

The Evolution of SIV in Primates and the Emergence of the Pathogen of AIDS

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Introduction

Three decades have passed since the first reports of opportunistic diseases in previously healthy individuals and the description of acquired immunodeficiency syndrome (AIDS) as a new human disease (CDC 1981a, b, c). Shortly after, the causative agent was identified as a T-cell tropic retrovirus (Barre-Sinoussi et al. 1983) that eventually came to be termed human immunodeficiency virus 1 (HIV-1). HIV-1 is a retrovirus of the Lentivirus genus and the first primate lentivirus to be discovered. A second human lentivirus, HIV-2, was later discovered in patients suffering from AIDS in West Africa (Clavel et al. 1986).

Lentiviruses have since been discovered to naturally infect over 40 different African primate species, termed simian immunodeficiency viruses (SIVs). Study of SIV infection of the majority of these species is difficult, as many are endangered and (rightly) protected in the wild, with limited or no captive populations available for study. However, some important facts have been established. Firstly, it is now clear that HIV-1 has originated from SIVcpz of the common chimpanzee (*Pan troglodytes*) and HIV-2 from SIVsmm of the sooty mangabey (*Cercocebus atys*). Secondly, some species of SIV-infected African primates are present in European and US research centers, and thus, the natural history of their infection has been studied in detail. In particular, the SIV infection of two African green monkey species (*Chlorocebus sabaeus* and *C. pygerythrus*) and sooty mangabeys has been studied intensively. In these species, it is clear that the vast majority of individuals do not progress to AIDS.

In contrast, Asian macaques are not infected with SIV in the wild, but can develop AIDS when experimentally infected with SIV from other species,

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providing a model for disease in humans caused by HIV. Rhesus macaques (*Macaca mulatta*) and pig-tailed macaques (*Macaca nemestrina*) are the two species principally used in these studies. These models were first established after macaques in numerous American primate centers developed AIDS-like clinical signs and were also found to be infected with T-cell tropic retroviruses, which collectively came to be termed SIVmac (Benveniste et al. 1986; Daniel et al. 1984). Due to the similarity between SIVmac and SIVsmm, it was hypothesized early on that SIVmac could have its origins in SIVsmm infection of sooty mangabeys (Murphey-Corb et al. 1986), which has since been confirmed. It is likely that SIVsmm was unknowingly transmitted from sooty mangabeys into macaques during invasive experiments for the study of prion diseases in American primate centers and subsequently spread within captive macaque populations (reviewed by Apetrei et al. 2006).

Comparison of the pathogenic infection of humans and macaques with HIV/SIV with the nonpathogenic infection of sooty mangabeys and African green monkeys has provided key insight into the pathways most important in the development of AIDS in susceptible species and the host mechanisms that have evolved in African primate species to avoid disease as a result of lentivirus infection.

In this chapter, we will first discuss the age and diversity of primate/human lentiviruses, the outcome of SIV transmission into humans, and the mechanisms proposed to have promoted the pandemic spread of HIV-1. Next, we will compare the natural history of pathogenic HIV infection of humans and SIV infection of Asian macaques (the best available animal model of human HIV/AIDS) with the non-pathogenic SIV infection of sooty mangabeys and African green monkeys. We will discuss in depth the mechanisms that have been proposed to explain the dichotomous outcome of lentivirus infection between these groups. We will then examine the specific differences between HIV-1 and other primate lentiviruses, including potential mechanisms for the high pathogenicity of HIV-1. Finally, we will review what is known of the host–virus relationship in the species in which the HIV-1 lineage evolved and suggest that examination of this relationship is of special importance to HIV-1 and SIV research.

Age and Diversity of the SIV Lineage

SIVs observed in wild African primates are generally species-specific: multiple isolates of virus from one primate species generally form monophyletic lineages in phylogenetic trees. The degree to which SIVs differ within one species varies, but is largely biased by the number of isolates sequenced and their geographical distribution (Bibollet-Ruche et al. 2004; Liegeois et al. 2012). Species with highly divergent SIVs have also been observed, which are usually the result of cross-species transmissions, sometimes followed by recombination between distant SIVs (Aghokeng et al. 2007; Liegeois et al. 2012; Souquiere et al. 2001). High frequencies of recombination are a characteristic of primate lentiviruses (Chen et al. 2006), but such recombination events are most apparent when heterologous viruses

recombine. These so-called mosaic or chimeric viruses are described for African green monkeys, mandrills (*Mandrillus sphinx*), and chimpanzees (Bailes et al. 2003; Jin et al. 1994; Takemura and Hayami 2004) and can be identified when comparing phylogenetic trees created using alignments from different parts of the genome, as in Fig. 1.

A precise age of primate lentiviruses has been difficult to ascertain, but has been estimated in several studies. Such dating methods normally require the use of a “molecular clock,” in which sequences are compared, and a known or estimated rate of genetic change is applied to estimate the time to the most recent common ancestor. Estimates resulting from molecular clock methods are dependant on how this rate of change is estimated. While this is relatively simple for eukaryotic species, as the rate of genetic change is both slow and well established for different species, calibrating a molecular clock for retroviruses, which change extremely rapidly and often recombine, is much more challenging.

Using only relatively modern SIV and HIV sequences of known dates (from 1975 to 2005) to calibrate a molecular clock resulted in a estimate that the primate lentivirus lineage is only centuries old (Wertheim and Worobey 2009). However, this dating was controversial as it was already suspected that using only modern sequences to extrapolate the history of a possibly ancient lineage would lead to erroneous estimates (Sharp et al. 2000).

However, a recent study of SIV infection of primates on the African island of Bioko has allowed for a new calibration of the molecular clock estimate of the age of this lineage (Worobey et al. 2010). The island has been separated from the African mainland for a period of 10,000–12,000 years and accommodates a number of primate species. Individuals from four of these species were found to be infected with SIV. Most importantly, the Bioko drill (*Mandrillus leucophaeus poensis*) is infected with an SIV similar to that isolated from the mainland drill (*Mandrillus leucophaeus leucophaeus*). The time to the most recent common ancestor of SIVdrl from Bioko and SIVdrl from mainland Africa is therefore known to be at least 10,000 years old, providing a new method for calibrating the molecular clock. The resulting estimate is that SIVs have been present in African primates for 76,000 years.

Finally, evidence exists that the primate lentivirus lineage is ancient. The genomes of a number of lemur species of genera *Cheirogaleus* and *Microcebus* contain sequences of a lentivirus that has at some point infected germ line cells and become integrated into the genome—an endogenous lentivirus. After integration into the genome, the sequences of endogenous retroviruses are expected to be subject to the same rate of mutation as other host genomic sequences. This rate is well established for eukaryotic species and is much slower than the rate of mutation of exogenous retroviruses. Endogenous retroviruses are therefore ideal for estimating dates on ancient timescales. It seems that there were two independent integration events, both estimated to have occurred around 4 million years ago (Gifford et al. 2008; Gilbert et al. 2009). Unless SIV was introduced to Madagascar independently and prior to the introduction of SIV to the African mainland, this would indicate that the African primate lentivirus lineage is at least equally as ancient.

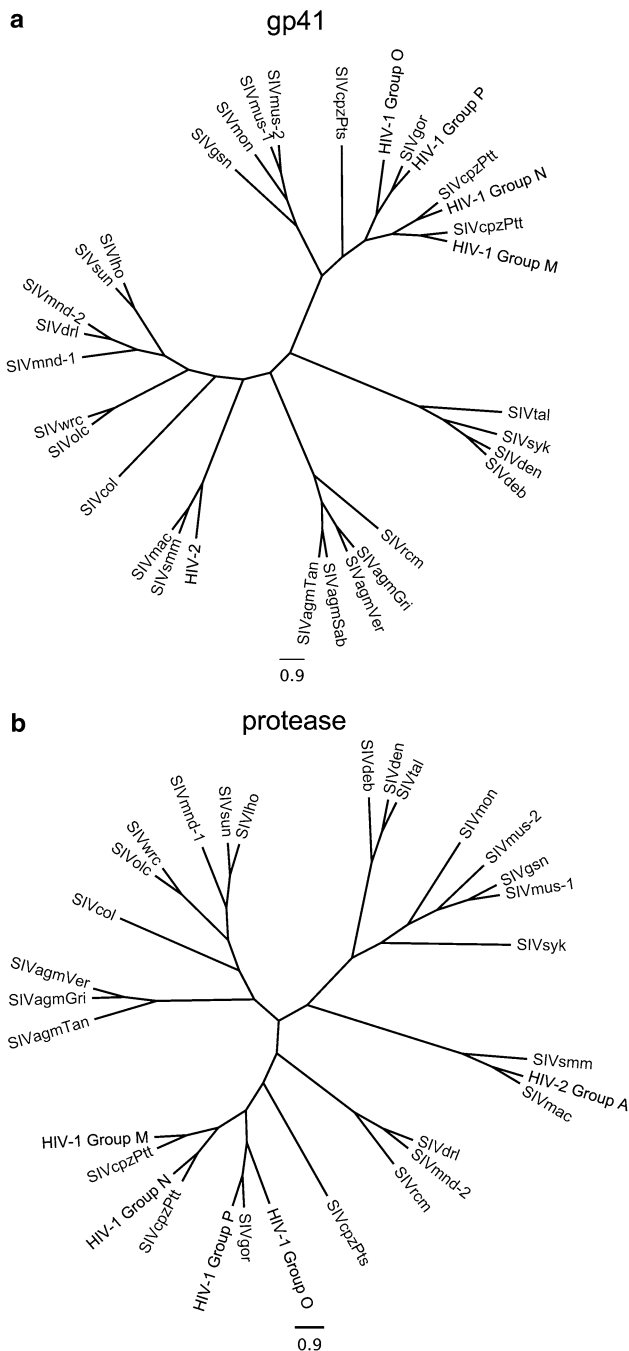


Fig. 1 Phylogenetic trees demonstrating the relationships between different SIVs and HIV-1 and HIV-2. Trees were created from alignments using nucleic acid sequences from the (a) gp41 and (b) protease genes. Scale bar indicates 0.9 substitutions per site. SIVagmSab is excluded from the protease tree as a recombination event has occurred in the region used for this alignment

In addition, in general, the relationship between SIVs of different species mirrors the relationships between their primate hosts, with SIVs from closely related primates being the most similar to one another. It has therefore been suggested that species-specific SIVs could be the result of concurrent host diversification, with splits in the SIV lineage occurring at the same time as splits in the primate lineage (host-dependant evolution) (Sharp et al. 2000). The SIVs of African green monkeys show particularly strong evidence of this. Each of the four species of African green monkey (*Chlorocebus aethiops*, *C. tantalus*, *C. pygerythrus*, *C. sabaues*) is infected with a species-specific SIV, and the genetic divergence between viruses mirrors the divergence of the host species (Jin et al. 1994; Muller et al. 1993; Sharp et al. 2000). For host-dependant evolution to occur, the most recent common ancestor of the four African green monkey species must have been infected with SIV. The time to the most recent common ancestor of these species is approximately 3 million years (Fabre et al. 2009).

Distribution of Accessory Genes in the Primate Lentivirus Lineage

HIV/SIV are retroviruses of the Lentivirus genus. The genomes of all retroviruses include the genes *gag*, *pol*, and *env*, the major structural and enzymatic proteins of the virus. All known members of the Lentivirus genus also possess the regulatory proteins Rev and Tat, including the oldest recognized lentivirus, “RELIK,” an endogenous retrovirus estimated to have integrated into the genome of the European rabbit (*Oryctolagus cuniculus*) over 12 million years ago (Katzourakis et al. 2007; Keckesova et al. 2009). All extant lentiviruses found in primates, cats, sheep, and cattle possess an additional gene, *vif*.

In contrast, four genes are unique to extant primate lentiviruses; *nef* and *vpr* are found in all primate lentiviruses, while *vpx* and *vpu* are found in nonoverlapping subsets of these viruses. Our understanding of the functions of *vif*, *nef*, *vpr*, *vpx*, and *vpu* has increased dramatically during recent years, and it can be concluded that all factors have evolved to play a role in counteracting host defense mechanisms called restriction factors (Ayinde et al. 2010; Kirchhoff 2010).

Vpx, one of the two genes unique to primate lentiviruses, evolved in the *Papionini* tribe of primates, and the distribution of this gene within primate SIVs is likely to have been increased as a result of several recombination events between SIVs of different primate species (Takemura and Hayami 2004). It is found in SIVsmm (of sooty mangabey), SIVrcm (red-capped mangabey, *Cercocebus torquatus*), SIVmnd-2 (mandrill), and SIVdrl (drill). The other gene unique to primate lentiviruses, *vpu*, was acquired by an SIV within a subset of guenon species (Bailes et al. 2003). Guenons (tribe *Cercopithecini*) are a species-rich group of primates; however, only four guenon species, which associate in the wild, carry SIVs with the *vpu* gene. These are the mona monkey (*Cercopithecus mona*), greater spot-nosed monkey (*C. nictitans*), and mustached monkey (*C. cephus*), infected with SIVmon,

SIVgsn, and SIVmus, respectively. A fourth *Cercopithecus* species, Dent's mona monkey (*C. mona denti*), was found to be infected with an SIV harboring the *vpu* gene (SIVden), but with a shorter coding region (Dazza et al. 2005; Schmokel et al. 2010). Two other nonhuman primate species are infected with a *vpu*-carrying virus—the chimpanzee, *Pan troglodytes*, infected with SIVcpz, and the western gorilla (*Gorilla gorilla*) infected with SIVgor. SIVcpz has been identified in two subspecies of chimpanzees, *Pan troglodytes troglodytes* and *P. t. schweinfurthii*, while surveys of wild *P. t. verus* and *P. t. ellioti* (previously known as *P. t. vellerosus*) have demonstrated with some confidence that they are not infected (Sharp and Hahn 2011). SIVgor has been identified in the western lowland gorilla subspecies (*Gorilla gorilla gorilla*) and has thus far been found exclusively in Cameroon (Neel et al. 2010). SIVgor is highly related to SIVcpz and gorillas have most likely become infected more recently through cross-species transmission of SIVcpz from *Pan troglodytes troglodytes*.

The recombination events involved in the genesis of SIVcpz/SIVgor are of particular interest. Phylogenetic analyses suggest that a *vpx*-expressing virus found in red-capped mangabeys was transmitted into chimpanzees where it recombined with an SIV expressing the accessory gene *vpu*. The chimpanzee mosaic virus shows homology with SIVs found in a subset of guenons within the 3' half of its genome (Courgnaud et al. 2002). The 5' region of the genome and possibly the *nef* gene at the 3' end are closely related to SIVrcm (Beer et al. 2001; Kirchhoff 2009). One recombination crossover is therefore likely to have occurred in the short region between *vpr* and *vpu* and another between *env* and *nef* (Kirchhoff 2009; Sharp et al. 2005). It is believed that the *vpx* gene was transferred within the initial recombination, but must have subsequently been lost as no remnant of this gene is apparent in contemporary SIVcpz. The *vpu* gene however remained conserved.

Transmission of SIV into Humans and the Spread of HIV

There are four recognized HIV-1 groups: M, N, O, and P. As each of these HIV-1 groups is closest in sequence homology to different isolates of SIV in chimpanzees or gorillas, it is clear that there have been at least four cross-species transmission events into humans, with M and N group viruses having their source in chimpanzees of the *Pan troglodytes troglodytes* subspecies and O and P group most closely related to SIV of gorillas (Keele et al. 2006; Plantier et al. 2009; Van Heuerswyn et al. 2006). To prevent confusion, it should also be noted that there is a separate alphabetical nomenclature for describing different subtypes (also referred to as clades) of HIV-1 group M viruses. Based on sequence homology, HIV-1 group M viruses are assigned to subtypes from A to K or identified to have been generated through recombination between viruses of previously identified subtypes.

Non-M HIV-1 viruses are mostly restricted to Cameroon. Group O infection accounts for around 1 % of all HIV-1 infection in Cameroon (Vergne et al. 2003),

while N has been identified in less than 20 individuals (Vallari et al. 2010a) and group P in only two cases so far (Plantier et al. 2009; Vallari et al. 2010b). Clinical data regarding non-M infections is limited, but it is important to note that group O and group N infections have been identified in patients with AIDS (Ayoub et al. 2000; Gurtler et al. 1994), while the first group P infection to be identified was associated with depleted CD4+ T cells and a high viral load (Plantier et al. 2009). There is therefore no evidence that HIV-1 non-M infections are less pathogenic than HIV-1 M infections, despite their more limited spread.

In addition to HIV-1, there is a second human immunodeficiency virus, HIV-2. In contrast to HIV-1, HIV-2 infects globally only between 1 and 2 million individuals and is predominantly confined to West Africa (Campbell-Yesufu and Gandhi 2011). In common with HIV-1, HIV-2 consists of several groups, each the result of a different cross-species transmission event. Eight groups, A–H, have been recognized, with only groups A and B having spread more extensively within the human population. The remaining groups are limited to infections of single individuals. HIV-2 is the result of transmission of SIV from the sooty mangabey, and because of this different source, HIV-2 has a different genetic structure to HIV-1. Viral genomes of several primate lentiviruses, along with HIV-1 and HIV-2, are compared in Fig. 2. There are critical differences between HIV-1 and HIV-2 infection of humans that are discussed at the end of this chapter.

As with dating the age of the primate lentivirus lineage, dating the cross-species transmission events leading to HIV has been difficult. However, the availability of two HIV-1 group M sequences attained from archived samples from 1959 and 1960, from Kinshasa (formally Leopoldville), Democratic Republic of Congo (DRC, formally Belgian Congo and, later, Zaire), allows for greater confidence in dating the origin of the HIV-1 group M pandemic. While the chimpanzees infected with SIVcpz isolates most closely related to HIV-1 group M are found in Cameroon, it seems that Kinshasa is a candidate for the epicenter of the HIV-1 pandemic. A study conducted in 1997 indicated that there is unparalleled genetic diversity of HIV-1 M in the DRC, with all subtypes represented, along with recombinant forms not represented outside of the DRC (Vidal et al. 2000). Notably, HIV-1 extracted from the two samples from 1959 and 1960 show a high degree of genetic divergence—comparable to the genetic difference between two contemporary isolates of different subtypes. This suggests that by 1960, HIV-1 had already circulated extensively in humans in this region (Worobey et al. 2008).

Using sequences from these two early samples, along with later samples to calibrate a molecular clock, leads to an estimate that the cross-species transmission event leading to HIV-1 group M most likely occurred near the start of the twentieth century, between 1873 and 1924 (Worobey et al. 2008). Dating the cross-species transmission events that resulted in the other HIV-1 and HIV-2 groups is more problematic due to the markedly fewer available sequences and the lack of sequences from older achieved material. Estimates for the date of the four cross-species transmission events leading to HIV-1 groups O and N and HIV-2 groups A and B are all also within or near the beginning of the twentieth century (de Sousa et al. 2010; Wertheim and Worobey 2009).

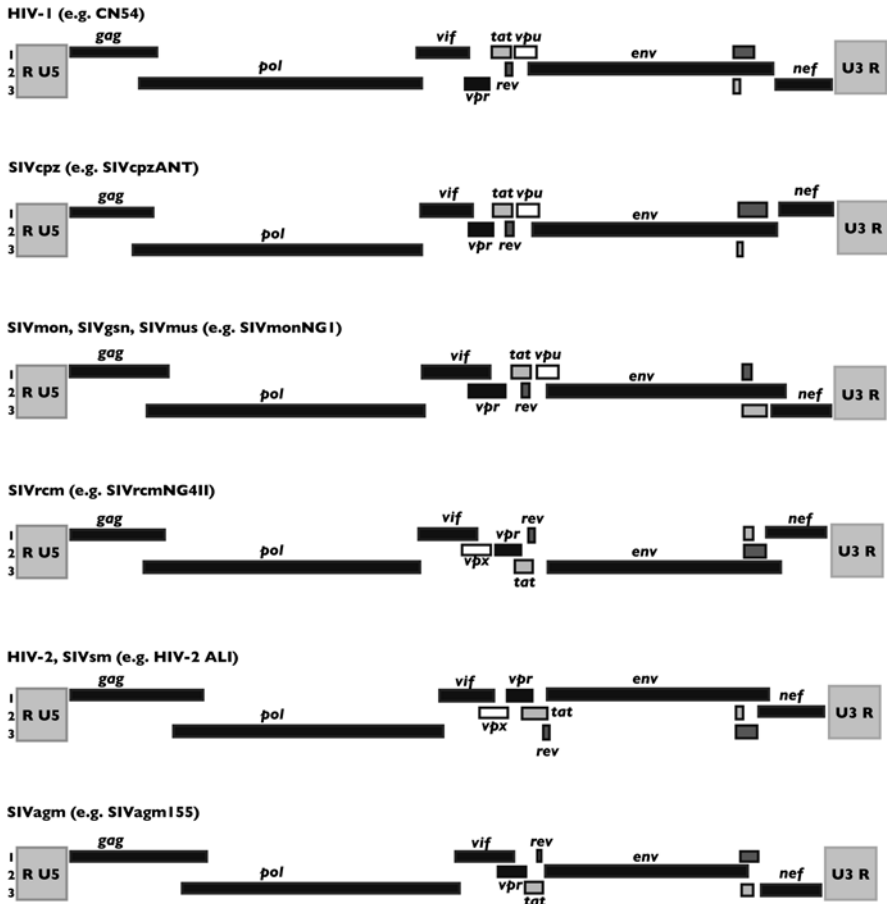


Fig. 2 Annotated depiction of the genomes of HIV-1, HIV-2, and relevant SIVs. Diagrams are based on annotated sequences, with the sequence used named in brackets. Numbers 1–3 at left indicate reading frames

Pandemic Spread of HIV

Human exposure to SIV-infected primates is unlikely to be novel to the late nineteenth and early twentieth century. Notably, some strains of another human retrovirus, human T-cell lymphotropic virus (HTLV), present in Africa seem to be the result of cross-species transmission events from primates occurring thousands of years ago (Switzer et al. 2006; Van Dooren et al. 2001), also most likely through bushmeat. Several authors have therefore attempted to identify mechanisms to explain why only the cross-species transmission events in this recent time frame have resulted in the several HIV-1 and HIV-2 epidemics and the HIV-1 group M pandemic—i.e., mechanisms that promoted the spread of HIV that are unique to the twentieth century.

Firstly, Worobey and colleagues have suggested that the development of large urban centers, not present in western Central Africa prior to 1900, facilitated the spread of HIV-1. They assert that prior to 1910, there was not a single site with a population greater than 10,000 people in western Central Africa (Worobey et al. 2008). Kinshasa underwent particularly rapid growth, from only a few thousand people in 1905, to around 40,000 in 1940, and over 400,000 in 1961 (Chitnis et al. 2000).

However, this rapid urbanization, combined with the (often-forced) movement of workers, led to disruption of social norms that may have been a greater contributing factor than the size of the urban centers alone. De Sousa and colleagues carried out extensive analysis of colonial medical articles and reports regarding Kinshasa from the start of the twentieth century to the country's independence (and general expulsion of Belgian authorities) in 1960 (Chin 2007; de Sousa et al. 2010). They note that in 1929 there were a large number of commercial sex workers, possibly due to the heavily male biased population, at 4:1 males to females. They also find that sexually transmitted diseases, including syphilis and other genital ulcerative diseases, were highly prevalent, with one survey in 1930–1932 finding that 5 % of the female population had active genital ulcers (de Sousa et al. 2010). While the low risk of HIV-1 transmission from heterosexual sex, estimated to be between 0.01 and 1.1 % per act (Boily et al. 2009), could be viewed as a barrier to early spread of HIV-1 through purely sexual contact, the risk of transmission is considerably increased when genital ulcers (and other non-ulcerative sexually transmitted diseases) are present in either the HIV-positive or HIV-negative sexual partner, with most studies finding a 2–5-fold increase in risk of infection, but some finding the risk of transmission to be almost 20-fold higher (Boily et al. 2009; Fleming and Wasserheit 1999).

The role of non-sterile injections throughout sub-Saharan Africa in the twentieth century has also been proposed as a major factor allowing the early spread of HIV-1. Marx and colleagues propose that initial “serial human passage” of the virus through non-sterile injections allowed the adaptation to humans which they suggest would be required for subsequent spread by sexual transmission (Marx et al. 2001). They point to numerous mass injection campaigns in sub-Saharan Africa and evidence for large numbers of injections involving the reuse of non-sterilized injection materials in the twentieth century, especially since the discovery of penicillin and its use in Africa from the 1950s onwards.

The mechanisms reviewed above that are proposed to have facilitated the spread of HIV-1 span the entirety of the twentieth century. Interestingly, in their 2008 analysis, Worobey et al. propose a model of the growth of HIV-1 that suggests relatively slow growth prior to 1960, followed by much more rapid expansion after this date. Although their analysis is likely to be subject to bias due to the limited availability of samples available, this computational analysis has some support from the early reports of AIDS in Africa, as it correlates with marked increases in the opportunistic diseases that now define AIDS, such as Kaposi's sarcoma and esophageal candidiasis, occurring in Kinshasa, Uganda, Zambia, and Rwanda from the late 1970s to the early 1980s (Quinn et al. 1986). This would be consistent with aggressive spread of

HIV-1 in the 1960s and early 1970s, due to the approximately decade-long incubation period between HIV-1 infection and the development of AIDS (see below).

Together, these lines of evidence tend not to favor extensive spread in urban centers in the early part of the twentieth century. May and colleagues have proposed an elegant model of rural spread among “loosely interlinked villages” (May et al. 2001). One significant attraction of this model is that it predicts that HIV-1 could persist at a very low level for decades within rural villages, with only limited spread within each village compensated for by introduction to new villages, preventing the virus from becoming extinct. In this model, the period of extremely slow spread is then followed by much more rapid expansion of HIV, without requiring mechanisms postulated above. Of course, this does not exclude a role for the other factors reviewed, especially as urbanization, high levels of other sexually transmitted diseases, and the reuse of non-sterilized injection materials could all have contributed to the introduction of HIV-1 to urban centers and extensive spread within these centers—which was almost certainly a requirement for HIV dissemination throughout and beyond Africa.

While HIV-1 group M subtype B causes only a minority of HIV-1 infections in Africa, it is the most prevalent subtype in a large number of countries outside of Africa, including the USA and Europe. The disparity between the prevalence of subtype B outside and within Africa could indicate that the pandemic beyond Africa was the result of a single transmission from Africa. Gilbert and colleagues examined sequences from archived samples collected in 1982 and 1983 of Haitian nationals that had immigrated to the USA after 1975 and hospitalized with AIDS prior to 1981 (Gilbert et al. 2007). They focused on these patients as shortly after the recognition of AIDS as a novel syndrome firstly primarily in homosexual men in the USA in 1981 (Gottlieb et al. 1981), and intravenous drug users in 1982 (CDC 1982b), there were reports of Haitian nationals in the USA suffering from AIDS (CDC 1982c). The majority of these Haitian patients indicated they had practiced neither homosexual sex nor intravenous drug use, suggesting that being a recent Haitian immigrant was an independent risk factor for the development of AIDS.

In their analysis of sequences from these patients, in addition to other sequences of HIV-1 isolates from Haiti, and sequences representing HIV-1 subtype B isolates from multiple other countries, Gilbert and colleagues find that subtype B is the most genetically diverse within Haiti, indicating an earlier introduction of HIV-1 subtype B into this nation than any other, and that the HIV-1 epidemic in Haiti was the result of a single introduction of the virus from Africa. They also show that with few exceptions, the pandemic spread of HIV-1 subtype B beyond Haiti (including North American, South American, European, and Asian countries) is the result of another single founder event linked to Haiti, which they postulate to be most likely the introduction of HIV-1 to the USA through immigration.

The authors estimate that the introduction of HIV-1 from Africa into Haiti occurred between 1962 and 1970. Interestingly, it seems that there was a large movement of Haitians to the DRC (then Zaire) in the early 1960s following two events: firstly, political problems appearing in Haiti after Francois Duvalier

(‘Papa Doc’) took power in 1957 and, secondly, the vacancies for “executive” positions (administrators, healthcare workers, and teachers) in Zaire following the expulsion of the Belgian authorities in 1960. Many Haitians returned to Haiti or to other nations in the late 1960s and early 1970s (Chin 2007; Molez 1998; Piot et al. 1984), possibly indicating a potential mechanism by which HIV-1 was introduced into Haiti. Gilbert et al. also estimate that the single founder event leading to the spread of HIV-1 subtype B from Haiti occurred between 1966 and 1972 (Gilbert et al. 2007), which is constant with the earliest cases of AIDS in the USA, retrospectively diagnosed as occurring in 1978 (CDC 1982a).

Natural History of HIV/SIV Infection of AIDS-Resistant and AIDS-Susceptible Species

The clinical progression of HIV-1 infection of humans is normally monitored by assessing the number of peripheral blood CD4+ T cells and the peripheral blood viral load. In the acute stage of infection, the highest levels of virus replication are reached, with viral loads frequently in the region of 10^6 – 10^7 copies of the RNA genome per ml of blood (Kaufmann et al. 1998; Rieder et al. 2010). This occurs concurrently with a sudden drop in the CD4+ T-cell count that is partly recovered after the first few months of infection. In the chronic phase of infection, a lower, relatively stable “set point” viral load is established, generally in the region of 10^4 – 10^6 copies/ml, with the chronic viral load correlating with the rate of disease progression (Mellors et al. 1996; Rodriguez et al. 2006). Levels of peripheral blood CD4+ T cells slowly decline, until they are depleted to the point that the immune system can no longer function. This depletion of CD4+ T cells is thought to be due to a number of factors, including, but certainly not limited to, the direct infection of CD4+ T cells by HIV-1. The mean CD4+ T-cell count in healthy HIV-negative adult humans has been found to be between 700 cells/ μ l and 1,200 cells/ μ l in studies of numerous different populations (Aina et al. 2005; Hazenberg et al. 2000; Kibaya et al. 2008; Tugume et al. 1995). The risk of developing opportunistic infections—the clinical manifestations of AIDS—is greatly increased when the CD4+ count drops below 200 cells/ μ l (Begtrup et al. 1997; Phair et al. 1990; Phillips et al. 1989). The median survival time following untreated HIV-1 infection is approximately 8–12 years (Collaborative Group on AIDS Incubation and HIV Survival 2000; Morgan et al. 2002).

Two primate species are commonly used in modeling the pathogenesis of HIV: the rhesus macaque and the pig-tailed macaque. SIV_{mac}/SIV_{smm} infection of rhesus macaques follows a similar, albeit accelerated, course to HIV-1 infection of humans, with progression to AIDS normally occurring within 6 months to 3 years of infection (Brown et al. 2007). Pig-tailed macaques seem to have an even higher susceptibility to developing AIDS. In addition to developing AIDS as a result of SIV_{smm} or SIV_{mac} infection, they also can develop AIDS following infection with SIV_{agm}, which does not cause disease in rhesus macaques (Favre et al. 2009; Hirsch et al. 1995).

The natural history of the SIV infection of African green monkeys or sooty mangabeys with SIV_{agm} and SIV_{smm}, respectively, is very different. These animals generally do not develop disease despite peripheral blood viral loads similar to those of humans and rhesus macaques. A recent study of sooty mangabeys has demonstrated that SIV infection does result in an extremely slow depletion of CD4⁺ T cells (Taaffe et al. 2010), but unlike in humans and rhesus macaques, the magnitude of CD4⁺ T-cell loss does not correlate with viral load. CD4⁺ T-cell loss has not been reported in African green monkeys. However, in both African green monkeys and sooty mangabeys, measurements of CD4⁺ T cells are complicated by factors relating to expression of CD4 (see below). For both of these species, only a single case of an AIDS-like condition in an SIV-infected animal has been described (Ling et al. 2004; Traina-Dorge et al. 1992). The mechanisms by which these species circumvent disease development are of great interest and are discussed below.

Limiting Target Cell Availability

Entry of HIV-1 into the cell is mediated by the use of CD4 as a receptor, along with a coreceptor. CD4 is expressed principally on CD4⁺ T cells, and it binds to MHC-II on antigen-presenting cells. These T cells, upon activation, become “T helper cells,” which direct the adaptive immune response primarily through cytokine production. The coreceptor used by HIV-1 is principally the chemokine receptor C-C chemokine receptor type 5 (CCR5), but in some cases a different chemokine receptor, C-X-C chemokine receptor type 4 (CXCR4). Interestingly, humans lacking CCR5 expression through an inherited mutation are almost completely resistant to infection by both sexual and parenteral routes (Dean et al. 1996; Wilkinson et al. 1998). Partly because of the restriction of CCR5 expression to memory T cells, memory CD4⁺ T cells are preferentially infected compared to naïve CD4⁺ T cells. In humans and rhesus macaques, quantitative PCR detection of the HIV-1 genome in different CD4 T-cell subsets consistently finds that the majority of infected cells have a memory CD4⁺ cell phenotype, though infected naïve T cells are also found (Brenchley et al. 2004a; Mattapallil et al. 2005; Ostrowski et al. 1999). Macrophages and dendritic cells, the primary antigen-presenting cells of the immune system, also express CD4 and CCR5 and can be productively infected by HIV-1. An obvious potential mechanism by which species may adapt to SIV infection would therefore be to restrict the expression of the viral receptor and coreceptor.

Interesting observations have been made regarding CD4 expression in sooty mangabeys and African green monkeys. Adult uninfected African green monkeys have a much lower frequency of peripheral blood CD4⁺ T cells than other primates, including humans, sooty mangabeys, and rhesus macaques (Beaumier et al. 2009). They have a large peripheral blood T-cell population with a unique phenotype of CD4-CD8 α^{dim} . Interestingly, it seems that while naïve T cells express normal levels of CD4, activation and development of a subset of these into a memory phenotype is associated with down-modulation of CD4 and upregulation of CD8 α . Curiously,

these cells retain the functionality of T helper cells and are restricted to antigen presented on MHC-II, despite the lack of CD4 expression (Beaumier et al. 2009). As in humans and rhesus macaques, CD4+ T cells with a memory phenotype make up the majority of SIV_{agm}-infected CD4+ T cells. However, while the limited number of memory T cells that maintain CD4 expression has the highest level of infection, the CD4-CD8 α^{dim} population contains relatively low numbers of infected cells. Thus, the loss of CD4 expression in differentiation from naïve to memory apparently protects a subset of CD4+ memory T cells from infection.

Similarly, a large population of CD4-CD8- (“double-negative”) peripheral blood T cells has been identified in both infected and uninfected sooty mangabeys (Milush et al. 2011). These cells were first identified when it was discovered that some strains of SIV_{smm} are in fact capable of causing very rapid and severe loss of CD4+ T cells in sooty mangabeys, to levels that would be associated with AIDS in humans and macaques. Despite this, these animals maintain a competent immune system, and this led to the discovery that the CD4-CD8- T cells seem to be capable of performing functions normally associated with CD4+ T cells. In both species, the segregation of functions normally carried out by CD4+ T cells to cells resistant to infection means that regardless of the extent of CD4+ T-cell depletion, a minimum level of immune function can be maintained.

Expression of the coreceptor CCR5 has also been examined in primate species, in the context of SIV infection. One report has compared the frequency of CCR5+ CD4+ T cells in the blood and lymph nodes of uninfected individuals of multiple primate species—comparing those species that are known to be SIV infected with the wild (including African green monkeys and sooty macaques) with humans and rhesus macaques. This report demonstrates that sooty mangabeys, African green monkeys, and numerous other African species that are host to SIV have a much lower frequency of CD4+ T cells that express CCR5 (Pandrea et al. 2007a). The low frequency of CCR5 expression has therefore been assumed to be convergent evolution by SIV-exposed species to restrict target cell availability.

A recent study has further demonstrated that upon *in vitro* stimulation, naïve T cells from sooty mangabeys show more restricted CCR5 upregulation compared to naïve T cells from rhesus macaques. This failure to upregulate CCR5 is especially pronounced in cells that take on a central memory phenotype after activation. This may protect central memory T cells from infection; as in sooty mangabeys, this population shows a much lower frequency of infection than the T_{cm} population of rhesus macaques (Paiardini et al. 2011). However, it should be stressed that in this comparison, different viral isolates were used to infect the two different species, and the possibility of minor differences in viral tropism cannot be excluded.

Further examination of sooty mangabeys has demonstrated a relatively high frequency of CCR5 deletion mutant alleles, with 8 % homozygous for CCR5 deletions in a large captive population (Riddick et al. 2010). Interestingly, in contrast to HIV-1-infected humans, these animals are not resistant to SIV infection. In the captive population studied, prevalence of naturally acquired SIV infection was similar in the CCR5 deletion homozygous animals as in heterozygous animals or those with two functional CCR5 alleles (Riddick et al. 2010). Viruses isolated from both

homozygous CCR5 deletion animals and those expressing CCR5 were able to use a variety of additional coreceptors, including CXCR6, GPR15, and GPR1, in addition to maintaining CCR5 utilization. Similarly, in red-capped mangabeys, two studies have shown a high frequency of one CCR5 deletion (CCR5 Δ 24), with approximately 60–70 % of animals being homozygous for this deletion (Beer et al. 2001; Chen et al. 1998). Cells from red-capped mangabeys with the homozygous CCR5 deletion were completely resistant to infection by CCR5-using viruses from other species. Interestingly, SIV of red-capped mangabeys has apparently adapted to this selection pressure, as this virus uses principally CCR2b as a coreceptor and cannot use CCR5 (Beer et al. 2001; Chen et al. 1998).

Damage to the Mucosal Immune System and Bacterial Translocation

The clinical picture of HIV-1 infection of humans suggests that damage to the immune system is a chronic, gradual process, resulting in the cumulative immunological collapse that allows the onset of opportunistic disease. In contrast, a number of studies suggest that a great deal of irreversible damage occurs early in infection in the secondary lymphoid organs and gut-associated immune system.

The gut-associated lymphoid system (GALT) can be divided into inductive sites (gut-draining mesenteric lymph nodes and Peyer's patches), at which T-cell responses are generated through interaction with antigen-presenting cells and effector sites, primarily lymphocytes residing in the lamina propria (lamina propria lymphocytes, LPLs) and between the epithelial cells of the mucosal surface (intraepithelial lymphocytes, IELs). There are a large number of CD4+ T cells in the Peyer's patches and the lamina propria, with expression of CCR5 at a much higher frequency in these compartments than CD4+ T cells in the peripheral blood or other secondary lymphoid tissues.

Several studies have demonstrated a dramatic depletion of CD4+ T cells in one or more of these compartments from the very earliest stage of HIV-1 infection, with little or no recovery of these cells in the chronic phase of infection (Brenchley et al. 2004b; Estes et al. 2008; Guadalupe et al. 2003; Mehandru et al. 2004). The result of this T-cell loss has been the topic of much discussion in the field. Some authors have stated that the gut mucosal immune system contains the majority of lymphocytes in the body (Guadalupe et al. 2003; Mehandru et al. 2004; Veazey et al. 1998), with some further stating that the acute loss of CD4+ T cells in the gut therefore "reflects the loss of most CD4+ T-cells in the body" (Brenchley and Paiardini 2011). However, available literature on this subject (Ganusov and De Boer 2007) finds that it is more likely that at most around 20 % of all lymphocytes are resident in the human gut, with a similar percentage of the total CD4+ T cells found there.

Despite this, there does seem to be at least one important consequence of damage to the mucosal immune system by HIV-1 infection, as it appears to result in the loss of integrity of the mucosal barrier. This allows translocation of bacteria and

bacterial products and their systemic dissemination, which in turn causes the production of pro-inflammatory cytokines by cells of the innate immune system. The level of bacterial translocation, as measured by concentration of lipopolysaccharide (LPS) in the peripheral blood, is significantly upregulated in chronically infected HIV-1 patients when compared to uninfected controls in European and US cohorts (Brenchley et al. 2006). LPS translocation also shows a significant correlation with the level of peripheral blood activated CD8+ T cells, as measured by expression of the markers CD38 and HLA-DR (Brenchley et al. 2006). This acute damage to the gut mucosa therefore seems to be a major contributing factor to the chronic immune activation that is thought to drive the progression from chronic HIV-1 infection to AIDS (see below). The damage to the gut mucosal immune system in SIVmac-infected rhesus macaques is similar to humans, with profound depletion of CD4+ T cells occurring within weeks of infection at multiple sites of the GI tract and increased levels of plasma LPS (Brenchley et al. 2006; Ling et al. 2007; Mattapallil et al. 2005; Veazey et al. 1998).

The importance of LPS translocation in HIV-1 pathogenesis, supported by data from HIV-1+ patients in the USA and Europe, is not entirely supported by two studies carried out in sub-Saharan Africa. One study finds no difference in LPS levels between patient samples taken from pre-infection to AIDS (Redd et al. 2009), while another finds a significant difference only between uninfected patients and patients that have already progressed to AIDS—not earlier in the disease process (Nowroozalizadeh et al. 2010). In this second study, there is however a nonsignificant trend for increased plasma LPS in HIV-1-positive patients compared to negative control individuals and a significant inverse correlation between peripheral blood CD4+ T-cell counts and plasma LPS. However, these findings would be compatible with a theory that LPS translocation is allowed to occur due to loss of CD4+ T cells by other mechanisms and becomes progressively worse throughout the course of disease—rather than necessarily indicating that LPS translocation is a driving factor in immune activation and loss of CD4+ T cells from the outset of infection.

However, the importance of loss of the integrity of the gut mucosal barrier in pathogenic lentivirus infections is emphasized by the different outcome in African nonhuman primates. Surprisingly, two studies have demonstrated that in nonpathogenic infection of African green monkeys and sooty mangabeys, there is also massive depletion of gut mucosal T cells, comparable with depletion seen in SIVmac-infected rhesus macaques (Gordon et al. 2007; Pandrea et al. 2007b). Recovery of CD4+ T cells in this compartment after acute infection is variable, with some animals restoring numbers of cells to near pre-infection levels and some maintaining very low levels throughout the chronic phase of infection. Despite this, the mucosal barrier appears to remain intact, as SIV-infected African green monkeys and sooty mangabeys do not show increased levels of plasma LPS (Brenchley et al. 2006; Gordon et al. 2007; Pandrea et al. 2007b).

The critical difference between the different outcomes may involve a specific subset of CD4+ T cells, Th17 cells. These cells are postulated to be involved in defense against bacterial pathogens through the production of the cytokines IL-17

and IL-22 (Brenchley et al. 2008; Liang et al. 2006) and are found at higher frequency in the gut mucosa compared with peripheral blood or lungs (Brenchley et al. 2008; Cecchinato et al. 2008). In HIV-1-infected humans and SIVmac-infected rhesus macaques, in addition to the general destruction of gut CD4⁺ T cells, there is a specific greater loss of Th17 cells—they are underrepresented in the residual CD4⁺ T cells (Brenchley et al. 2008; Cecchinato et al. 2008). In contrast, in the SIV infection of sooty mangabeys, total gut CD4⁺ T cells are depleted in SIV infection but the percentage of Th17 cells within the remaining CD4⁺ cells is not altered (Brenchley et al. 2008). Furthermore, in a study directly comparing SIVagm infection of pig-tailed macaques and African green monkeys, significant specific depletion of Th17 only occurs in pig-tailed macaques, which progress to AIDS after SIVagm infection (Favre et al. 2009). Thus, maintenance of the Th17 cell population seems to play an important role in sustaining a competent mucosal barrier, which in turn prevents systemic spread of bacteria from the gut and the subsequent immune activation which follows in AIDS-susceptible species. How natural host species have evolved to avoid this specific depletion of Th17 cells in the face of massive general loss of CD4⁺ T cells in the gut has yet to be elucidated.

Persistent or Resolving Innate and Adaptive Immune Activation

As mentioned above, elevated levels of immune activation in the chronic phase of infection is seen as an integral part of HIV-1 pathogenesis. Numerous markers of activation of the innate and adaptive immune system are elevated in HIV-1-infected humans, with many showing correlation with the rate of disease progression, especially markers of activation of CD4⁺ and CD8⁺ T cells. High levels of immune activation are thought to drive CD4⁺ T-cell depletion by inducing multiple rounds of expansion, followed by activation-induced cell death (AICD), or infection of activated cells by HIV-1 (as they are more susceptible than naive/resting cells). The level of increased expression of markers of immune activation on CD8⁺ T cells such as CD38 can be used to predict disease progression with power similar to that of set point viral load measurement (Deeks et al. 2004; Hazenberg et al. 2003). These activated cells are unlikely to represent exclusively CD8⁺ T cells that are responding to HIV-1 antigens, as the proportion of HIV-1-specific CD8⁺ T cells in the peripheral blood is generally of a lower percentage than the proportion of CD8⁺ T cells expressing immune activation markers (depending on the markers measured) (Doisne et al. 2004; Gea-Banacloche et al. 2000; Saez-Cirion et al. 2007; Sieg et al. 2005). In addition, while increased frequency and level of CD38 expression on CD8⁺ T cells correlates with increased viral load (Deeks et al. 2004) and predicts faster disease progression in HIV-1-infected humans, the frequency of HIV-1-specific CD8⁺ cells has been shown to either correlate inversely with viral load (Edwards et al. 2002; Ogg et al. 1998) or show no correlation with viral load and survival (Addo et al. 2003; Schellens et al. 2008).

Studies using both flow cytometry to measure levels of activated T cells and microarray analysis to measure gene expression in the peripheral blood and lymphoid tissues, throughout the course of infection, have demonstrated striking differences in immune activation in SIV-infected African green monkeys and sooty mangabeys compared to disease susceptible HIV-1-infected humans and SIV-infected rhesus and pig-tailed macaques. In the acute stage of infection, in all species, there is a dramatic increase in the number of circulating activated T cells, expression of genes that are induced by type I interferon, and soluble markers of immune activation in the plasma (Harris et al. 2010; Kornfeld et al. 2005; Li et al. 2009; Meythaler et al. 2009; Stacey et al. 2009). In all species, the level of immune activation is reduced in the transition from acute to chronic phase of infection. However, the key difference between pathogenic and nonpathogenic infections is the magnitude of this reduction in immune activation after the acute phase. In humans and macaques, the reduction is only partial, and multiple markers of immune activation remain highly elevated compared to pre-infection levels or uninfected controls.

In contrast, in sooty mangabeys and African green monkeys, the reduction in immune activation after acute infection is more complete. In sooty mangabeys, a small number of markers remain slightly (but significantly) upregulated when chronically SIV-infected animals are compared to uninfected controls (Meythaler et al. 2009; Silvestri et al. 2003). Interestingly, the extent of low-level chronic immune activation does correlate inversely with CD4+ T-cell counts (Silvestri et al. 2003). Chronically infected African green monkeys are indistinguishable from uninfected animals in the majority of markers, as immune activation is completely suppressed (Kornfeld et al. 2005; Lederer et al. 2009; Lozano Reina et al. 2009).

Of particular interest is the strong induction of interferon-sensitive genes in the lymph nodes of all species, which are then reduced to near-normal levels in sooty mangabeys and African green monkeys, while remaining high in humans and rhesus and pig-tailed macaques. Continuous immune activation has severe consequences for the secondary lymphoid environment in pathogenic infections (see below). In addition, the type I interferon response is likely connected to the other elements of immune activation. Purified activated CD4+ T cells from HIV-1-infected humans show much higher expression of interferon-sensitive genes than activated cells from uninfected humans (Sedaghat et al. 2008), suggesting that type I interferon plays a role in the excessive T-cell activation seen in HIV-1 infection. In addition, the down-modulation of a type I interferon receptor on monocytes (which is likely to be a measure of previous type I interferon exposure) correlates with lower CD4+ T-cell counts, higher viral loads, and higher expression of CD38 on CD8+ T cells (Hardy et al. 2009).

The mechanism by which sooty mangabeys and African green monkeys restrict the interferon response and other elements of immune activation after the acute stage of infection has been difficult to elucidate and may well be different for each species. Down-modulation of the interferon response in the lymphoid tissue occurs in natural host species despite similar levels of viral replication in secondary lymphoid tissues (Gueye et al. 2004). One study has shown that *in vitro*,

plasmacytoid dendritic cells (pDCs), a major interferon-producing cell population, from sooty mangabeys produce much less interferon in response to a range of stimuli, compared to humans or rhesus macaques, and suggested this results in reduced immune activation in SIV infection (Mandl et al. 2008). However, this is somewhat at odds with the high levels of expression of interferon-sensitive genes in the acute stage of infection in this species, which does not suggest a reduced capacity for interferon production (Bosinger et al. 2009). Furthermore, immunohistochemical stainings of lymph node sections from rhesus macaques, African green monkeys, and sooty mangabeys during acute infection found pDCs to be strongly producing type I IFNs in all three species (Harris et al. 2010). Crucially, in sooty mangabeys and African green monkeys, the interferon response is down-regulated after the acute phase of infection, while it remains elevated throughout the infection of rhesus macaques.

Several studies have analyzed gene expression throughout infection, comparing species with different outcomes. In African green monkeys, there is an early induction of the immunosuppressive cytokine *IL-10* (Jacquelin et al. 2009; Kornfeld et al. 2005; Lederer et al. 2009) when compared to rhesus macaques and pig-tailed macaques, but this is not found in sooty mangabeys. Several other immunosuppressive genes are upregulated in sooty mangabeys, such as the enzyme indoleamine-pyrrole 2,3-dioxygenase (*IDO/INDO*) (Bosinger et al. 2009). However, other studies using similar methods of analysis at the gene expression level, in addition to immunohistochemistry to analyze expression at the protein level, have found increased expression of IL-10 and IDO, along with other immunosuppressive molecules postulated to restrict immune activation in natural host species, in pathogenic infections of humans (Li et al. 2009) and rhesus macaques (Estes et al. 2006; Jacquelin et al. 2009). Thus, no convincing mechanism has been postulated by which the immune system is consistently able to bring itself under control in nonpathogenic infections of these African primates.

Destruction of the Lymph Node Environment

One consequence of high and persistent levels of immune activation appears to be severe damage to the secondary lymphoid environment. The structure of secondary lymphatic tissue is of vital importance in mediating interactions between antigen-presenting cells, T cells, and B cells, which are required to induce an immune response. The T-cell zones of secondary lymphoid tissues are also the major anatomical site in which naïve T cells may reside. Pathological changes have been recognized in the lymph nodes of HIV-1 patients since the first description of the disease, with severe lymphadenopathy being a symptom of HIV-1 infection. Lymph nodes from HIV-1-infected patients usually show hyperplasia and, in the later stages of disease, follicular lysis and involution. Damage to the secondary lymph node environment has long been postulated to be an important underlying factor in AIDS pathogenesis (Heeny 1995).

Important changes occur in the T-cell zone, causing dramatic effects on the whole body T-cell population. Firstly, infected humans and rhesus macaques show significantly higher levels of collagen deposition in this area compared to uninfected controls (Diaz et al. 2010; Estes et al. 2007). As might be expected, the level of collagen deposition correlates inversely with the number of naïve (and total) CD4+ T cells resident in the lymph node, suggesting that collagen deposition discourages habitation of this niche. In addition, the degree of collagen deposition before the start of antiretroviral treatment inversely correlates with the increase in peripheral blood T cells after 6 months of treatment (Schacker et al. 2002) or after an even longer duration of treatment (Kumarasamy et al. 2009). Deposition of collagen may therefore physically restrict the size of the niche available for CD4+ T cells to occupy. In addition, a study in rhesus macaques has demonstrated that collagen deposition restricts access of naïve T cells to the fibroblastic reticular cell (FRC) network. This network provides the framework for migration of T cells through the T-cell zone, and cells of this network also produce IL-7, a key stimulus for naïve T-cell survival. Loss of access to this network in these animals leads to apoptosis of naïve T cells in the node (Zeng et al. 2011).

The cause of this damage to the secondary lymphoid tissues has been connected to two factors. First, in HIV-1-infected humans, there is abnormal accumulation of CD4+ and CD8+ effector memory T cells in lymphoid tissues. Effector memory cells are rare in the lymphoid tissue of uninfected humans, as their normal role is to respond to antigen in non-lymphoid tissue. The extent of the infiltration correlates with the area of collagen deposition in the tissue (Brenchley et al. 2004b). These cells are presumably recruited to the lymph nodes as a result of the pro-inflammatory environment induced by HIV-1, and so the presence of such cells could either be a cause of damage or only a consequence of the inflammation ongoing in the lymph node.

The second factor is the increased prevalence of TGF β 1-producing regulatory T cells (Tregs) in the lymphatic tissue of infected humans and rhesus macaques. Tregs are CD4+ T cells with an immunosuppressive function, including the production of the cytokine TGF β 1. This cytokine has multiple functions, most prominently as an immunosuppressant and in mediating wound repair. However, inappropriate expression is known to have a role in tissue fibrosis in other disease pathways (Branton and Kopp 1999). In both humans and rhesus macaques, increased numbers of TGF β 1-expressing cells and increased collagen deposition occur in the acute stage of infection and become exacerbated through the chronic stage of infection. Interestingly, increased numbers of T cells producing the immunosuppressive factors IDO and IL-10 are also found in infected rhesus macaques (Estes et al. 2006). It seems likely that TGF β 1 is produced as part of a negative feedback response to the high levels of immune activation, with the side effect of promoting damaging fibrosis in the immune microenvironment.

The damaging effect of this immunosuppressive response is somewhat paradoxical, especially given that greater or similar levels of IL-10, IDO, and even TGF β 1 are found in gene expression analyses of SIV-infected African green monkeys and sooty mangabeys when compared to rhesus and pig-tailed macaques (Bosinger

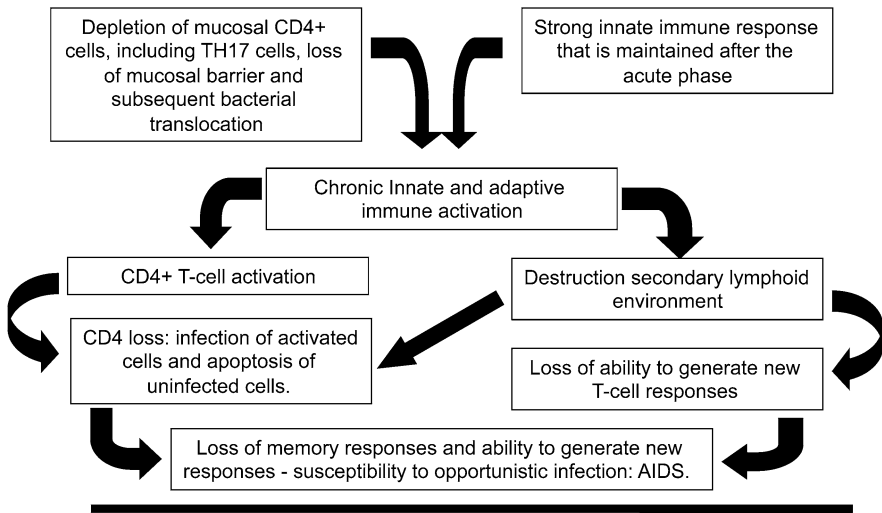
et al. 2009; Jacquelin et al. 2009; Lederer et al. 2009). However, when using immunohistology to analyze expression at the protein level, SIV-infected sooty mangabeys do not show increased numbers of TGF β 1-producing T cells in the lymph node, and increased collagen deposition is not found in the T-cell zone. It seems likely that the pathological aspect of TGF β 1 production in the lymph nodes of humans and macaques is due to the failure, despite an immunosuppressive response, to bring levels of immune activation down after acute infection. The ability mentioned above of sooty mangabeys and African green monkeys to resolve innate and adaptive immune activation after chronic infection therefore likely saves the lymph node environment from destruction.

The destruction of the lymph node environment in pathogenic infection leads to loss of naïve T cells and the inability to generate *de novo* CD4+ and CD8+ T-cell responses by preventing normal interactions between T cells and antigen-presenting cells. Both naïve and memory T cells may become inappropriately activated due to the high levels of interferon and are lost through subsequent apoptosis or direct HIV infection. The combination of loss of memory T cells and the environment required to generate new responses presumably drives the immune system to the critical point at which AIDS occur (Heeney 1995). Existing memory cells to a specific antigen/pathogen are sufficiently depleted that there is no longer a meaningful memory response to opportunistic infections, and the generation of new responses is sufficiently delayed by the loss of proper lymph node environment and depletion of naïve T cells that an immune response cannot be mounted in time to prevent illness and death. The key pathways leading to disease in humans and macaques and how they are prevented in African green monkeys and sooty mangabeys are outlined in Fig. 3.

The HIV-1 Viral Lineage Has Increased Pathogenic Potential: Limitations of Available Animal Models

As discussed, SIVsmm generally does not cause disease in sooty mangabey but has the potential to cause an AIDS-like disease upon direct inoculation of Asian macaques (McClure et al. 1989; Silvestri et al. 2005). The disease caused in rhesus macaques is a commonly used animal model for AIDS in humans caused by HIV-1. SIVsmm has also been transmitted into humans, causing the HIV-2 epidemic. Numerous lines of evidence demonstrate that in humans, HIV-2 is not as pathogenic as HIV-1. In surveys taking place in Guinea-Bissau, Holmgren and colleagues found only a twofold increase in mortality in individuals infected with HIV-2, comparable with previous findings within the same geographical region (Holmgren et al. 2007; Poulsen et al. 1997; Ricard et al. 1994). In contrast, HIV-1 is associated with a 10–15-fold increase in mortality rate (reviewed in (Jaffar et al. 2004)). Longitudinal investigations with statistically meaningful cohorts indicate that about 80 % of HIV-2-infected individuals do not develop disease and maintain a normal life expectancy (van der Loeff et al. 2010). One-third of all HIV-2-infected

Progressive HIV/SIV infection of humans/ macaques



Non-progressive SIV infection of Sooty Mangabeys/African green monkeys

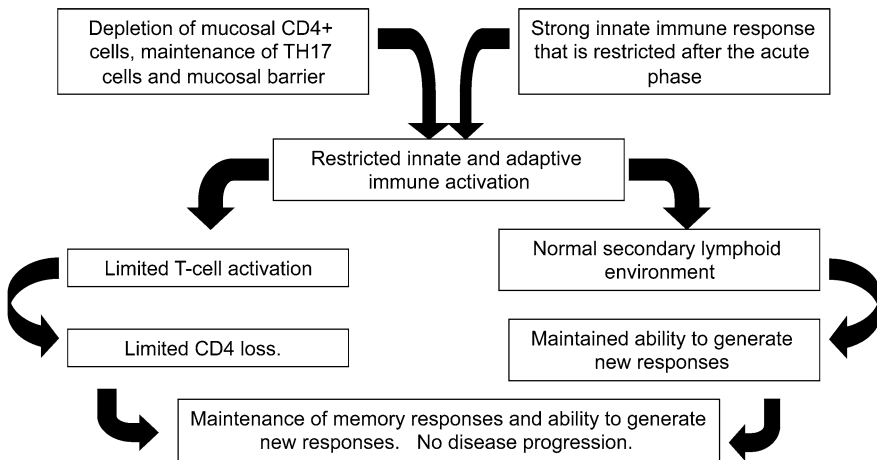


Fig. 3 Pathways leading to the development of AIDS in progressive SIV/HIV infection compared with the non-progressive SIV infection of African primates

individuals have an undetectable plasma viral load (van der Loeff et al. 2010). Nevertheless, progressive HIV-2 infections show clinical features that are indistinguishable from AIDS caused by HIV-1 (Martinez-Steele et al. 2007).

Given the considerable difference in the outcome of HIV-1 and HIV-2 infection of humans, is it appropriate to use the disease of rhesus macaques infected with viruses of the SIVsm/SIVmac/HIV-2 lineage as a model for disease caused by HIV-1 in humans? If it is the case that there are specific aspects of the HIV-1 lineage that make this virus more pathogenic than HIV-2 in humans, then this model becomes less attractive in understanding HIV-1 pathogenesis. We will now examine the differences between these viruses to establish if this is the case.

Despite their different origins, HIV-1 and HIV-2 are relatively closely related retroviruses with 60 % similarity at the amino acid level in the capsid and polymerase proteins and 30 % similarity in the envelope protein (Guyader et al. 1987). However, the genomes of both viral lineages differ by two genes. While *vpx* is present in the HIV-2/SIVsm lineage (in addition to SIVrcm, SIVdrl, and SIVmnd2), the accessory gene *vpu*, not *vpx*, is found in HIV-1, in addition to SIVcpz and the SIVs of four species of the *Cercopithecus* genus (Barlow et al. 2003; Courgnaud et al. 2002, 2003; Huet et al. 1990; Strebel et al. 1988).

Both *vpu* and *vpx* seem to have evolved to allow lentiviruses to escape host restriction mechanisms. In macaques, the accessory viral gene *vpx* has been directly shown to contribute to virulence. Animals infected with an SIVmac mutant lacking the *vpx* gene show lower virus burdens, delayed declines in CD4 lymphocytes, and either a lack of disease or delayed progression to disease (Gibbs et al. 1995; Hirsch et al. 1998). The Vpx of the SIVsmm/SIVmac/HIV-2 viral lineage enables the virus to efficiently replicate in primate macrophages by antagonizing a cellular restriction factor termed SAM domain and HD domain 1 (SAMHD1) that is expressed in this cell type (Laguetta et al. 2011; Sharova et al. 2008). That *vpx* can provide a fitness advantage to the virus was further confirmed in vivo when a wild-type and a *vpx*-deleted SIVsmm isolate were inoculated into pig-tailed macaques, resulting in the *vpx* mutant showing a strong competitive disadvantage in the early virus dissemination (Hirsch et al. 1998).

vpu, the accessory gene uniquely expressed in the SIVcpz/HIV-1 lineage, including the small subset of guenon SIVs, also seems to possess various functions that may impact pathogenicity. *Vpu* helps HIV-1 to escape host restriction and enhances release of virus particles (Klimkait et al. 1990). *Vpu* contributes to HIV-1-induced CD4 receptor downregulation, which enhances virus replication (Willey et al. 1992). In addition, it increases the release of progeny virions from infected cells and cell-to-cell spread of viral particles by antagonizing tetherin, an interferon-induced host restriction factor that directly cross-links virions on the host cell surface (Neil et al. 2008). However, both CD4 and tetherin downregulation are not exclusive to the lineage of HIV-1 and are facilitated by the *nef* or *env* gene in other lentiviruses (Gupta et al. 2009; Le Tortorec and Neil 2009; Zhang et al. 2009). However, two functions of *vpu* have recently been discovered that are thus far unique to HIV-1. Firstly, *Vpu* inhibits the recycling of CD1d receptor from endosomal compartments, strongly inhibiting the ability of infected DC to activate CD1d-restricted natural killer T cells (NKT cells) (Moll et al. 2010). Secondly, *Vpu* downregulates the NKT and B cell coactivator (NTB-A) at the surface of infected cells and as a result interferes with the degranulation of NK cells that recognize the infected cells (Shah et al.

2010). Importantly, HIV-2-infected cells do not downregulate NTB-A and are killed more efficiently by NK cells than HIV-1-infected cells (Shah et al. 2010). Furthermore, *vpu* seems to have influenced the evolution of the other viral genes. A mechanism encoded in the viral gene *nef* is believed to have evolved to restrict T-cell activation, through down modulation of the T-cell receptor (also referred to as CD3) in infected cells. However, in all viruses that carry *vpu* this function of *nef* is reported to be lost (Schindler et al. 2006). Immunodeficiency viruses depend on activated T cells for replication, but accelerated immune activation induces a range of host defense mechanisms. It has been suggested that acquisition of the *vpu* gene by this viral lineage has allowed the virus to trigger immune activation, increasing viral replication, without the consequence of host-mediated restriction (Kirchhoff 2009). There are therefore reasons to believe that *vpu* plays an important role in HIV-1-induced disease, and models of human AIDS should include this factor.

While pig-tailed macaques can become transiently infected with HIV-1 (Agy et al. 1992), the infection does not persist. Other macaque species are resistant to infection, as macaque-encoded restriction factors provide dominant-acting blocks the establishment of infection (Stremlau et al. 2004). Using the macaque model to investigate influence of the *vpu* gene in vivo therefore requires more complex approaches. Our increased understanding of host restriction factors has led to novel approaches in which HIV-1 isolates have been artificially equipped with viral gene variants capable of antagonizing the macaque's host restriction factors (Hatzioannou et al. 2009). However, to date, these artificial HIV variants are not pathogenic. An alternative approach has been to infect macaques with partial recombinants between SIVs and HIV-1 isolates, called SHIVs. The first SHIVs were created by exchanging the SIV envelope for an HIV-1 envelope sequence in order to test HIV-1 vaccine candidates (Stremlau et al. 2004). Some SHIVs are equipped with the HIV-1 *vpu* gene in addition to the HIV envelope, and a few studies indicate that the presence of *vpu* can influence the pathogenic outcome in pig-tailed macaques (Hout et al. 2005; Singh et al. 2001, 2003; Stephens et al. 2002). However, the mechanistic background remains unknown, especially as the various described functions of *vpu* are yet not characterized for these Asian primate hosts. The lack of a suitable model for HIV-1 has driven the search for alternative animal models such as the rodent model in which mice were "humanized" with bone marrow/liver/thymus grafts from human donors (Melkus et al. 2006). To date, these models are still in a premature state and only further research will establish whether insights into HIV-1 virulence can be gained with such models.

Examining the Virus–Host Relationships Responsible for Generating HIV-1

As stated previously, other than HIV-1, only SIVcpz of chimpanzees and SIVmon/mus/gsn/den of four primate species of the guenon genus carry the *vpu* gene. Given the difficulties in assessing the role of *vpu* in existing in vivo models described

above, it would be extremely informative to understand the outcome of SIV infection in these species. Here, we will review what is known of SIV infection of chimpanzees and in these guenon species.

Before the origin of HIV-1 was traced to chimpanzees, it was found that chimpanzees can be persistently infected with HIV-1 (Alter et al. 1984). As no other species can be persistently infected with HIV-1, the lack of alternatives made this animal model initially attractive to study HIV-1. However, as the vast majority of animals infected with HIV-1 failed to develop clinical signs, and due to cost and ethical reasons, the use of the chimpanzee model for HIV-1 study has been generally abandoned. Nevertheless, by 1996, over 200 chimpanzees had been infected with HIV-1 (Committee on Long-Term Care of Chimpanzees 1997). Many of these animals have now been infected for over 20 years. Of these, only 5 animals, all at the Yerkes Primate Centre, have been described as developing AIDS and subsequently euthanized (Juompan et al. 2008). The majority of these 200 HIV-1-infected chimpanzees were infected with the CXCR4 coreceptor using HIV-1 virus isolate, IIIb. It would be tempting to postulate that due to the expansion of this virus *in vitro* and the artificial nature of infection with a CXCR4 using virus, this isolate is inherently less able to induce disease. Unfortunately, data exists that this strain remains able to induce disease in humans, as a laboratory worker was accidentally infected with HIV-1_{IIIb} and progressed to AIDS after 8 years of infection (Beaumont et al. 2001). In general, captive chimpanzees infected with HIV-1 rapidly control viral load to undetectable levels. There is therefore direct evidence that HIV-1 is generally not pathogenic in chimpanzees.

The vast majority of chimpanzees held in European and US primate centers and therefore the majority of HIV-1-infected chimpanzees were of the *Pan troglodytes verus* subspecies. This subspecies is not naturally infected with SIVcpz—SIV infection has only been found in the *troglodytes* and *schweinfurthii* subspecies despite extensive surveys of captive and wild populations of the *verus* subspecies. It is worth noting, however, that while SIV infection has not been found in the *verus* subspecies, these animals must have a significant history of exposure to the SIV of the western red colobus monkey. The red colobus monkey is frequently hunted by chimpanzees (Boesch and Boesch-Achermann 2000) and has a high prevalence of SIV infection (Locatelli et al. 2008), though this virus has not been found in *verus* chimpanzees (Leendertz et al. 2011). This could suggest that some resistance mechanisms shared with naturally SIV-infected primate species, such as low frequency of CCR5 expression on CD4+ T cells (Pandrea et al. 2007a), have evolved in the *verus* subspecies due to historic exposure to SIVwrc.

Given the close relationship between HIV-1 and SIVcpz, it would seem reasonable to assume that SIVcpz would also not be pathogenic in the chimpanzee. However, a recent report studying wild chimpanzees has found the opposite. A study of wild, habituated animals (wild animals accustomed to being observed very closely) of the *P. t. schweinfurthii* subspecies has found that SIVcpz-infected animals within the group showed greater risk of mortality of the study period (Keele et al. 2009). In addition, the bodies of three infected animals were recovered for necropsy, along with the bodies of two uninfected animals. Significant depletion of

CD4+ cells in the periarteriolar lymphoid sheaths (PALS) of the spleens of these animals was shown in the SIVcpz-infected animals. Particularly severe depletion was shown in an animal that had become infected during the study, three years prior to death, whose death was attributed to an “AIDS-like” disease by the group reporting this finding. A more recent article reports also identified a *Pan troglodytes troglodytes* chimpanzee with AIDS-like clinical signs in a Cameroonian sanctuary (Etienne et al. 2011). A pathogenic outcome of SIVcpz infection would lend further support to the importance of *vpu* in HIV-1 infection.

From 1989 to 2005, seven SIVcpz-infected chimpanzees were housed in primate centers in Europe and the USA (Heeney et al. 2006): one naturally infected *schweinfurthii* animal, two experimentally infected *schweinfurthii* animals, and four experimentally infected *verus* animals. Of these seven animals, four are still alive, including Noah, a naturally infected animal that first tested positive in 1989, aged around 2 years old, and remains asymptomatic after over 20 years of infection (Greenwood et al., unpublished data). Three animals have died of cardiac conditions, which are common in captive chimpanzees (Seiler et al. 2009).

Two of these chimpanzees have already been studied in some detail as part of a cohort of HIV-1-infected chimpanzees. As with the HIV-1-infected chimpanzees, these two SIVcpz-infected chimpanzees seem to lack the profound changes to the immune system that are found in HIV-1-infected humans (Gougeon et al. 1997; Rutjens et al. 2008, 2010). Given the apparent pathogenic outcome of SIVcpz infection of wild chimpanzees, it should be possible to identify, in these captive animals, disease mechanisms that are shared with HIV-1-infected humans. Further study of samples from these and other captive SIVcpz-infected animals is therefore warranted, especially if this is possible using previously archived samples and/or non-invasive methods.

As previously mentioned, SIVcpz is the result of recombination between SIVrcm and SIVgsn/mon/mus. The importance of the *vpu* gene seems to be emphasized by the fact that it is retained in the chimeric virus in favor of *vpx*. The small subset of *Cercopithecus* species infected with these *vpu*-carrying viruses have not been investigated for their outcome of infection. The only knowledge we have of these viruses is their genomic sequences and their prevalence in the wild. Interestingly, the few studies that investigated significant numbers of these *Cercopithecus* animals found an exceptionally low prevalence of the *vpu*-harboring SIVs in mustached and greater spot-nosed guenon populations in Cameroon (2–4 %). This is in stark contrast to the seroprevalence seen in primate populations that carry an SIV lacking the *vpu* gene, which reported seroprevalence of 50–90 % (Aghokeng et al. 2006, 2009; Ellis et al. 2004). It therefore seems that the outcome of SIVgsn/SIVmon infection is likely to differ from other SIV infection of natural hosts. It is possible to postulate two possible mechanisms for this low prevalence. SIV infection in these species could be much more pathogenic than in other species, perhaps due to the presence of *vpu*—which leads to infected animals being rapidly removed from the population. Alternatively, these species could have evolved novel mechanisms to prevent the spread of the virus within the population, though presumably the evolutionary pressure for this to occur would again have to be the result of

increased pathogenicity of SIV infection of these specific species. The opportunity of further study for research on these monkeys is restricted, as they are not found in primate research centers and are (rightly) protected in the wild. While surveys of bushmeat samples from African countries have allowed some limited analysis, the low prevalence of SIV carrying will make further studies a major challenge. Nevertheless, due to their possible key role in our understanding of HIV-1 pathogenicity, such efforts may be justified.

Conclusion

The African primate origins of HIV-1 and HIV-2 are now well established, and a relatively thorough history of how HIV-1 has spread from western Central Africa throughout the world has been proposed. However, the mechanisms by which HIV causes AIDS in humans remain heavily debated. It should be noted that it is not possible to review here the entirety of the vast and conflicting literature describing the observed alterations to the immune system in HIV infection and the various mechanisms proposed to cause CD4+ T-cell loss and AIDS in HIV in infected humans.

Instead, we have highlighted the key differences found throughout the course of infection between the pathogenic HIV/SIV infection of humans and macaques and the nonpathogenic SIV infection of two well-studied African primate species and used these differences to propose a relatively straightforward model by which lentivirus infection induces AIDS in humans and macaques but not in sooty mangabeys and African green monkeys.

Finally, we have reviewed the possible limitation of current animal models that specifically the HIV-1/SIVcpz viral lineage may have greater potential to cause disease than other primate lentiviruses, which is not well addressed by current primate models. Specifically, we have noted the functions of the *vpu* gene. While some of the functions of *vpu* are carried out by other genes in primate lentiviruses (such as down-modulation of CD4 and tetherin), other functions are so far described uniquely for this gene. It is also noted that the virus–host relationship in primate species infected with a *vpu*-harboring virus seems to differ from that of other African primates. While further examination of primate species infected with *vpu*-carrying viruses—chimpanzees, gorillas, and members of the *Cercopithecus* genus—is clearly complicated by ethical and practical considerations, noninvasive studies of these species have already proven to be fruitful. Expansion of such noninvasive studies may lead to new insights in the subject of lentivirus pathogenesis and host adaptation not available in other animal models.

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