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The Evolution of Resistance to Simian Immunodeficiency Virus (SIV): A Review

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Abstract Examining how pathogens cross species boundaries, spread within species, and persist within their hosts is an essential part of understanding the factors that underpin the evolution of virulence and host resistance. Here, we review current knowledge about the genetic diversity, molecular epidemiology, prevalence, and pathogenicity of simian immunodeficiency viruses (SIVs). SIVs have crossed species boundaries from simian hosts to humans on at least 12 separate occasions, one of which led to the global HIV–AIDS crisis. Though SIVs infect a wide range of primates, scientists have only recently begun to describe the natural history of SIV infection in their natural hosts. Several new studies reveal how both viral and host factors are responsible for the transmission to, and adaptation in, new hosts. These studies also suggest that the spread of the virus may be affected by host-specific traits, including social structure, mating system and demographic history. These studies challenge the traditional view that SIV is relatively benign in its natural host, and instead suggest that a highly dynamic relationship exists between SIV and its simian hosts.

Keywords HIV · Pathogen · Prevalence · Social structure · Virulence · Zoonosis

Introduction

It is widely recognized that the human immunodeficiency viruses, HIV-1 and HIV-2, are the result of cross-species transmissions of the simian immunodeficiency viruses

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(SIV) naturally infecting nonhuman primates in sub-Saharan Africa (Hahn *et al.* 2000). SIVsmm from sooty mangabeys (*Cercocebus atys atys*) is recognized as the progenitor of HIV-2 (Hirsch *et al.* 1989b), whereas SIVcpz from chimpanzees (*Pan troglodytes troglodytes*) and SIVgor from gorillas (*Gorilla gorilla gorilla*) in western equatorial Africa are the likely progenitors of HIV-1 (Gao *et al.* 1999; Keele *et al.* 2006; Plantier *et al.* 2009; Van Heuverswyn *et al.* 2006). HIV-1 group M is most closely related to SIVcpz. Group M is largely responsible for the ongoing acquired immunodeficiency syndrome (AIDS) pandemic (Keele *et al.* 2006), which has infected more than 60 million people. In humans HIV is quite virulent, with infections contributing to 33 million deaths worldwide in the last 30 yr (UNAIDS 2010).

Although a great deal is known about HIV infections in humans, very little is known about SIV infections in their natural hosts. An improved understanding of this may provide insight into the likelihood of future zoonotic introductions of SIVs into human populations and help to define the ecological and evolutionary factors that influence viral pathogenicity and virulence. Both viral and host genetic variation may contribute to the observed variation in the expression of virulence and pathogenicity. It is generally assumed that the highly virulent nature of HIV infections is a consequence of the recent association of the virus with humans. A corollary to this assumption is that a state of apathogenicity has evolved in SIVs sharing a long coevolutionary history with their simian hosts (van de Woude and Apetrei 2006). This view has been challenged by recent studies showing that eastern and central African chimpanzees naturally infected with SIV do develop an AIDS-like syndrome (Etienne *et al.* 2011; Keele *et al.* 2009). These observations lead to several questions concerning the evolutionary ecology of interactions between SIV/HIV and their primate hosts: When did SIV become virulent? Why are HIV and SIV more virulent in chimpanzee and human hosts? What viral factors promote virulence and what host factors have evolved to provide resistance? Lastly, in what ways have host ecological and behavioral factors influenced coevolutionary interactions between these viruses and their primate hosts? The goals of this review are to 1) summarize current knowledge about the origin, genetic diversity, and molecular epidemiology of SIVs; the origin and distribution of HIV-1 and HIV-2; and the prevalence of SIV infection in the wild; 2) describe the factors affecting the zoonotic spillover of SIV into human populations; 3) examine how host ecology and behavior affect transmission of SIV within and between species; 4) review the role of viral and host factors affecting the transmission, infection, adaptation to new hosts, and the expression of AIDS; and 5) review current knowledge about the pathogenicity of HIV and SIV infections, by describing the clinical manifestation of HIV in humans, SIV in macaques and in other nonhuman primates, and by reporting evidence of pathogenesis in SIV-infected natural hosts.

Origin, Genetic Diversity, and Molecular Epidemiology of SIV; Origin and Distribution of HIV-1/HIV-2; and Prevalence of SIV Infection in the Wild

Origin, Genetic Diversity, and Molecular Epidemiology of SIV

SIV and HIV are exogenous viruses belonging to the genus *Lentivirus* of the *Retroviridae* family. Exogenous lentiviruses are known to infect primates (SIV and

HIV), felids (feline immunodeficiency virus), and a variety of wild and domesticated ungulates (bovine immunodeficiency virus and its relatives) (King *et al.* 2012). SIVs have been isolated from at least 45 species of African primates including Old World monkeys belonging to tribe *Papionini* of the *Cercopithecinae*, i.e., sooty mangabeys, as well as cercopithecines and colobines (Locatelli and Peeters 2012; van de Woude and Apetrei 2006;). Phylogenetic analysis of the available SIV strains has shown a high level of genetic diversity and a starburst phylogenetic pattern, suggesting that these viruses shared a single common ancestor (van de Woude and Apetrei 2006). Asian species of Old World monkeys (colobines and macaques) are not naturally infected with SIVs, which suggests that the last common ancestor of the catarrhines (Old World monkeys and apes) was not infected by SIV when these groups diverged 25 million yr ago (Beer *et al.* 1999). The emergence of SIV probably followed infection after radiation of these species, possibly from a nonprimate source (Sharp *et al.* 2000).

Analysis of endogenous lentiviruses suggests that exogenous forms of these viruses have been infecting mammals for more than 100 million yr (Katzourakis *et al.* 2009). Early estimates using a molecular clock suggested a very recent origin of SIV in primates, occurring in the last 500–1000 yr (Wertheim and Worobey 2009), a date that would rule out a long coevolutionary history between SIV and its primate hosts. However, recent evidence points to a much longer association. Drills (*Mandrillus leucophaeus*), guenons (*Cercopithecus* spp.), and colobus monkeys (*Colobus* spp.) on the island of Bioko are infected with SIVs that are related to viruses infecting their sister species on the mainland. This discovery facilitated a recalibration of the SIV molecular clock, pushing back the date for the origin of SIV in primates to a minimum of 77,000 yr ago and perhaps even millions of years ago (Worobey *et al.* 2010; Gifford 2012). This wide time interval is likely due to the observation that estimating rates of viral molecular evolution on short time scales may bias estimates when applied to longer time scales as a consequence of purifying selection and convergent evolution (Wertheim and Kosakovsky Pond 2011; Gifford 2012). More recent analyses, examining the timing of lentivirus viral infectivity factor (vif)-driven adaptive evolution of the host protein apolipoprotein B mRNA-editing, enzyme-catalytic, polypeptide-like 3G (APOBEC3G) (Compton and Emerman 2013) and SIVs infecting African green monkeys (genus *Chlorocebus*) (Ma *et al.* 2013) are also consistent with an ancient origin of primate–SIV interaction, dating back millions of years.

The genetic diversity among SIVs infecting different host species is the result of complex factors, including host–virus co-speciation, cross-species transmissions, and recombination of SIVs from different hosts (Locatelli and Peeters 2012; van de Woude and Apetrei 2006). Cross-species transmission occurs among sympatric primates that are in contact with each other through predation, habitat competition, food competition, or sexual contacts and is responsible for HIV-1 and HIV-2 infections in human populations (Hahn *et al.* 2000). Frequent cross-species transmission obscures concordance in viral and host phylogeny. Furthermore, viral recombination may occur in hosts coinfected with different strains of SIV resulting in different phylogenetic histories inferred from different genes in the viral genome. Consistent with frequent host switching, the approximate equidistance among the major SIV lineages does not always match the genetic relationships between their hosts. Virus phylogeny corresponds in many cases to host phylogeny, but, in general, the SIV phylogenetic clusters are only partially superimposable on primate phylogenetic trees. In many cases, discordant virus-

host phylogenies are obtained depending on which viral genes are studied, which has been attributed to viral recombination (Hu *et al.* 2003; Jin *et al.* 1994; Souquiere *et al.* 2001). SIVcpz infecting chimpanzees is an example of a virus resulting from the recombination between viruses infecting red-capped mangabeys (SIVrcm) and viruses infecting monkeys from the greater spot-nosed monkeys lineage (SIVgsn) (Bailes *et al.* 2003).

Humans are infected by HIV-1 and HIV-2, which are derived from recent cross-species transmission of SIVs infecting nonhuman primates. Based on the biology and phylogenetic similarities of the simian and human viruses, humans most likely acquired the precursor of HIV-1 and HIV-2 through cutaneous or mucous membrane exposure to infected ape/monkey blood and/or body fluids. Such exposures occur in the context of bushmeat hunting (Peeters *et al.* 2002). Although both viruses are capable of causing CD4+ T-cell depletion and AIDS, they differ vastly in their distribution and virulence.

Origin and Distribution of HIV-1

HIV-1 comprises four distinct viral groups, termed groups M, N, O, and P. Each group resulted from independent cross-species transmission events into humans of SIVs that infect certain subspecies of chimpanzee and gorilla (Fig. 1). In chimpanzees (*Pan troglodytes*), SIVcpz naturally infects two of four subspecies: *P. t. troglodytes* (*Ptt*) from

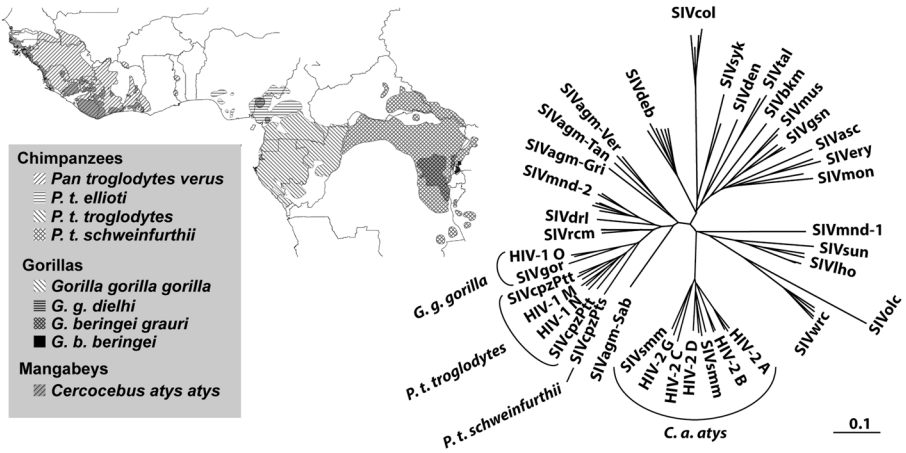

Fig. 1 Geographical range of sooty mangabeys, chimpanzees, and gorillas infected with SIV and phylogenetic tree from different SIVs infecting nonhuman primates and HIVs infecting humans. (**Left**) The geographical range of Cross river gorillas (*Gorilla gorilla diehli*), western lowland gorillas (*Gorilla g. gorilla*), Grauer's gorillas (*Gorilla beringei graueri*), and mountain gorillas (*G. b. beringei*); the geographical range of the four chimpanzee subspecies (*Pan troglodytes verus*, *P. t. ellioti*, *P. t. troglodytes*, and *Pt. schweinfurthii*), and of sooty mangabeys (*Cercocebus atys atys*) are also represented on this map. Sooty mangabeys are infected with SIVsmm, west-central chimpanzees with SIVcpz*Ptt*, western lowland gorillas with SIVgor, and eastern chimpanzees with SIVcpz*Pts*. No naturally occurring SIV has been identified yet in in *Pan troglodytes verus* or *P. t. ellioti*. (**Right**) A neighbor-joining phylogenetic tree of a *pol* gene fragment from different SIVs infecting nonhuman primates and the human infecting HIV-1 and HIV-2 lineages, which are interspersed with the SIVcpz/SIVgor and SIVsmm lineages respectively. Branch lengths are drawn to scale (the scale bar indicates 0.1 substitutions per site). SIVs are identified by a lowercase three-letter code, corresponding to letters of the common species name, such as SIVcpz for chimpanzees. When different subspecies of the same species are infected, an abbreviation referring to the name of the subspecies is added to the virus designation, e.g., SIVcpz*Ptt* and SIVcpz*Pts* to differentiate between the two chimpanzee subspecies, *Pan troglodytes troglodytes* and *P. t. schweinfurthii* respectively (Adapted from Locatelli and Peeters; *AIDS* 2012, 26, 659–673.).

Central Africa (which harbors SIVcpz*Ptt*) and *P. t. schweinfurtii* (*Pts*) from East Africa (which harbors SIVcpz*Pts*). SIVcpz infections are conspicuously absent in the two other chimpanzee subspecies (Leendertz *et al.* 2011; Prince *et al.* 2002; Van Heuverswyn *et al.* 2007), *Pan troglodytes verus* (*Ptv*) from West Africa and *P. t. ellioti* (*Pte*, previously known as *P. t. vellerosus*) inhabiting Nigeria and western Cameroon, north of the Sanaga River (Oates *et al.* 2009). SIVcpz*Ptt* and SIVcpz*Pts* are common and widespread in each subspecies. Only SIVcpz*Ptt* has crossed the species barrier into the human population (Worobey *et al.* 2004). Phylogenetic evidence shows that HIV-1 groups M and N are likely independently derived from divergent SIVcpz*Ptt* (Gao *et al.* 1999; Keele *et al.* 2006; Santiago *et al.* 2002). Group M is the pandemic form of HIV-1, infecting millions of people worldwide. Group N infections have a very limited distribution and prevalence, with fewer than 20 described cases, all in individuals from Cameroon (Simon *et al.* 1998; Vallari *et al.* 2011).

The ancestors of HIV-1 groups O and P were most likely derived from SIVs that currently infect western lowland gorillas (*Gorilla gorilla gorilla*: Van Heuverswyn *et al.* 2006). There are two species of gorilla: *Gorilla gorilla* of West Africa and *Gorilla beringei* of East Africa. Each species is further divided into two subspecies: *Gorilla gorilla gorilla* and *G. g. diehli*, and *G. beringei beringei* and *G. b. graueri* respectively (Groves 2001). Comprehensive molecular epidemiological surveys of wild gorillas, including western lowland gorillas and eastern *Gorilla beringei graueri*, failed to detect any SIVgor infection except for two sites in Cameroon inhabited by *Gorilla gorilla gorilla* (Neel *et al.* 2010). All identified SIVgor strains cluster according to their field site of origin and form a monophyletic lineage within the SIVcpz radiation that is most closely related to HIV-1 groups O and P (Neel *et al.* 2010). In addition, analyses of complete SIVgor genomes revealed phylogenetic proximity to HIV-1 group O across the entire genome, with no major recombination event identified (Takehisa *et al.* 2009). Like HIV-1 group N, HIV groups O and P have very limited distribution in human populations. Group O represents <1% of global HIV-1 infections (Gurtler *et al.* 1994), and is largely restricted to Cameroon, Gabon, and neighboring countries (Mauclere *et al.* 1997; Peeters *et al.* 1997). HIV group P was discovered only in 2009, and has been found only in two people, both of whom are of Cameroonian origin (Plantier *et al.* 2009; Vallari *et al.* 2011).

Origin and Distribution of HIV-2

Unlike pandemic HIV-1 group M, HIV-2 is largely restricted to West Africa, with its highest prevalence found in Guinea-Bissau and Senegal (de Silva *et al.* 2008). The prevalence of HIV-2 in most West African countries is declining, whereas the prevalence of HIV-1 is increasing (Hamel *et al.* 2007; van der Loeff *et al.* 2006). Viral loads are lower in HIV-2– than in HIV-1–infected individuals (Andersson *et al.* 2000; MacNeil *et al.* 2007; Raugi *et al.* 2013). This likely explains the lower transmission rates of HIV-2, the near complete absence of mother-to-infant transmission, and its reduced virulence (Berry *et al.* 2002; O'Donovan *et al.* 2000; Popper *et al.* 2000).

Eight different groups of HIV-2 (A–H) have been described but only two of these groups (HIV-2 A and B) are known to have spread widely in human populations (Damond *et al.* 2004; Lemey *et al.* 2003; Santiago *et al.* 2005). Phylogenetic analysis indicates that each HIV-2 group represents an independent cross-species transmission event of SIVs infecting sooty mangabeys (SIVsmm) in West Africa (Hahn *et al.* 2000).

The isolation and characterization of SIVsmm strains from captive (Hirsch *et al.* 1989a; Marx *et al.* 1991) and free-ranging (Apetrei *et al.* 2005; Chen *et al.* 1996; Peeters *et al.* 1994) sooty mangabeys in their natural habitat in West Africa (from the Casamance river in Senegal to the Sassandra/N'zo Rivers in Côte d'Ivoire) (Kingdon 1997) demonstrated that mangabeys are the natural host for SIVsmm (Fig. 1). SIVsmm strains closely related to five of the eight recognized groups of HIV-2, including the epidemic groups A and B, were found circulating in sooty mangabeys in Taï National Park, pointing to a likely geographic origin of human infections in the eastern part of the sooty mangabeys range (Santiago *et al.* 2005). Recently, a new HIV-2 lineage has been characterized in rural Côte d'Ivoire and most likely emerged following an independent transmission event of a recombinant SIVsmm strain (Ayouba *et al.* 2013).

Prevalence of SIV Infection in the Wild

SIVcpz*Ptt*, the closest ancestor of HIV-1, is common and widespread in chimpanzees in equatorial Africa but its distribution is uneven, with a prevalence ranging from 0 to 4% in western and central Cameroon to 30% in southeastern Cameroon (Keele *et al.* 2006; Van Heuverswyn *et al.* 2007). SIVcpz*Pts*, which does not appear to be a reservoir for zoonotic transmission to humans, is similarly variable among populations in its occurrence and prevalence. In the Democratic Republic of Congo, prevalence ranged 5–56% among 18 sample sites (Li *et al.* 2012). SIVcpz*Pts* is highly prevalent (31%) in Tanzania, although these chimpanzees live at very low densities (Rudicell *et al.* 2011). SIVcpz*Ptt* and SIVcpz*Pts* viruses appear similarly equipped to infect human cells efficiently and persistently, suggesting that biological properties of the SIVcpz*Pts* virus are not the main cause of the lack of SIVcpz*Pts*-like viruses in the human population (Li *et al.* 2012). Whether this absence depends on environmental factors and/or on human behavior(s) that may reduce the risk of cross-species transmission, or whether interspecies transmission has occurred but escaped detection is still to be determined. In contrast to SIVcpz, SIVgor is more patchily distributed and does not appear to be as common or widespread. The prevalence of SIVgor in Cameroon was initially estimated at 1.6% (range 0–4.6%) (Van Heuverswyn *et al.* 2006). An isolated hotspot of SIVgor-infected gorilla communities was discovered recently in southwestern Cameroon at Campo Ma-an National Park, where four social gorilla groups composed of 7–15 individuals each were infected with SIVgor at rates ranging 13–29% (Etienne *et al.* 2012).

These studies show that SIV prevalence is highly variable. However, data collected so far indicate that the reservoir of HIV-1 group M is located in southeastern Cameroon, where SIVcpz*Ptt* is at its highest prevalence (Keele *et al.* 2006; Van Heuverswyn *et al.* 2007). Recent findings also provide first clear evidence that SIVgor has been transmitted to humans and that gorilla populations from southwest Cameroon were the source of HIV-1 group P, although SIVgor in gorillas is less widespread than SIVcpz in chimpanzees. Thus, ongoing contact between humans and infected gorillas represents a continuous source of interspecies viral transmission (D'arc *et al.* 2013).

Monkeys also represent a source of cross-species transmission to human populations. For example, SIVsmm is the reservoir of HIV-2 infections. This virus is quite common in mangabeys, and has a prevalence rate higher than 50% in wild individuals (Apetrei *et al.* 2005; Santiago *et al.* 2005). At least 45 of the 73 recognized species of

primates in Africa have tested positive for SIV, and prevalence can be >50%. Given that there are abundant contacts with humans providing opportunity for zoonotic transmission (Locatelli and Peeters 2012; Peeters *et al.* 2002; van de Woude and Apetrei 2006), the absence of infections in humans from most monkey SIVs suggests that cross-species transmission is very rare. It also suggests that several factors may contribute to the likelihood of transmission and infection of another species, including the prevalence of SIVs in local monkey populations, and viral and host molecular characteristics (Locatelli and Peeters 2012; Peeters *et al.* 2002; van de Woude and Apetrei 2006). Thus it is important to continue monitoring the prevalence of SIV in these other species because the risk of cross-species transmission of a viral type capable of infecting humans persists owing to continued exposure of humans to species with high SIV prevalence through bushmeat hunting (Locatelli and Peeters 2012).

Data regarding the prevalence of SIV infection in other wild primates remain sparse and are equivocal. In some species, SIV infection appears to be common and widespread. For example, studies of wild mandrills (*Mandrillus sphinx*) and red colobus monkeys (*Piliocolobus badius badius*) have shown that these species have a fairly high prevalence of SIV of *ca.* 50% and higher (Leendertz *et al.* 2010; Locatelli *et al.* 2008; Souquiere *et al.* 2001). African green monkeys represent the largest reservoir of SIV in the wild, with 46% prevalence rate of endemic SIV (Ma *et al.* 2013). The majority of SIV prevalence data from monkeys have been obtained by estimating the prevalence in captive individuals, which may be an underestimate of prevalence in the wild. This may be due to the fact that monkeys are generally captured at a young age and mother–infant transmission is low in African primate species (Apetrei *et al.* 2004b). Studies of bushmeat samples are another way of measuring SIV prevalence rates in wild monkeys. Thus far, bushmeat studies suggest that SIV prevalence varies greatly among species. For example, a study of SIV prevalence in bushmeat samples gathered from different regions in Cameroon and in the Democratic Republic of Congo revealed an overall SIV prevalence of 2.93% and 19%, respectively. These studies also showed significantly different prevalence rates per species (0% to >40%), and local variation in prevalence rates within species according to sampling site (Aghokeng *et al.* 2010; Ahuka-Mundeke *et al.* 2011).

Factors Affecting the Zoonotic Spillover of SIV into Human Populations

While SIVs have likely been infecting old world primates for perhaps millions of years, humans have probably only recently acquired these viruses. Pandemic HIV-1 group M can be traced to a single cross-species transmission from SIVcpz*Ptt*, that most likely occurred within the last 100 yr (Korber *et al.* 2000; Worobey *et al.* 2008), and multiple independent spillover events of closely related viruses into human populations have occurred that have only recently been identified. This raises the rather obvious question of whether there may be future spillover events into humans and, if so, whether these viruses could be as devastating as the current HIV-1 pandemic. A series of events occurs during the evolutionary transition of an infectious disease exclusively infecting another species to one exclusively infecting humans (Morse *et al.* 2012; Wolfe *et al.* 2007). These stages include pathogens infecting only animals, those that occasionally infect humans but that are not transmitted among humans, pathogens that infect humans

and are capable of transmission among humans but remain localized, and, lastly, pathogens that are exclusively transmitted among humans that persist in human populations and are capable of widespread dissemination. The emergence of novel zoonotic HIV infections depends on at least three factors, including the likelihood of cross-species transmission, the ability of the pathogen to colonize and replicate in the new human host, and the ecological and evolutionary factors promoting transmission among humans. The risk of cross-species transmission depends on factors that put human populations in contact with infected primates, such as bushmeat hunting, handling, and consumption, and on viral load and prevalence of infection in those populations. Ecological and behavioral factors in primate populations are likely to affect the prevalence of infection and may also affect the likelihood of transmission. On contact, viral and host factors play important roles in determining the likelihood of successful colonization, which, combined with adaptation to the new human host, may also determine the pathogenicity of the infection. In the following sections, we review current knowledge of SIV infections in primates and how this may aid in understanding the spillover of viruses into human populations and their pathogenicity better.

Ecological and Behavioral Factors Affecting Intra- and Inter-species Transmission of SIV

The prevalence of SIV or HIV infection in a population and the likelihood of interspecies zoonotic transmission will depend on the various routes of transmission open to the virus, behavioral and ecological factors affecting rates of transmission; viral load; and physiological and immunological factors in the host affecting the likelihood of successful colonization, infection, and transmission of encountered viruses. Though much is known about how these factors combine to affect patterns of disease prevalence and transmission in humans infected with HIV, little is known about how similar interactions affect the prevalence of SIV in primate populations or affect the likelihood of cross-species transmissions among nonhuman primates. Such information is important in assessing the risk of cross-species transmission of SIVs into human populations, and has the potential to elucidate the factors contributing to successful defense against the virus in primate populations that appear to be immune to infection and/or to developing obvious signs of disease.

Like HIV, SIV can be transmitted vertically (*in utero*, perinatally, or via breast milk) or horizontally (through exposure and contact with blood or other bodily fluids of an infected animal) (van de Woude and Apetrei 2006). In the few primate species in which mother-to-infant transmission (MTIT) of SIV has been studied, the incidence appears much lower than the estimated rate in humans, which occurs at a rate of 35–40% without intervention (UNAIDS 2010). A recent study of MTIT of SIV in a large colony of sooty mangabeys naturally infected with SIV reported that only 6.8% of the 161 infants tested may have acquired SIV by MTIT. Moreover, no increased morbidity or mortality in infected offspring was observed, indicating that the infection is nonpathogenic even when acquired early in life (Chahroudi *et al.* 2011). Similarly, MTIT in wild African green monkeys has been reported to be significantly lower than that observed in HIV-1–infected humans or in rhesus macaques (10 out of 14 infants infected) (Amedee *et al.* 2004), although it is possible that low levels of viremia went undetected

(Ma *et al.* 2013). Why MTIT is so much lower in these species when compared to humans is not completely understood. Data from studies of mandrills and African green monkeys show that, compared to adults, infants exhibit lower expression of CCR5 on their CD4+ T cells, which may explain the near absence of MTIT in these species (Pandrea *et al.* 2012).

The routes of horizontal transmission in wild primates will depend on the social structure, mating behavior, and migration patterns of the species. As in humans, horizontal transmission of SIV appears to be primarily through sexual contact (Diop *et al.* 2002; Phillips-Conroy *et al.* 1994). The risk of acquiring SIV (or other sexually transmitted diseases [STDs]) should be higher in more polygynandrous species (Loehle 1995; Nunn *et al.* 2000). The mating system will influence both the overall prevalence of infection within a primate community and sex differences in prevalence. For example, as variance in mating success between sexes increases, the prevalence of an STD in the sex with lower variance in mating success is expected to increase. In a species with a large skew in male mating success, a single male with many sexual partners can serve as "super spreader" to females in the population, while the prevalence in males remains low because many males simply fail to find a mate (Thrall *et al.* 2000).

SIV can also be transmitted vertically or via aggressive contact between individuals. Indeed, in some species nonsexual horizontal transmission of the virus can be quite common. For example, in a semi-free-ranging colony of mandrills most new infections were established after aggressive contacts during fights for dominance (Nerrienet *et al.* 1998). A recent study of the same colony suggested that nonaggressive interactions such as allogrooming, wound care, play, and food testing might be further vehicles for horizontal transmission (Fouchet *et al.* 2012). More cases of nonsexual horizontal transmission during aggressive encounters have been described in captive African green monkeys (Phillips-Conroy *et al.* 1994), sooty mangabeys (Rey-Cuille *et al.* 1998), chimpanzees (Corbet *et al.* 2000), and macaques (Lowenstine *et al.* 1992). Whether similar rates of transmission would be observed in wild populations is unknown. Nonsexual routes of horizontal transmission are expected to be more likely in primate species that often engage in agonistic behavior (territorial fights, intrasexual mate competition, infanticide) and possibly in reconciliatory or social bonding behavior afterwards (Arandjelovic *et al.* 2011; Rudicell *et al.* 2010; Watts *et al.* 2002).

Group density and size, dominance rank among individuals, patterns of migration, diet, habitat use, and environmental factors, such as habitat characteristics and seasonality, all shape the structure of a social group and the frequency of interactions allowing for horizontal transmission, sexual or otherwise. Teasing apart the contribution of these various behavioral and ecological factors is a difficult undertaking, but a recent network analysis of behavioral encounters in a habituated wild chimpanzee community in Kibale National Park, Uganda, revealed that family size and male rank were strongly associated with the risk of infectious disease transmission (Rushmore *et al.* 2013).

Few studies have detailed routes of transmission of SIVcpz*Ptt* and SIVsmm, the progenitors of HIV-1 and HIV-2. Phylogenetic analysis suggested that vertical transmission might be an important mechanism of SIVsmm transmission in the wild (Apetrei *et al.* 2005; Santiago *et al.* 2005). SIVcpz*Pts* spread both vertically and horizontally among the habituated chimpanzee communities of Gombe National Park in Tanzania (Keele *et al.* 2009). To date, no study has examined the patterns of

transmission of SIVcpz*Ptt* in chimpanzees (*P.t.troglodytes*) or SIVgor in gorillas (*G.g.gorilla*), the direct ancestors of HIV-1.

The proximate causes of interspecies transmission remain poorly understood. Although sexual contact is the primary cause of horizontal transmission within a species, this is an unlikely route of infections between species. The general consensus among researchers is that most interspecies SIV transmissions have occurred as a consequence of hunting other primates for food. This seems certainly to be the case with the acquisition of SIV in humans through bushmeat hunting, handling and consumption (Hahn *et al.* 2000), although recent work failed to detect SIV infection in a large Cameroonian cohort with high nonhuman primate exposure (Djoko *et al.* 2012). SIVcpz, the precursor of HIV-1, is an example of a recombinant virus acquired from SIVs infecting greater spot-nosed monkeys (*Cercopithecus nictitans*), moustached (*Cercopithecus cephus*), and mona monkeys (*Cercopithecus mona*) and red capped mangabeys (*Cercocebus torquatus*) (Bailes *et al.* 2003), all of which are prey of chimpanzees. Interestingly, West African chimpanzees (*Pan troglodytes verus*) are known to prey heavily on Western red colobus, which are infected with SIVwrc at high prevalence (Leendertz *et al.* 2010; Locatelli *et al.* 2008). However, no SIVcpz or SIVwrc-like virus has been detected in these chimpanzees (Leendertz *et al.* 2011). Interspecies transmission of simian foamy viruses (SFV) from colobus monkeys to *Pan troglodytes verus* does occur, suggesting that there is also the potential for SIV transmission (Leendertz *et al.* 2008). Together, these data suggest that given the opportunity, successful cross-species transmission may depend on the viral compatibility between donor and receiver, i.e., whether the host restriction factors are equipped to fight viral entry, transcription, viral budding and spread to other host cells and eventually to other individuals.

Viral and Host Factors Affecting Transmission, Infection, Adaptation to New Hosts, and the Expression of AIDS

In addition to opportunities for transmission between species, establishing cross-species infection requires the virus to thrive in the new host: efficiently finding and entering host cells, replicating within those host cells, and ultimately being transmitted to a new host. Incompatibilities between the pathogen and its new host at any of these stages would act to prevent cross-species infections from occurring. In this section we first describe how the virus enters and replicates in the host cell. We then focus on how changes in cell function related to the expression, regulation, overall abundance, and genetic diversity of host cell receptors and coreceptors targeted by HIV/SIV have contributed to tolerance or apathogenicity, and, in some cases, coevolutionary responses in viral populations. We then focus on antiviral factors in human and nonhuman primates acting to block viral replication and proliferation at different stages of the cell infection and on coevolutionary changes in HIV/SIV counteracting these antiviral factors. Finally, we describe current knowledge about the genetic changes that allowed cross-species transmission events between chimpanzees or mangabeys and human beings and further spread into the human population.

As described in the previous section, HIV enters the human body via mucosal sites, blood-to-blood contact, or breast milk (Levy 2007). After entry, the virus directly

infects CD4+, CCR5+ T cells primarily at mucosal associated lymphoid tissues (MALT), resulting in a substantial loss of these memory/activated T cells (Levy 2007; Veazey and Lackner 2004). Binding and entry into host cells is facilitated by the interaction of gp120 proteins on the surface of virion capsules, which bind CD4+ receptors along with CC-chemokine receptor-5 (CCR5) coreceptors on the surface of host cells (Lasky *et al.* 1987; Nygren *et al.* 1988). On entry into the host cell, viral RNA is reverse-transcribed into DNA and the HIV DNA is integrated into the host genome, where it can be transcribed into HIVmRNA by host RNA polymerase. The mRNA is then packaged into virions, along with HIV reverse transcriptase, integrase, and protease that are budded off and disperse to infect new cells. As viral titers increase, there is a concomitant decrease in CD4+ T cells, which, beyond a critical threshold, compromises host immune regenerative capacity, resulting in the onset of AIDS. For transmission to occur between individuals of the same or different species, each of the steps of the virus life cycle must be completed. Hosts possessing traits blocking various steps of the viral life cycle are resistant to infection. These traits therefore act as important barriers to transmission (Krupp *et al.* 2013; Pandrea and Apetrei 2010; Sauter *et al.* 2011). In addition, in many primate species transmission of SIV occurs, but individuals appear to possess a high tolerance to infection and do not appear to progress to an AIDS-like state. Understanding traits promoting resistance or tolerance to SIV in their natural primate hosts may provide insight into avenues of controlling infections in humans. For obvious ethical reasons, experimental studies on chimpanzees infected with SIVcpz*Ptt* are no longer carried out. Two model organisms, the sooty mangabey infected with SIVsmm, and the African green monkey infected by SIVagm, have been used most frequently in the study of natural infections with SIV. Neither species progresses to an AIDS-like state, despite initial CD4+ cell loss during the acute phase of infection and high viremia and viral replication during the chronic phase, which can last decades. These findings suggest that tolerance is an important component of defense in sooty mangabeys and African green monkeys (Pandrea *et al.* 2008b, 2008c).

The inability to bind host cells efficiently could prevent viral entry and transmission. In humans, genetic variation in the CCR5 coreceptor has been associated with differences in susceptibility to HIV-1 infection. Specifically, a 32-base pair deletion at the CCR5 locus, termed Δ32, appears to affect the rate at which HIV-1 enters leukocytes (Lin *et al.* 2002). Homozygotes for the Δ32 mutation of CCR5 appear to have complete immunity to HIV and heterozygotes show delayed disease progression (Samson *et al.* 1996).

Both CD4 and CCR5 appear to play important roles in mediating tolerance to natural infections with SIV in nonhuman primates (Silvestri *et al.* 2005). Sooty mangabeys have a much lower proportion of CD4+CCR5+ T cells compared to humans and macaques (Pandrea *et al.* 2007). Further, following SIV infection, their CD4+ cells do not upregulate CCR5, especially in CD4+ T Central Memory (TCM), resulting in reduced susceptibility both *in vivo* and *in vitro* when compared to rhesus macaques, which show a marked upregulation of CCR5 in CD4+ cells (Paiardini *et al.* 2011). The lack of upregulation appears to protect this vital class of cells from viral infection. In African green monkeys, there is a similar reduction in the proportion of CD4+CCR5+ cells (Pandrea *et al.* 2007), and low level CCR5 expression has been implicated in providing protection from SIV in breastfeeding infants (Pandrea *et al.*

2008a). Further, CD4 downregulation upon infection acts to protect cells from SIV (Beaumier *et al.* 2009). Patas monkeys (*Erythrocebus patas*) are not a natural host of SIV, but are tolerant of SIVagm infection (van de Woude and Apetrei 2006). This tolerance appears to be due in part to a low level of CCR5 expression on CD4+ cells in patas monkeys (Apetrei *et al.* 2010), again illustrating how the regulation of these cell surface receptors may play an important role in disease progression.

Changes in CD4+CCR5+ cell function and reductions in their numbers could alter the regulation of immune responses and contribute to disease progression. Interestingly, in sooty mangabeys the immunological role of CD4+ TCM cells appears to have been taken over by a subset of double negative T cells (CD3+CD4–CD8–) that are refractory to SIV infection, and carry out T-helper functions following SIV-induced CD4+ T-cell depletion (Milush *et al.* 2011; Sundaravaradan *et al.* 2013). In African green monkeys, downregulated CD4− memory T cells maintain functions like interleukin production, normally attributed to CD4+ cells. These cells not only are protected from infection by SIVagm *in vivo*, but also maintain major histocompatibility complex class II restriction (Beaumier *et al.* 2009). Together, these data demonstrate that the absence of SIV-induced disease progression in natural host species involves downregulation of receptors for the virus by otherwise susceptible host target cells and the preservation of a subset of T cells that maintain CD4+ T-cell function while being resistant to SIV infection *in vivo* (Vinton *et al.* 2011).

Changes in the expression, regulation, or overall abundance of receptors used by SIV/HIV for binding and entry into host cells can provide a source of selection promoting a coevolutionary response in the virus. In HIV infections in humans, viruses that are capable of binding the CXCR4 coreceptor present on naïve T cells appear very late in the chronic phase of infection (Moore *et al.* 2004; Shankarappa *et al.* 1999). This appears to be an evolutionary "dead end" as this change results in a more precipitous loss of T cells (Blaak *et al.* 2000) and more rapid progression of AIDS and patient death. Species that are infected with SIV but that do not progress to AIDS-like disease sometimes show low levels of CCR5 expression along with modifications in coreceptor use. For example, red-capped mangabeys have a very high frequency of CCR5-null individuals (≥70%). The SIVrcm infecting this species has adapted to use CCR2b as a coreceptor and lost the ability to use CCR5 (Beer *et al.* 2001; Chen *et al.* 1998; Georges-Courbot *et al.* 1998; Zhang *et al.* 2000).

The SIV precursors of HIV-1, SIVcpz and SIVgor, possess many of the biological properties required for persistent infection of human cells, including CD4 and CCR5 dependence and neutralization resistance (Takehisa *et al.* 2007). These viruses readily replicate in both human and chimpanzee CD4+CCR5+ T cells (Takehisa *et al.* 2009). It is not clear, however, why disease progression and pathology is so much greater in humans than in the natural hosts of these viruses. There is some evidence of reduced genetic diversity at the 5 CCR5 locus of *Pan troglodytes verus* compared to other chimpanzees subspecies. This has been used as evidence that this subspecies has experienced a selective sweep, in response to selection by a SIVcpz-like ancestor (Wooding *et al.* 2005). A more recent analysis suggests that a selective sweep at the CCR5 occurred before subspeciation events in *Pan troglodytes* (MacFie *et al.* 2009). The Major Histocompatibility Complex (MHC) Class 1 gene region also shows reduced genetic variation in chimpanzees, with evidence suggesting a retrovirus-driven selective sweep occurring 2–3 million yr ago (de Groot *et al.* 2008). There are

also substantial genetic differences between humans and chimpanzees, and among chimpanzee subspecies, in the first variable region and intron 6 of CD4 (Hvilsom *et al.* 2008). Although the precise functional consequences of this evolutionary change are not known, in chimpanzees it has been observed that peripheral blood mononuclear cells (PBMCs) have a lesser capacity to support HIV-1 replication after cell entry (Ondoa *et al.* 2002), consistent with some role in providing protection (de Groot *et al.* 2008; MacFie *et al.* 2009; Wooding *et al.* 2005). Similarly, rhesus macaques infected with SIVmac239, but expressing the MHC allele *MamuB-17*, displayed conspicuous reduction in plasma virus concentration, and were able to suppress SIV replication long term, showing that heritable variation in SIV-related immunity (based in MHC) exists even in non-natural SIV hosts (Yant *et al.* 2006).

In addition to defense provided by changes in CD4 and CCR5 cell surface receptors and their regulation, humans, and other mammals have evolved specific antiviral factors, along with conventional innate and acquired immune responses, that counteract viral entry, replication, and spread (Malim and Emerman 2008; Neil and Bieniasz 2009)). To date, four restriction factors have been identified that specifically block HIV-1 replication: apolipoprotein B mRNA-editing, enzyme-catalytic, polypeptide-like 3G (APOBEC3G) (A3G) (Harris *et al.* 2003; Mangeat *et al.* 2003; Sheehy *et al.* 2002) expressed in natural targets of HIV-1 infection, including lymphocytes and macrophages; tripartite interaction motif (TRIM)5-α, revealed through studies of species-specific post-entry blocks to HIV and SIV infections (Stremlau *et al.* 2004); bone marrow stromal cell antigen 2 (BST-2) (also known as CD317,theterin or HM1.24), induced by interferon-α, capable of "tethering" nascent virions to the cellular plasma membrane (Jouvenet *et al.* 2009; Neil *et al.* 2008); and sterile α motif and HD domain 1 (SAMHD1), the most recently discovered restriction factor, highly expressed and functional in myeloid cells (Hrecka *et al.* 2011; Laguette *et al.* 2011). However, it is obvious from the high levels of viremia during acute infection that these antiviral defenses fail to protect humans against HIV-1 infection. HIV-1 and other primate lentiviruses have evolved a multitude of strategies to evade or counteract the host defenses, by regulating the host intrinsic immunity, via the "accessory" genes, so called because they are not absolutely required for viral replication in cell lines (for in-depth reviews of the mechanisms underlying the function of these accessory genes, see Chiu and Greene 2009; Kirchhoff *et al.* 2008; Malim 2009; Malim and Emerman 2008; Neil and Bieniasz 2009; Planelles and Benichou 2009). These accessory genes are *vif*, Viral protein R (*vpr*), and Viral protein U (*vpu*). Together with the Negative regulatory Factor (Nef) protein, these proteins allow HIV-1 to replicate continuously at high levels in the presence of strong innate, intrinsic, and adaptive virus-specific immune responses and thus they play important roles for viral persistence, pathogenesis, and transmission *in vivo*.

For cross-species transmission of SIV to occur, the virus must be in some way "preadapted" by possessing the ability to colonize a new host; bind and enter host cells; and overcome host antiviral, innate, and adaptive immune defenses to replicate and eventually be transmitted to another host (Sawyer *et al.* 2005). Recent studies provide the first insights into how primate lentiviruses managed to jump from one species to another (Gaddis *et al.* 2004; Kratovac *et al.* 2008; Krupp *et al.* 2013; Sauter *et al.* 2009; Schindler *et al.* 2006). For example, the inability of chimpanzee TRIM5-α to restrict the SIVs found in small monkeys most likely facilitated coinfection by different

lentiviruses and thus the generation of the chimeric virus that adapted to chimpanzees. Subsequently, the transmission of the virus from chimpanzees to humans was successful because SIVcpz Vif is fully capable of antagonizing human APOBEC proteins (Gaddis *et al.* 2004). The chimeric virus that gave rise to SIVcpz contained the *vpu* gene of the SIVgsn/mus/mon precursor and the *nef* gene of the progenitor of SIVrcm, two potential tetherin antagonists (Schindler *et al.* 2006). Subsequently, *nef*, and not *vpu*, evolved to become an effective tetherin antagonist in SIVcpz-infected chimpanzees, but *vpu* maintained its capability to degrade the CD4 receptor (Sauter *et al.* 2010)). Another recent study showed that *vpx*, which in other lentiviruses antagonizes SAMHD1, has been deleted during the creation of SIVcpz. This genomic deletion resulted in the reconstruction of the overlapping *vif* gene by "overprinting" (Etienne *et al.* 2013). All these gene loss and adaptation events made the SIVcpz species jump into the humans possible.

After transmission of SIVcpz from chimpanzees to gorillas, the virus adapted to this new host because the chimpanzee and gorilla tetherin sequences differ by two amino acid changes in the cytoplasmic domain targeted by Nef (Sauter *et al.* 2009). The species jump of SIVs from chimpanzees and gorillas to humans was different. The human tetherin variant contains a deletion in the cytoplasmic region, which most likely evolved to escape an ancient viral antagonist and renders human tetherin resistant to Nef (Jia *et al.* 2009; Sauter *et al.* 2009; Zhang *et al.* 2009). However, pandemic HIV-1 M strains overcame this barrier by switching from Nef to Vpu to regain efficient anti-tetherin activity in the new human host (Sauter *et al.* 2009). In contrast, the Vpu proteins of nonpandemic HIV-1 O strains remained poor tetherin antagonists, and those of the rare HIV-1 group N strains gained some anti-tetherin activity but lost their capability to degrade CD4.

The direct simian precursor of HIV-2, SIVsmm from sooty mangabeys, does not contain a *vpu* gene and counteracts tetherin by *nef* (Jia *et al.* 2009; Zhang *et al.* 2009). Recently, it has been shown that HIV-2 uses its Env protein to antagonize human tetherin instead (Le Tortorec and Neil 2009). Thus, the deletion in human tetherin forced both human immunodeficiency viruses to switch from Nef to a different tetherin antagonist, i.e., Vpu or Env.

Vpu-containing primate lentiviruses lost their capability to block T-cell activation, and this may have implications for their pathogenicity (Paiardini *et al.* 2009; Sodora and Ross 2009). Accumulating evidence suggests that the acquisition of a *vpu* gene may have allowed the viral lineage that gave rise to HIV-1 to evolve toward greater pathogenicity by removing the selective pressure for a protective Nef function that prevents damaging levels of immune activation (Kirchhoff 2009). The observations that HIV-1 is more pathogenic than HIV-2 and that SIVcpz causes AIDS in its natural chimpanzee host (Keele *et al.* 2009) are in agreement with this hypothesis.

In addition to their intrinsic capability of infecting human cells, SIVcpz, SIVgor, and SIVsmm experienced further adaptation after their introduction into the human population. Research conducted by Wain and colleagues found a single site, Gag-30, in the gag-encoded matrix protein p17, that may promote infection and spread of the virus in humans. In SIVcpz*Ptt* strains infecting chimpanzees, there is a conserved Methionine (Met) at this site, and there is a conservative replacement by Leucine (Leu) in SIVcpz*Pts*. A replacement of Met with Arginine (Arg) was observed in all three separate HIV-1 lineages in humans. This site has been conserved as a basic residue

(Arg or Lysine [Lys]) in most HIV-1 lineages (Wain *et al.* 2007). Further, the serial passage of HIV-1 through chimpanzees resulted in reversion back to Met at this site (Mwaengo and Novembre 1998). Whereas the Met-to-Arg change in the lineages leading to HIV-1 could have occurred before cross-species transmission, possibly predisposing particular chimpanzee viruses to greater fitness in humans, the reversion to Met in chimpanzees infected with HIV-1 argues that the adaptive changes occurred after the cross-species transmission events. The residue present at Gag-30 varies among SIVs infecting different primate species. Interestingly, it is also Met in SIVsmm from sooty mangabeys, the progenitor of HIV-2. Remarkably, this residue changed to Arg in the inferred ancestor of the most widespread form of HIV-2, group A. However, it has been conserved as Met in HIV-2 group B, and was not found to have changed in any of the sporadic forms of HIV-2. These observations provide additional evidence that a basic residue at Gag-30 enhances the replication potential, and possibly the secondary spread, of primary lentiviruses after transmission to humans.

Together these data are beginning to shed light on the variation in pathogenicity of SIVs infecting different primate species as well as the factors allowing spillover events of SIVs into new species. Primate species, which have shared a presumably long evolutionary history with SIV, show evidence of evolving changes in the regulation of CD4+ and CCR5 receptors as well as antiviral factors limiting the pathogenicity of SIV infection. This has been accompanied by coevolutionary changes in SIVs infecting those species. For spillover of the virus to occur, SIVs must be somewhat "pre-adapted" to the new host, possessing the ability to bind host target cells as well as having accessory genes acting to overcome host innate immune defenses and antiviral factors. Accessory genes may also predispose viruses to be of higher or lower pathogenicity after introduction into a new species. Lastly, virulence and pathogenicity may further change as the virus adapts to its new host.

Pathogenicity of HIV and SIV Infections

HIV infections in humans are highly pathogenic, with 100% mortality for infections that have entered the chronic phase in the absence of intervening therapies (UNAIDS 2010). Although it is difficult to study the health impact of SIV infection in other primates, the observation that populations with relatively high prevalence of SIV were not severely affected led many researchers to conclude that these infections are apathogenic in their natural primate hosts (Broussard et al. 2001; Muller-Trutwin *et al.* 1996; Onanga *et al.* 2002; Rey-Cuille et al. 1998; Silvestri 2005; Silvestri *et al.* 2003; Villinger *et al.* 1996). Based on these observations it has been suggested that the increased pathogenicity of HIV in humans was due to its recent introduction and that the apathogenicity of SIV infections in their natural hosts was a consequence of a long period of coevolution resulting in evolutionary changes in both the host and virus populations, promoting reduced virulence (Charleston and Robertson 2002; Sharp *et al.* 2000; Wertheim and Worobey 2007). Recent results have, however, called into question many of the specifics of this paradigm (Wertheim and Worobey 2009).

Clinical Manifestation of HIV in Humans and SIV in Macaques and in Other Nonhuman Primates

Clinical studies demonstrate that HIV and SIV affect their human and nonhuman primate hosts differently. In humans, HIV infection and its progression to AIDS are divided into three stages: acute stage, chronic stage, and AIDS. The acute stage immediately follows the individual's exposure to HIV and is characterized by a high viral replication and by a significant drop of circulating CD4+ T cells. The chronic stage is represented by the clinical latency or asymptomatic stage of infection, during which viral loads decline to low levels. The virus lies dormant within infected cells and constitutes an inactive reservoir of provirus in the lymphoid organs. The third stage is reached when the number of CD4+ T cells declines below a critical level. At this critical point host immunity is compromised and the patient progresses to AIDS (Levy 2007).

Rhesus macaque (*Macaca mulatta*) and other Asian macaques are not natural hosts of SIV. When experimentally infected with SIV from African green monkeys, which is apathogenic in this natural host, macaques develop pathogenic infections characterized by high level virus replication, progressive CD4+ T-cell depletion, chronic immune activation, and establishment of a mucosal and systemic immunodeficiency that closely resembles HIV infection in humans. In HIV and in SIV in macaques, viral loads spike then decline to low levels during the latent phase.

The difference between the course of SIV infection in macaques vs. what is observed in their natural hosts provides insight into viral factors and host responses, contributing to pathogenesis. The early dynamics of SIV replication have also been studied in the African green monkeys, mandrills, and sooty mangabeys (Diop *et al.* 2000; Kornfeld *et al.* 2005; Onanga *et al.* 2006). SIV infection in these natural hosts is typically nonpathogenic despite persistent high viral loads (due to robust virus replication), and results in a substantial preservation of the immune system function, lack of chronic immune activation, and a lifespan similar to SIV-uninfected individuals (Brenchley *et al.* 2010; Paiardini *et al.* 2009). Interestingly, in both natural and non-natural hosts there is initially a robust innate immune response to the virus. However, unlike HIV infection in humans and SIV infection in macaques, immune activation during the acute stage appears transient in natural hosts and is further controlled during the chronic stage by anti-inflammatory mechanisms (Kornfeld *et al.* 2005; Onanga *et al.* 2006; Pandrea *et al.* 2005; Silvestri *et al.* 2003, 2005). The current view is that tolerance to infection through control of immune activation, rather than limiting viral replication, is the major mechanism through which natural hosts are protected against disease (Pandrea and Apetrei 2010).

Evidence of Pathogenesis in SIV-Infected Natural Hosts

Tests of the pathogenesis of SIV have not been conducted in most of the African primates known to harbor the virus, often because the viruses have been identified only by sequence data, and have not been isolated, or because they infect hosts listed as endangered or critically endangered in the IUCN Red List, i.e., chimpanzees and gorillas, and experimental tests are not possible. The general assumption that SIV infection is nonpathogenic in natural hosts is supported by data from studies of captive primates (mostly African green monkeys, sooty mangabeys and mandrills) (Pandrea and Apetrei 2010; Pandrea *et al.* 2008c; Silvestri *et al.* 2007) but a growing body of

data from wild apes has called this assumption into question. In studies of captive primates that acquired the virus naturally, progression to AIDS is rare, and has only been observed in older individuals and those infected over long periods of time (Pandrea *et al.* 2001; Traina-Dorge *et al.* 1992). In these cases increased viral replication, weight loss, opportunistic infections, and lymphomas were observed, suggesting progression to an AIDS-like disease. Experimental studies involving the introduction of heterologous virus into captive African primates such as black mangabeys, baboons, and chimpanzees have reported evidence of progression to an AIDS-like disease (Apetrei *et al.* 2004a; Barnett *et al.* 1994; Novembre *et al.* 2001; O'Neil *et al.* 2000).

Clinical manifestations of SIV infections in chimpanzees are mixed. No AIDS-like syndrome developed in nine captive-bred chimpanzees infected with SIVcpz, although six of them were coinfected with HIV-1 (Heeney *et al.* 2006). A rescued East African chimpanzee naturally infected with SIVcpz*Pts* has been monitored for >7 yr (Kestens *et al.* 1995; Nyambi *et al.* 1997; Ondoa *et al.* 2001; Peeters *et al.* 1992). This individual developed a strong humoral response, a strong but transient neutralizing antibody response, and severe thrombocytopenia, typical patterns found in macaques infected with SIV, chimpanzees experimentally infected with HIV-1, or untreated humans infected with HIV-1 (Alcantara *et al.* 2009; Rieg *et al.* 2007; Scaradavou 2002), but never displayed any sign of AIDS-like disease (Weiss and Heeney 2009).

In a recent epidemiological study on wild chimpanzees of the *schweinfurthii* subspecies, from Gombe National Park, Tanzania, researchers reported a 10- to 16-fold higher age-corrected death hazard for SIVcpz-infected chimpanzees ($N = 17$) compared to those that were uninfected ($N = 77$) (Keele *et al.* 2009). In addition, this study reported that SIVcpz-infected females were less likely to give birth and experienced higher infant mortality rate than uninfected females. Moreover, researchers observed that the Mitumba and the Kasakela chimpanzee communities from Gombe with low rates of SIVcpz*Pts* infection (prevalence <13%), continued to grow, while the heavily infected Kalande community (prevalence 46%), suffered a significant population decline (Rudicell *et al.* 2010). Data on a natural SIV infection in *Pan troglodytes troglodytes*, the reservoir of the ancestors of HIV-1 in humans, are available for only a single chimpanzee confiscated in southern Cameroon. Clinical follow-up and biological analyses over 7 yr showed a significant decline of CD4+ counts, severe thrombocytopenia, weight loss, and frequent periods of infections with diverse pathogens. There was also evidence of increasing viral diversity during the course of infection, which suggests clinical progression to an AIDS-like disease (Etienne *et al.* 2011). These findings, combined with the epidemiological data (Keele *et al.* 2009; Rudicell *et al.* 2010), challenge the prevailing view that all natural SIV infections are nonpathogenic, and provide evidence that SIVcpz has a substantial negative impact on the health, reproduction, and lifespan of chimpanzees.

Limited data suggest that SIVgor may also affect gorilla health negatively. A longitudinal study, combining field, virology, and genetic data of SIVgor infecting a small number of nonhabituated gorillas in southwestern Cameroon found evidence of viral adaptation characteristic of escape mutants, i.e., V1V2 loop elongation and increased number of glycosylation sites (Etienne *et al.* 2012). These V1V2 characteristics were recently associated with disease progression in humans (Curlin *et al.* 2010). Whether they are also associated with an AIDS-like disease progression in gorillas still needs to be determined.

Taken together, these studies suggest that species-specific SIV viruses may share a relatively benign coevolutionary relationship with their hosts. In contrast, recombinant viruses that have crossed species boundaries and that have succeeded in establishing a persistent infection are characterized by more dynamic coevolutionary relationships. Moreover, it is only recently that data has begun to emerge from studies of wild populations naturally infected with SIV (Etienne *et al.* 2011; Keele *et al.* 2009; Ma et al. 2013; Rudicell *et al.* 2010). More large-scale studies are needed to draw definitive conclusions about SIV pathogenicity in their natural hosts in the wild.

Conclusion and Future Directions

SIVs have been infecting nonhuman African primates for thousands, possibly millions of years (Gifford 2012; Worobey *et al.* 2010). In contrast, the overwhelming majority of the evidence shows a more recent emergence of HIV in humans after several independent zoonotic transmissions of SIVs infecting chimpanzees, gorillas, and sooty mangabeys (Locatelli and Peeters 2012). Pandemic HIV-1 group M is mostly closely related to SIVcpz*Ptt* and is highly virulent in humans (Keele *et al.* 2006; UNAIDS 2010). Although much still needs to be learned concerning the fitness consequences of SIV infection in nonhuman primate hosts, they do appear to be less virulent than HIV infections in humans, a trend perhaps reflecting a longer coevolutionary history between the virus and its host (van de Woude and Apetrei 2006). However, recent studies have shown that SIV infections in their natural hosts can cause disease and fatality at least in chimpanzees (Etienne *et al.* 2011; Keele *et al.* 2009), which suggests that there is still much to learn about the progression of SIV infection in chimpanzees and other less well known nonhuman primates.

There are several fertile areas of research on this topic. For example, SIV infections in natural hosts share numerous features with pathogenic HIV infection; however, the effective control of immune activation in natural hosts appears to be a major contributor to reduced pathogenicity (Pandrea and Apetrei 2010). Investigating the molecular interactions between SIVs and their natural hosts may provide critical insight into factors contributing to human HIV/AIDS pathogenesis and guide development of new therapeutic strategies for treating HIV infection. Antiviral factors interfering with different steps of the viral life cycle, such as reverse transcription, uncoating, and virion release have already been identified in both human and nonhuman hosts (Kirchhoff 2010). It seems likely that other antiviral factors remain to be identified. However, a better understanding of viral accessory gene products capable of counteracting host defenses has illustrated the enormous plasticity by which lentiviruses can adapt to new hosts.

HIV-AIDS has killed more than 30 million people around the world (UNAIDS 2010), but little is known about the health impact SIV is having on wild populations of primates. Studies in natural hosts have focused on three animal models: the mandrill, the African green monkey, and the sooty mangabey (Apetrei *et al.* 2012), leaving the great majority of naturally infected nonhuman primates unexamined. Extensive behavioral and ecological research has been conducted on different social groups of chimpanzees (Boesch and Boesch-Achermann 2000; Goodall 1986; Nishida *et al.* 2010; Reynolds 2005; Wrangham *et al.* 1996) and gorillas (McGrew *et al.* 1996; Robbins

et al. 2005; Taylor and Goldsmith 2003) across Africa, as well as on a free-ranging, habituated community of sooty mangabeys in the Taï forest in Côte d'Ivoire (McGraw *et al.* 2007). Few studies have examined the impact of SIV infections on the health and population dynamics of wild primates (Etienne *et al.* 2012; Keele *et al.* 2009; Rudicell *et al.* 2010) as such an approach requires the monitoring of fully habituated wild communities or captive or semicaptive colonies. Examining a broader range of natural hosts will provide a better understanding of how ecological and behavioral factors affect the prevalence and transmission of the virus, as well as disease progression and fitness consequences of SIV infections.

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