we inoculated three SMs and three RMs with uncloned SIV derived from the plasma of an SIVsmm-infected SM [150]. While high levels of virus replication were observed in both species, only RMs developed chronic immune activation and increased T cell apoptosis, with two out of three animals sacrificed due to the development of simian AIDS within 2 years. In contrast, only minimal immune activation and T cell apoptosis were observed in the three experimentally SIVsmm-infected SMs that are all still alive and symptom-free after five years [150]. It is important to note that the lack of chronic immune activation in naturally SIVsmm-infected SMs that do not progress to AIDS is consistent with the hypothesis that chronic immune activation is a main determinant of disease progression during HIV infection [156–159].

To collect a more comprehensive set of immunological data on SIVsmm-infected SMs we then conducted a cross-sectional survey of all 110 animals of the Yerkes colony [160]. Confirming our previous observations [18], we found no correlation between CD4+ T cell count and viral load, suggesting that the level of virus replication is not the main determinant of CD4+ T cell dynamics in SIVsmm-infected SMs. As natural SIVsmm infection of SMs typically occurs around the time of sexual maturity [10], age may be used as a surrogate marker for length of infection, but no correlation was found between CD4+ T cell count and age of the animals. Thus, it is unlikely that CD4+ T cell counts in those natural hosts is simply a reflection of the duration of infection in SIVsmm-infected SMs. As seen previously, though, [18], increased levels of T cell activation were significantly correlated with low CD4+ T cell counts. Importantly, this study led us to discover that while 85–90% of SIV-infected SMs exhibit the healthy levels of CD4+ T cells previously described [18], a subset (10–15%) of SIVsmm-infected SMs show significant CD4+ T cell depletion, *i.e.* <500 cells/mm^3 [161]. Irrespective of their low CD4+ T cell counts, these SMs are still asymptomatic, although the recent description of a case of AIDS in a CD4-depleted, SIVsmm-infected SM at the Tulane Primate Center [139] suggests that this asymptomatic phase may be temporary, at least in some animals. It should be noted that we did not find a CD4+ T cell count of <500 in any of over thirty tested SIVsmm-uninfected SMs, indicating that the "CD4-low" phenotype is specific for SIVsmm-infected animals. This previously unrecognized phenotype (CD4"low") of the asymptomatic natural SIV infection of SMs may represent an "intermediate" outcome of infection between the typically pathogenic HIV infection of humans, and the vast majority of non-pathogenic SIVsmm infections of SMs that are characterized by normal CD4+ T cell counts. When compared to SIVsmm-infected "CD4-high" SMs, "CD4-low" animals show similar levels of viremia, a non-significant trend towards older age, and significantly increased expression of markers of T cell activation [162]. Interestingly, the two SIVsmm-infected SMs with the lowest CD4+ T cell counts (*i.e.*, <50/mm^3) showed normal levels of T cell activation, suggesting a complex pathogenesis for this relatively rare phenotype that likely involves viral as well as host factors [162]. A similar phenotype (*i.e.*, very low CD4 count, no increase in T cell activation, and absence of clinical symptoms of AIDS) was also ob-

served in two out of six SMs that were experimentally inoculated with uncloned SIVsmm [163]. Understanding why SIVsmm-infected SMs rarely develop AIDS symptoms even when their CD4+ T cell counts reach AIDS-defining levels could be helpful to delineate the mechanisms that cause the highly variable time to clinical manifestations of AIDS in CD4+ T cell-depleted HIV-infected patients.

4.3 Attenuated cellular immune responses to SIV in SMs.

A number of observations support the possibility that during pathogenic HIV and SIV infections the generation of HIV/SIV specific cellular immune responses, and in particular those mediated by CD8+ T cells, may protect from disease progression (reviewed in [164]). By contrast, it has been proposed that the prevailing level of immune activation in HIV-infected humans, which is at least partly dictated by HIV-specific cellular immune responses, plays a role determining the loss of CD4+ T cell homeostasis [156–159]. To better understand the nature of the interaction between host cellular immune responses and disease progression during retroviral infections, we systematically analysized the SIV-specific T cell responses in naturally SIVsmm-infected SMs [161]. We measured the magnitude and breadth of the SIV-specific responses in both CD3+CD8+ and CD3+CD8- (*i.e.*, predominantly CD4+) T cells in all 110 SIV-infected SMs of the Yerkes colony, and investigated whether a relationship exists between the magnitude or breadth of these responses and the markers of disease progression (*i.e.*, viral load and CD4+ T cell count). We found that while SIV-specific T cell responses can be detected in the majority of naturally SIVsmm-infected SMs, their magnitude is generally lower than what has been described, using the same technique, in HIV-infected patients [165]. In addition, no correlation was found between either breadth or magnitude of SIV-specific T cell responses and either viral load or CD4+ T cell count. It is interesting to note that the magnitude of the SIV-specific cellular responses did not appear to determine the level of T cell activation and proliferation in SIVsmm-infected SMs. Taken together, these results indicate that: (i) the presence of a strong and broadly reactive T cell response to SIV antigens is not a requirement for the lack of disease progression in SIVsmm-infected SMs; and also the converse, that: (ii) the complete suppression of SIV-specific T cell responses (*i.e.*, immunologic tolerance and/or ignorance) is not required for the low levels of T cell activation that are likely instrumental in avoiding AIDS in these animals [161]. It would be interesting to know what genetic factors (*i.e.*, different MHC and KIR alleles) are involved in determining the variability in the level of cellular responses to the virus in naturally SIV-infected monkeys- in particular in SMs, However, the most important implication of this study concerns the nature of the evolutionary co-adaptation of SIVs and their natural host monkey species, and indicates clearly that SMs, and perhaps other natural hosts for SIV as well, have adapted to the selective pressure of SIV infection and reached a disease-free state without the generation of a strong and broadly reactive antiviral cellular immune response. Instead, a general attenuation of the SIV-specific T cell responses appears to be a favorable evolutionary trait. It is tempting to speculate that this host-virus adaptation that results in low levels of SIV-specific cellular immune responses reflects the extreme elusiveness of SIV as a target for immunity. In this regard, these studies of the immunological features of SIVsmm infection in natural hosts emphasizes the tremendous challenge of artificially inducing, with an AIDS vaccine, a type of protective immunity that has not been selected for in many thousands years of evolutionary pressure posed by retroviruses on the primate immune system.

4.4 HIV and SIVcpz infection of chimpanzees.

Chimpanzees are the closest relatives of humans that are known to be natural hosts for SIV infection [1], and, in contrast to other non-human primates, can also be experimentally infected with HIV-1. For both budgetary and ethical reasons experiments involving HIV-1 infection of captive chimpanzee have been infrequently carried out. At this time approximately 150 chimpanzees have been experimentally infected with HIV-1 and only one chimpanzee infected with multiple strains of HIV was reported to progress to AIDS [166]. This lack of disease progression may or may not be due to the fact that, unlike SIVcpz during natural infection, HIV-1 does not replicate well in chimpanzees [59, 167, 168]. Of the chimpanzees that were infected with HIV-1 at the Yerkes Primate Center, three animals showed evidence of CD4+ T cell decline with less than 200 cells/mm^3 of peripheral blood without clinical signs

of AIDS [169]. Interestingly, disease progression in these animals was associated with elevated HLA DR and CD38 expression on CD8+ T cells, loss of naïve CD45RA+ T cells, and a significantly increase in CD29+ memory CD8+ T cells [169]. To the contrary, low levels of T cell activation and bystander apoptosis were found in HIV-infected chimpanzees with no evidence of immunodeficiency [170–172]. The presence of an activated phenotype in the HIV-1-infected chimpanzees that show CD4+ T cell depletion is again consistent with a pathogenic role of the chronic immune activation during HIV/SIV infections. While only limited data are available on the immunological features of natural SIVcpz infection of chimpanzees, it appears that the infection is non-pathogenic in these animals, with absence of AIDS-like symptoms, preserved CD4+ T cell counts and absence of either chronic T cell activation or increased T cell susceptibility to apoptosis (Reviewed in [59]). It is hoped that further studies of the immunological features of natural SIVcpz infection of chimpanzees will be carried out in the future, as a better understanding of the virological and phylogenetic similarities between HIV-1 and SIVcpz and their association with apparently divergent infection outcomes of humans and chimpanzee, respectively, may help elucidate the mechanisms of AIDS pathogenesis.

5. Progression to AIDS in natural hosts for SIV infection.

For many years, it was believed that SIV infection was never pathogenic in their natural African primate hosts. As perhaps expected, given the natural variability of infection outcomes in this large outbred population with great genetic diversity, a number of cases of AIDS-like illnesses in natural hosts for SIV infection have recently been described. Studying these rare cases of AIDS (as well as the instances of CD4+ T cell loss without AIDS observed in naturally SIV-infected SMs) may aid in the identification of virus and host factors that influence the development of progressive immunodeficiency after infection with primate lentiviruses.

As shown in Table 3, occurrence of an AIDS-like disease has now been reported in mandrills infected with SIVmnd-1 and SIVmnd-2 [12, 140] in SMs infected with SIVsmm [139, 173], and in one AGM co-infected with SIVagm and STLV [174]. Moreover, AIDS has resulted in African non-human primates after infection with heterologous virus, including baboons infected with HIV-2 [175], a subset of chimpanzees infected with HIV-1 [169, 175, 176], and a black mangabey infected with SIVsmm [177]. As mentioned above, these cases involve a very small minority of animals, and thus represent a rare occurrence. Interestingly, the animals that develop simian AIDS show a consistent pattern of disease progression that appears to be characterized by levels of viremia that are significantly higher than those observed in the majority of the non-progressor monkeys [132]. In all cases of natural SIV infection that progressed to AIDS, the incubation period was very long (>15 years) and, in fact, approximated or even exceeded the normal lifespan of the animals. An interesting hypothesis, then, is that SIV has adapted to induce a persistent infection that does not cause AIDS within the normal lifespan of natural host monkeys, and that AIDS may occur in those relatively rare monkeys that live longer than their expected lifespan and were infected at young age [140].

Table 3. Immunological Features of Natural SIV Infection of Sooty Mangabeys

- Normal or slightly decreased CD4+ T cell count
- Low levels of T cell activation during the acute and chronic phases of infection
- Preserved T cell regenerative capacity, with normal lymph node architecture, thymic and bone marrow function.
- Low levels of spontaneous and activation induced T cell apoptosis
- Inverse correlation between CD4+ T cell count and prevailing level of immune activation
- Limited SIV-specific T cell responses

6. Why is AIDS so rare in natural hosts for SIV infection?

HIV-infection of humans causes AIDS in the vast majority of cases, while natural SIV infection is most often completely asymptomatic. As discussed above, the level of viral replication does not explain this difference in outcome, which most likely is due to more complex mechanisms that involve both host and viral factors. We will now discuss five hypotheses (see Table 4) that we and others have put

forward to explain the rarity of disease progression in natural hosts for SIV infection. We wish to emphasize that these hypotheses are not mutually exclusive, and that we discuss them separately for the sake of clarity only.

Table 4: Potential Mechanisms of Disease Resistance in the Natural Hosts of SIV (non mutually exclusive)

1. Increased lifespan on infected cells
2. Reduced number of available target cells
3. Limited immune activation and bystander apoptosis
4. More efficient T cell regeneration and redistribution
5. Effective immune control (unlikely, as the level of viral replication is usually high)

6.1 Are the SIV-specific immune responses more effective in natural hosts?

The discovery that natural hosts for SIV infection do not develop AIDS led to the somewhat obvious hypothesis that these animals avoid disease because they are able to exert better immune control of the virus. There is a major and still unresolved theoretical problem with this hypothesis, *i.e.*, that an effective SIV-specific immune response would be predicted to result in lower levels of virus replication than those observed in pathogenic HIV/SIV infections. Instead, all performed studies have consistently shown that naturally SIV-infected monkeys have levels of plasma viremia as high or even higher than those observed in HIV-infected humans [15–20]. One potential explanation is that, although high viremia in SIVsmm-infected SMs clearly indicates incomplete immune control, it is still possible that the level of virus replication could be even higher in the absence of cellular immune responses. Partial control of virus replication via the immune response may be critical, then, in avoiding disease progression. As mentioned above, an extensive study performed in SIVsmm-infected SMs showed that the magnitude of the SIV-specific cellular immune responses is limited when compared to that observed in HIV-infected humans and does not correlate with plasma viremia or CD4+ T cell counts [161, 178]. In addition, depletion of CD8+ T cells from naturally SIV-infected SMs did not result in major changes of viral replication (Mark Feinberg, unpublished observations). Although similar studies have not been performed in other natural hosts, based on the data obtained in SMs, it may be concluded that SIV-specific cellular immune responses are not likely to be a key determinant of the absence of disease progresson in natural hosts for SIV infection.

6.2 Is SIV intrinsically less cytopathic *in vivo* in natural hosts?

The lack of disease progression in natural hosts for SIV infection may be explained by reduced virus cytopathicity, or, to be more accurate, by a longer average lifespan of infected cells *in vivo*. If infection of CD4+ T cells from natural hosts is followed by a greater duration, as compared to HIV-infected humans, of virus production, a high level of viremia could be conceivably reached in the presence of a relatively low fraction of infected CD4+ T cells. If fewer CD4+ T cells are killed at any given time, it would be easier for the immune system to replace them and thus to avoid any progressive CD4+ T cell depletion. According to this hypothesis, in naturally SIV-infected monkeys that develop progressive CD4+ T cell loss and AIDS, the intrinsic *in vivo* cytopathicity of the virus would be higher and the resultant accelerated killing of infected cells would ultimately compromise the homeostasis of the CD4+ T cell pool.

In HIV-infected patients that were treated with potent antiretroviral therapy (ART), the *in vivo* lifespan of cells infected with HIV has been inferred by the kinetics of decline of viral load following ART [179–181]. These studies concluded that the bulk of HIV replication occurs in recently infected cells that die soon after infection, likely as a result of a direct cytopathic effect of the virus (however, it should be noted that HIV preferentially infects activated CD4+ T cells that may be primed to die of activation-induced cell death regardless of their infection status). A similar approach could be used to assess the average lifespan of infected cells in SIV-infected natural hosts, and these studies are currently being performed in our laboratories in both SMs and AGMs. The hypothesis that in natural hosts for SIV infection the lifespan of infected cells is longer than in pathogenic HIV/SIV infections would predict that naturally SIV-infected animals manifest a slower decline of viremia post-ART. This poten-

tial prolonged lifespan of infected cells would contribute to the maintenance of high CD4+ T cell counts in natural hosts, with the exception of the animals with low CD4+ T cell counts that may show a slope of viremia decline similar to that described in HIV-infected patients. As mentioned, these studies are in progress ion our laboratory and we are now eagerly anticipating the results.

6.3 Are CD4+ T cells of natural hosts less susceptible to infection? (*i.e.*, does the virus target a more limited subset of these cells?)

Pathogenic HIV/SIV infections are associated with early and persistent depletion of memory/activated CD4+CCR5+ T cells from the mucosal associated lymphoid tissues (MALT) [111, 182–185]. In these pathogenic infections, the virus co-receptor usage is a key factor in determining which CD4+ T cell subsets are depleted and from which anatomic sites, with an observed depletion of naïve CD4+ T cells from blood and lymph nodes by CXCR4-tropic viruses and depletion of memory CD4+ T cells in the blood and MALT by CCR5-tropic viruses [183, 186]. As CCR5 has been shown to be the main co-receptor used by SIV in natural hosts [187], it could be hypothesized that these animals, unlike non-natural hosts, avoid CD4+ T cell depletion from the mucosal tissues because their memory CD4+ T cells are less susceptible to SIV infection due to reduced CCR5 expression. In fact, natural hosts for SIV infection, and in particular SMs and AGMs, both SIV-infected and uninfected, do show decreased CCR5 expression on their memory CD4+ T cells, but not CD8+ T cells, in both peripheral blood and mucosal tissues, as compared to non-natural hosts such as macaques, baboons, and humans [155, 188, 189] . These results suggest that natural hosts have fewer CD4+ T cells that are susceptible to SIV infection then non-natural hosts, in which HIV/SIV infection is followed by progression to AIDS. In this perspective, the expression of CCR5 on a smaller fraction of memory/activated CD4+ T cells likely favors the preservation of the memory CD4+ T cell pool, especially in mucosal tissues, even if the virus infects and kills the majority of CD4+CCR5+ T cells. This hypothesis would be strongly supported by data indicating that memory CD4+ T cells are not depleted and/or are less extensively infected in the MALT during acute SIV-infection of natural hosts. In naturally SIV-infected monkeys with disease progression, a chronic loss of CD4+ T cells may be related to either an increased fraction of memory CD4+ T cells that express CCR5 or the presence of virus with expanded co-receptor usage. Both of these scenarios would induce CD4+ T cell depletion as the virus would now be capable of infecting and killing a larger fraction of memory CD4+ T cells. This hypothesis would provide an elegant evolutionary mechanism of "pacific co-existence" between SIV replication and natural host immune system function: with CCR5 expression restricted to a small subset of memory CD4+ T cells that are able to sustain the chronic high viremia in the majority of SMs, only this subset would be lost due to the direct cytopathic effect of SIV, but even a progressive depletion of this subset would not induce a major disruption of the memory CD4+ T cell homeostasis.

It should be noted, however, that to incorporate the unquestionable finding that SIV replicates to high levels in natural hosts, this hypothesis would predict either that the bulk of the measured SIV replication takes place in long-lived non-T cells (*i.e.*, tissue macrophages), or that the infected CD4+ T cell produce a significantly higher amount of virus per individual infected cell (*i.e.*, they have an increased lifespan). Interestingly, combined immunohistochemical analysis of SIV replication and phenotypic staining for T cells and macrophages in chronically SIVsmm-infected SMs and black mangabeys show that a greater number of macrophages than T cells is SIV-infected in the intestinal mucosa, suggesting that a significant proportion of productively SIV-infected cells in African non-human primates may be long-lived [177, 190]. More studies of the *in vivo* dynamics of SIVagm and SIVsmm replication are still needed to confirm that the major target cells of these viruses differ from those of SIVmac and HIV.

6.4 Are natural hosts for SIV infection protected from disease progression by lower levels of immune activation and bystander apoptosis?

A number of recent studies performed in SMs, AGMs, and mandrills indicate that both acute and chronic SIV infection of natural hosts is associated with lower levels of T cell activation, pro-inflammatory responses, immunopathology, and bystander apoptosis than pathogenic HIV/SIV infection [16, 18,

149, 150, 191]. Taken together, these results strongly support the hypothesis that an important (although not exclusive) mechanism favoring the preservation of CD4+ T cell homeostasis in natural hosts is the absence of generalized immune activation. In fact, the observation that SIV infection of natural hosts is associated with low levels of immune activation and apoptosis is in sharp contrast with the state of chronic generalized immune activation seen in HIV-infected individuals that is thought to contribute to the AIDS-associated T cell depletion [156, 158, 159, 192–195] and to predict disease progression [157, 196–200]. The well-demonstrated low level of immune activation in naturally SIV-infected monkeys may thus be a key factor in their lack of disease progression despite chronic high levels of viral replication. In this perspective, the observation of low SIV-specific cellular immune responses in SIVsmm-infected SMs can also be interpreted as a mechanism protecting naturally SIVsmm-infected SMs from the establishment of a state of chronic generalized immune activation. This hypothesis would predict that in the few animals that do lose CD4+ T cells (and may ultimately progress to AIDS) the level of immune activation is higher than in animals with higher CD4+ T cell counts. Studies are currently ongoing to test this hypothesis in several models of SIV infection of natural hosts. Ultimately, as low levels of immune activation may also be a consequence, rather than a cause, of a lack of pathogenicity due to other factors, we hope to more directly determine whether artificial enhancement of immune activation results in disease progression in natural hosts for SIV infection.

6.5 Is SIV infection of natural hosts associated with normal or even increased CD4+ T cell regeneration?

The possibility that a preserved or perhaps even enhanced T cell regenerative capacity plays a key role in determining the lack of disease progression in naturally SIV-infected monkeys is intriguing as, in HIV infection, a failure of the lymphoid regenerative capacity has been proposed to be an important factor in the pathogenesis of the immunodeficiency [156]. In particular, bone marrow suppression, reduced thymic output and loss of naive T cells have all been observed in HIV-infected individuals [201–207]. In marked contrast with this picture, our previous studies in SIV-infected SMs showed that the regenerative capacity of the CD4+ T cell compartment is fully preserved [18]. Two recent observations illustrate the critical role for interleukin-7 (IL-7)-dependent preserved T cell regeneration in avoiding CD4+ T cell depletion and disease progression in SIV-infected SMs. First, the timely triggering of an IL-7-dependent homeostatic mechanism is involved in maintaining high CD4+ T cell levels in experimentally SIVsmm-infected SMs [208]. Second, a direct correlation was found in SIVsmm-infected SMs between plasma levels of IL-7 and CD4+ T cell counts [209]. The hypothesis of a preserved lymphocyte regenerative compartment during non-pathogenic SIV infection of natural hosts is of interest as it may reflect an evolutionary adaptation of natural hosts whereby the chronic infection and killing of CD4+ T cells mediated by SIV is more effectively compensated by the production of new CD4+ T cells.

Concluding remarks and open questions.

We have reviewed the main epidemiological, virological, and immunological features of SIV infection of natural hosts, and find that the crucial but still unanswered question remains: why do SIV-infected natural hosts avoid AIDS while most HIV-infected humans do not? At this time, unfortunately, a simple and straightforward answer to this question is still missing. However, more pieces of the puzzle are fitting together. While the viral factor (*i.e.*, reduced intrinsic cytopathicity and/or restricted tropism for CD4+ T cells) is far from being ruled out, it is fair to say that most of the available studies suggest that specific features of the host immune response play a key role in determining the specific phenotype of SIV infection in natural hosts. These features appear to be crucial not in terms of controlling viral replication per se (a task that is obviously not accomplished in natural SIV hosts), but instead by avoiding the generation of a state of chronic hyperactivation of the immune system that is ultimately more harmful than beneficial to the host. The molecular and cellular mechanisms responsible for the attenuated immune response observed in naturally SIV-infected monkeys in the face of a chronically high antigen load are currently under investigation and are likely to be complex. While additional evolution-

ary mechanisms may play an important role in avoiding disease progression in natural hosts (*i.e.*, lower CCR5 expression, more effective CD4+ T cell regeneration) it is now clear that the co-evolution of SIV and its natural host monkey species has led to a state of disease-resistance that does not involve immunity to viral infection or viral replication, but rather reflects an evolutionary adaptation that allows for a pacific co-existence of host and virus. The importance of this observation, in our opinion, is in its implications for an understanding of the interactions between HIV and the human immune system. We feel strongly that further studies of the virology and immunology of natural SIV infections are needed to improve our understanding of the pathogenesis of HIV infection in humans. It is our hope that these conceptual advances will eventually translate into substantial improvements in the clinical management of HIV-infected patients.

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