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The Well-Tempered SIV Infection: Pathogenesis of SIV Infection in Natural Hosts in the Wild, with Emphasis on Virus Transmission and Early Events Post-Infection that May Contribute to Protection from Disease Progression

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Abstract

African NHPs are infected by over 40 different simian immunodeficiency viruses. These viruses have coevolved with their hosts for long periods of time and, unlike HIV in humans, infection does not generally lead to disease progression. Chronic viral replication is maintained for the natural lifespan of the host, without loss of overall immune function. Lack of disease progression is not correlated with transmission, as SIV infection is highly prevalent in many African NHP species in the wild. The exact mechanisms by which these natural hosts of SIV avoid disease progression are still unclear, but a number of factors might play a role, including: (i) avoidance of microbial translocation from the gut lumen by preventing or repairing damage to the gut epithelium; (ii) control of immune activation and apoptosis following infection; (iii) establishment of an anti-inflammatory response that resolves chronic inflammation; (iv) maintenance of homeostasis of various immune cell populations, including NK cells, monocytes/macrophages, dendritic cells, Tregs, Th17 T-cells, and γδ T-cells; (v) restriction of CCR5 availability at mucosal sites; (vi) preservation of T-cell function associated with down-regulation of CD4 receptor. Some of these mechanisms might also be involved in protection of natural hosts from mother-to-infant SIV transmission during breastfeeding. The difficulty of performing invasive studies in the wild has prohibited investigation of the exact events surrounding transmission in natural hosts. Increased understanding of the mechanisms of SIV transmission in natural hosts, and of the early events post-transmission which may contribute to avoidance of disease progression, along with better comprehension of the factors involved in protection from SIV breastfeeding transmission in the natural hosts, could prove invaluable for the development of new prevention strategies for HIV.

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Keywords

SIV; natural hosts; African NHPs; pathogenesis; transmission; CCR5

Introduction

A family of retroviruses, collectively referred to as simian immunodeficiency viruses (SIVs), naturally infect a large number of African NHP species. Currently, over 40 different SIVs are known to be circulating in wild African NHPs. As natural hosts of SIVs, these NHPs generally do not progress to AIDS, despite chronic, highly active viral replication that is in same range as or even greater than what is typically reported in HIV patients (Ansari and Silvestri, 2014; Chahroudi et al., 2012; Locatelli et al., 2014; Pandrea and Apetrei, 2010; Pandrea et al., 2008a; VandeWoude and Apetrei, 2006). However, there have been some rare cases where AIDS or AIDS-like symptoms have been reported in natural hosts. These cases occurred primarily in NHPs in captivity that had outlived their normal lifespan of their species in the wild and had been infected and followed for decades (Apetrei et al., 2004; Ling et al., 2004; Pandrea et al., 2001, 2009). This clearly indicates that the lack of disease progression in the natural hosts of SIVs is not the result of infection by benign viruses, but rather that these species have adapted to avoid progression to AIDS. Although relatively sparse compared to the body of data on HIV, the research done on the pathogenesis of SIV-infection in natural hosts indicates that the lack of disease progression does not appear to be mediated by a more effective immune response by the host, but rather better management of the deleterious consequences of infection (Pandrea et al., 2008a).

The exact mechanisms by which natural hosts are able to avoid progression to AIDS in the face of a highly active infection are a subject of intensive research. Whatever they may be, the adaptations leading to control of the deleterious consequences of SIV infection in natural hosts are almost certainly the result of long-term coevolution between African hosts and their species-specific SIVs (Chahroudi et al., 2012; Fischer et al., 2012; Kobayashi et al., 2014; Ma et al., 2013; Pandrea and Apetrei, 2010). Here, we will review the current knowledge regarding SIV-infection in natural hosts, with an extra focus on the events surrounding transmission. The current research indicates that the key events involved in controlling and preventing disease progression appear to occur very early in infection, during the initial period following viral entry, and may be localized to the mucosal sites of infection. Understanding these mechanisms and comparing them to the mechanisms underlying progressive infections has the potential to unlock novel prevention strategies for HIV patients and potentially new paths to reaching a ‘functional cure’ for HIV.

1. Evolutionary History of SIVs in African NHPs

1.1. SIVs naturally infect only wild African NHPs

Before considering the exact features of SIV infection in African NHPs, it is important to understand the long evolutionary relationship that exists between these viruses and their hosts. SIVs have so far been found to infect over 45 species of African NHPs. This means that more than 40 genetically distinct SIVs are known to be circulating in the wild. While

most natural hosts are infected by a single species-specific SIV, there are several examples of African NHP species, including mandrills, mustached monkeys, and mantled guerezas, which have multiple SIVs cocirculating in the wild (Ansari and Silvestri, 2014). No SIVs have been found yet that infect any wild Asian or New World NHPs. Therefore, Asian macaques are nonnatural hosts of SIV (Ansari and Silvestri, 2014; Lowenstine et al., 1986; Ohta et al., 1988). The various SIVmac variants that are used to experimentally infect rhesus macaques (RMs), pigtailed macaques, crab-eating macaques and stump-tailed macaques in captivity actually represent cross-species transmissions of SIVs from sooty mangabeys (SM), an African NHP species (Apetrei et al., 2005). In macaques and other Asian NHPs, SIV infections are pathogenic and lead to the development of AIDS, which is why the RM has become the primary model for HIV in humans.

From an evolutionary perspective, humans could also be considered to be a nonnatural host for HIV, as HIV only appeared in human populations within the last century, when the virus was acquired from chimpanzees/gorillas and sooty mangabeys. The progression to AIDS reflects the poor evolutionary adaption between HIV and humans. A similar situation exists in chimpanzees, which also acquired SIVcpz from various monkey species through cross-species transmissions and recombination events (Bailes et al., 2003), and then became the source of the SIVgor that infects gorillas (D'arc et al., 2015; Faria et al., 2014; Hirsch et al., 1989; Keele et al., 2006; Van Heuverswyn et al., 2006). Like HIV in humans, progression to AIDS has been shown to be a possible outcome of SIVcpz infection in chimpanzees, both in captivity and in the wild, though it is as of yet unclear how prevalent progression to AIDS is amongst wild chimps (Etienne et al., 2012; Keele et al., 2009a).

1.2. African NPHs and SIVs have coexisted for an extremely long period of time

Various studies incorporating geology, phylogeny and molecular genetics point to very ancient origin of SIV, though the exact estimates vary greatly. Some of the most concrete evidence for the origin of SIV infections comes from a study of NHPs isolated on Bioko Island. Located off the northern coast of Equatorial Guinea, Bioko Island was separated from the mainland around 10,000 years ago. Phylogenetic analysis of the SIVs endemic to the NHPs on the island revealed that each SIV was most genetically similar to SIVs infecting NHPs of the same genus on the mainland. This suggests that SIVs were already circulated in these species at the time of Bioko Island separation from the mainland, i.e., that SIVs are at the very least over 10,000 years old (Worobey et al., 2010). On the other end of the spectrum, an endogenous lentivirus infecting the gray mouse lemur in Madagascar was shown to be genetically related to mainland SIVs. As the NHPs on Madagascar have been separated from African NHPs for at least 14 million years, this study points to an extremely ancient origin of SIVs (Gifford et al., 2008; Perelman et al., 2011). Due to the discrepancy with the molecular clock data, it generally can be surmised that SIVs have been infecting African primates for anywhere between tens of thousands to millions of years (Compton and Emerman, 2013; Gifford et al., 2008; Ma et al., 2013). In fact, it is possible that SIVs have been infecting NHPs since the time of primate speciation, given the complete absence of SIVs in Asian and New World NHPs (VandeWoude and Apetrei, 2006).

While the precise age of SIV infections in their natural hosts may be uncertain, they clearly share a long evolutionary history together. One notable example illustrating this relationship can be found in the phylogeny of the various strains of SIVagm, which infect African green monkeys (AGMs). AGMs are NHPs belonging to the genus *Chlorocebus*. The genus encompasses four species of AGM: sabaeus, grivet, tantalus, and vervet (Ansari and Silvestri, 2014; Pandrea et al., 2008a), which were shown to be infected with a species-specific virus (Allan et al., 1991). The AGM subspecies are known to have diverged from their common ancestor between 1.5–3 million years ago and then spread out over sub-Saharan African, each settling into a different region (Xing et al., 2007). Given the geographical and temporal divergence of the subspecies, it is likely that their respective viruses also evolved in tandem with their hosts (Ma et al., 2013). This conclusion is supported by a recent study examining the diversity of SIVagm in AGMs geographical separated by the Drakensberg mountains along the coast of South Africa. Phylogenetic analysis demonstrated that the costal viruses and the inland viruses clustered separately and were genetically distinct from each other. As the Drakensberg mountains are around 280 million years old, the divergence between the two groups could have occurred anywhere between the aforementioned spread of AGMs 3 million years ago to around 100,000 years ago, during the mass migrations that occurred in the Plio-Pleistocene glacial period (Ma et al., 2013).

1.3. SIVs are genetically diverse and readily undergo cross-species transmission and recombination

The extensive evolutionary history of SIVs is also reflected in part by the extreme genetic diversity of SIVs and, subsequently, HIVs. Phylogenetic analysis of SIVs has revealed that there have been numerous cross-species transmissions and recombination events in the past, with many SIVs arising after crossing over between two sympatric species (Pandrea and Apetrei, 2010). There are also multiple examples of cross-species transmission subsequently followed by recombination, including: (i) SIVmnd-2, which is the result of a recombination between SIVmnd-1 and SIVrcm; (ii) SIVsab, which is an ancient recombinant of an ancestral SIVsab and SIVrcm; (iii) SIVmus, SIVmon, and SIVgsn, three viruses from three different NHP species (mustached monkeys, mona monkeys and greater spot-nosed monkeys) which share genetic and phylogenetic features, suggesting recombination (Jin et al., 1994a; Liégeois et al., 2014; Takemura and Hayami, 2004).

Another notable example is SIVcpz, which shares genetic similarity to both SIVrcm and SIVgsn. Chimpanzees regularly hunt other primates for food and the recombination of these two viruses almost certainly occurred in chimps (Bailes et al., 2003). This emergence of SIVcpz is most likely a relatively recent event, as is reflected by the reports of 10- to 16-fold increase in mortality and AIDS-like disorders in wild SIVcpz-infected chimpanzees (Etienne et al., 2011; Keele et al., 2009a; Rudicell et al., 2010). Additionally, expression levels of the SIV coreceptor CCR5 on the surface of chimpanzee $CD4^+$ T-cells are intermediate between natural hosts and nonnatural hosts. As CCR5 expression levels are generally considered a marker of host adaptation to SIV (Pandrea et al., 2007a), this intermediary CCR5 expression on the $CD4^+$ T-cells of chimps suggests a relatively recent

cross-species transmission and consequently an incomplete adaptation of the chimpanzee host to the virus (Pandrea and Apetrei, 2010).

The propensity of SIVs to readily cross over between species is reflected by the fact that both HIV-1 and HIV-2 originated from multiple cross-species transmissions of SIVs to humans (Sharp and Hahn, 2011). HIV-1 arose from cross-species transmissions from two different primate sources. HIV Groups M and N are the result of SIVcpz transmission of from chimpanzees to humans (Keele et al., 2006). SIVgor, which is itself a cross-species transmission of SIVcpz from chimps to gorillas, went on to ultimately cross over to humans and generate HIV groups O and P (D'arc et al., 2015; Plantier et al., 2009; Takehisa et al., 2009; Van Heuverswyn et al., 2006). HIV-2, on the other hand, arose from multiple transmission of SIVsmm directly from SMs in Western Africa to humans (Ayouba et al., 2013; Hirsch et al., 1989; Sharp and Hahn, 2011). With increasing rates of interaction between African NHPs and humans due to poaching, hunting for bushmeat and deforestation (Cronin et al., 2015; Ziegler et al., 2016), it seems probable that further cross-species transmissions might occur and give rise to new HIVs. Consequently, it is important that further research be carried out to understand the evolutionary dynamics of SIVs in the wild (Aghokeng et al., 2010; Locatelli and Peeters, 2012).

2. General features of SIV transmission in natural hosts

2.1. Studying the natural history of SIV infection in African NHPs is extremely challenging

The information regarding the natural history of SIVs is relatively sparse. There are a variety of reasons for this: (i) lack of sufficient infrastructure to support field research; (ii) the endangered status of many African NHPs; (iii) reliance on alternative noninvasive sampling, including bushmeat and feces, which do not permit proper pathological or immunological studies. However, despite the intrinsic difficulty of field research, we carried out a number of studies that have been able to elucidate some of the characteristic features of SIV infection in the wild, including prevalence, viral loads (VLs) and routes of transmission.

2.2. Most features of SIV infection of natural hosts have been derived from studies on a limited number of species in captivity

Virtually all of the data regarding the characteristics of SIV infection of natural hosts have been derived from studies on a limited number of three animal models (AGMs, SMs and mandrills) in captivity (Ansari and Silvestri, 2014; Pandrea and Apetrei, 2010). There are several reasons for this. First, most SIVs are only known from their genetic sequences and have never been properly isolated or characterized. SIVagm, SIVsmm, and SIVmnd-1/SIVmnd-2 are among the minority of SIVs that have been studied in detail. Second, the majority of African NHPs are not widely available in primate facilities and importation of NHPs directly from Africa is virtually impossible. Third, as mentioned above, many NHPs are endangered and field work on wild animals is exceptionally difficult.

Our lab developed a new model of SIVsab infection in Caribbean AGMs that circumvents most of these problems. The difficulty in importation is averted, as AGMs (sabaeus) from the Caribbean are easy to import. Since the AGMs were brought from Africa to the

Caribbean over 300 years ago during the 17th and 18th centuries, they have become well established, to the point of being considered a pest in some areas (Denham, 1981). These animals have been shown to be both free of SIVagm, and genetically indistinguishable from the sabaeus found in Africa, making them ideal for experimental studies (Daniel et al., 1988; Hendry et al., 1986; Pandrea et al., 2006a). Finally, neither African nor Caribbean AGMs are endangered, meaning that more invasive methods can be used for the study of SIV pathogenesis in AGMs, including experimental infections, blood draws and tissue sampling.

2.3. SIVs can be highly prevalent in natural hosts in the wild

In many African NHP species and subspecies, SIV infections are very prevalent in the wild. Some examples include: red colobus, AGMs, SMs, red-capped mangabeys, De Brazza monkeys and mandrills (Bibollet-Ruche et al., 2004; Estaquier et al., 1991; Fouchet et al., 2012; Leendertz et al., 2010; Locatelli and Peeters, 2012; Ma et al., 2013). The prevalence rates in these species can be uniformly high across the population, as is the case in AGMs, where 80–90% of adult females and 50–60% of adult males in the wild test positive for SIVagm infection (Ma et al., 2013, 2014; Otsyula et al., 1995). However, the picture is less well defined in some other African NHP species. In gorillas and chimpanzees, SIVs tend to be distributed heterogeneously, with high prevalence in certain populations and low prevalence or absence of infection in others (Sharp and Hahn, 2011). There are also several species where the occurrence of SIV infection is quite low, like the greater spot-nosed monkey or the mustached monkey (Aghokeng et al., 2010). Whether this is the result of a more pathogenic outcome of SIV infection in these species, as it is observed with the chimpanzees, or merely lower transmission rates is not currently known. It could also be that there simply has not been enough testing of these species to ascertain the true prevalence of infection. Or, it is possible that prevalence in these species is sporadic, with only particular populations harboring SIV, as is the case with gorillas (Neel et al., 2010). The disparity in SIV prevalence between different African NHP species further illustrates the need for more studies of SIV transmission and pathogenesis in wild natural hosts.

2.4. Baboons and other primates lack species-specific SIVs, despite being African NHPs

Despite the ubiquity of SIVs in the wild, it is important to note that not all African NHPs are in fact natural hosts for SIVs. A significant exception is represented by the different baboon species, which do not carry species-specific SIVs of their own. Instead, the SIVs that are found circulating in baboons are cross-species transmissions of SIVagm from the sympatric AGM populations (Jin et al., 1994b; van Rensburg et al., 1998). Very little is currently known about the pathogenesis of these SIVs in wild baboons. However, it has been shown that when experimentally infected with HIV-2, baboons will progress to AIDS like humans and macaques (Locher et al., 2001, 2003). Accordingly, CCR5 expression on $CD4^+$ T-cells in baboons is similar to the levels expressed in humans and RMs (Pandrea et al., 2007a, 2009). Any other data on SIV-infection in baboons are extremely scarce, even when compared to the research done in other wild African NHPs. Since baboons have long cohabitated the same geographical locations as many SIV-infected NHP species, the lack of information regarding their place in the natural history of SIVs represents an important gap in the knowledge of the field.

Besides baboons, there are several other important African NHP species that have no species-specific SIV: (i) white crowned mangabeys (one study did report SIV infection, but that was in fact a cross species transmission of SIVagm that occurred in captivity) (Tomonaga et al., 1993); (ii) Patas monkeys (which were also reported to be infected with SIVagm, but have no species specific SIV) (Apetrei et al., 2010; Bibollet-Ruche et al., 1996); (iii) Bonobos and two species of chimps (Heuverswyn et al., 2007; Leendertz et al., 2011; Li et al., 2012; Prince et al., 2002). As with the baboons, the question remains how these animals can share habitats with other NHP species harboring SIV and not have their own species-specific virus, given the propensity of SIVs for cross-species transmissions and recombination.

2.5. Horizontal transmission of SIVs in natural hosts is common

Based on the prevalence of SIV-infection of natural hosts in the wild, it can be inferred that horizontal transmission of SIV from one animal to another must be a relatively common event. Horizontal transmission in NHPs has been reported to occur in a variety of ways, including: (i) sexual contact; (ii) biting; (iii) fighting; and (iv) grooming (Cooper et al., 1989; Estaquier et al., 1991; Etienne et al., 2012; Keele et al., 2009a; Ma et al., 2013; Otsyula et al., 1995; Phillips-Conroy et al., 1994; Rudicell et al., 2011; Santiago et al., 2005; Souquière et al., 2001). Compared to HIV in humans, where urogenital mucosal transmission constitutes the major route of horizontal transmission and where oral transmission is remarkably infrequent (apart from transmission during breastfeeding), in NHPs SIV transmission through oral exposure is fairly common (Baggaley et al., 2008; Chenine et al., 2010; Haase, 2011; Ruprecht et al., 1999). Consequently, transmission while grooming or cleaning wounds (i.e., oral exposure) most likely represents a significant route of infection in natural hosts. There have also been multiple descriptions of SIV transmission through biting in captive NHPs (Corbet et al., 2000; Lowenstine et al., 1992; Phillips-Conroy et al., 1994; Rey-Cuillé et al., 1998). Biting was also reported to constitute a route of transmission during fights for dominance between male mandrills in Gabon (Nerrienet et al., 1998). It is important to note that in these cases, whether through grooming or biting, NHPs are being exposed to blood, which typically has a significantly higher VL than breast milk or sexual secretions. This may explain in part why horizontal transmission via the oral mucosa is more frequent in NHPs than humans.

2.6. Vertical transmission of SIVs in natural hosts is rare

Unlike horizontal transmission, vertical transmission, also known as mother-to-infant transmission (MTIT), is exceedingly rare in natural hosts. In humans and macaques, exposure *in utero* or through breastfeeding represent the major routes of MTIT. The rates of MTIT via these routes can be quite high, with 35–40% of infants born to HIV-infected mothers becoming infected, especially if the mothers are acutely infected (Aldrovandi and Kuhn, 2010), and 40–70% of infant RM becoming infected when born to SIVmac-infected dams (Amedee et al., 2004). By comparison, in recent studies of wild vervets in South Africa and Gambia, the rates of MTIT were shown to be only 4–7% (Ma et al., 2013, 2014). Studies of natural hosts housed in various Primate Centers have also found a very low incidence of vertical transmission, supporting the findings of the surveys of animals in the

wild (Chahroudi et al., 2011; Fouchet et al., 2012; Fultz et al., 1990; Ogino et al., 2013; Pandrea et al., 2008b).

One implication of the lack of MTIT in natural hosts is that there must be some evolutionary pressure against vertical transmission in the wild. While further research on this subject is still necessary, one possible explanation is that in the wild natural hosts normally live less than 20 years. Assuming that SIVs originally were pathogenic in their natural hosts and had a time frame for progression to AIDS similar to HIV patients (~10 years from infection until death) or perhaps an even more rapid progression, like in RMs (~2 years from infection until death), a delayed infection occurring only after reaching the age of sexual maturity might have conferred a significant evolutionary advantage. Indeed, given that all the cases of AIDS-like disease occurred in natural hosts in captivity in monkeys that have far exceeded their normal life expectancy, it is possible that such an evolutionary pressure still exists today (Chahroudi et al., 2012; Pandrea et al., 2009; Sodora et al., 2009; VandeWoude and Apetrei, 2006).

3. Horizontal SIV transmission in natural hosts

3.1. Mucosal transmission has only been described at a detailed level in nonnatural hosts

Studying the events following mucosal transmission through sexual contact in wild natural hosts is nearly impossible, for the reasons described above. Much of what is currently known about horizontal SIV transmission via the urogenital mucosa originated from studies of intravaginal transmission of SIVmac in RMs (Cohen et al., 2011; Haase, 2010, 2011). A very recent study also confirmed that the same general events outlined below also occur during penile transmission of SIVmac in RMs (Ma et al., 2016). While some aspects surrounding mucosal transmission have been shown to differ between natural and nonnatural hosts, the studies of mucosal transmission in RMs should provide a good approximation of the general events (Haase, 2011).

From the RM studies, it appears that the very first phase of transmission occurs when the virus crosses the mucosal epithelium and infects a small ‘founder population’ of target cells. This can occur at multiple locations throughout the mucosal site of entry, leading to establishment of ‘foci’ of early virus replication. These foci may appear preferentially where there are higher densities of target cells in the epithelium, though this has only been shown in the RM intravaginal model of transmission (Stieh et al., 2014). The founder $CD4^+$ T-cell populations frequently exhibit markers indicating that they had been previously activated (i.e., still expressing enough CCR5 and transcriptional activators to support SIV infection) but are no longer active or proliferating ($CD69^{neg}$ $CD25^{neg}$ $Ki67^{neg}$), and therefore are referred to as being in a ‘resting’ state (Li et al., 2005).

These ‘resting’ $CD4^+$ T-cells were found to outnumber other resident immune cells types, such as dendritic cells and macrophages, at a ratio ranging between 4–5:1 (Zhang et al., 2004). However, mathematical modeling found that the number of these target cells normally present in the mucosa is not sufficient to sustain viral replication alone. In order to expand, the virus needs new target cells to be recruited to the early foci of replication by the innate inflammatory immune response stimulated by the virus. Following the recruitment of

the target cells and viral expansion, the virus disseminates to the draining lymph nodes, where there is a high enough concentration of $CD4^+$ T-cells to facilitate its rapid expansion. Traveling through the lymphatics, the virus is able to enter the bloodstream through the thoracic duct and spread systemically (Haase, 2011). One implication of this model is that there may be a window of opportunity for intervention prior to recruitment of additional target cells to the site of entry and viral dissemination, when infection is limited to a relatively small number of target cells. However, more research is necessary to test this hypothesis.

3.2. Target cell availability is reduced in the gut in natural hosts, but still correlates with rates of transmission

While most of the detailed knowledge on mucosal transmission comes from the RM intravaginal studies, there has also been significant research done on mucosal sites in natural hosts, particularly at the gastro-intestinal tract mucosa. A study of a large cohort of AGMs of varying ages demonstrated that the numbers of $CD4^+$ $CCR5^+$ cells are very low not only in the blood, but also in the gut and jejunum. A strong mathematical correlation was found between increases in levels of gut $CD4^+$ $CCR5^+$ T-cells and the rate of SIV mucosal transmission in these animals (Ma et al., 2014). Another experimental study established that a 10-fold higher dosage of SIVsab was needed to successfully intrarectally and intravaginally inoculate adult AGMs versus adult PTMs. This reduced susceptibly was correlated with the number of $CD4^+$ $CCR5^+$ T-cells in the rectum, which was shown to be 10-fold lower in the AGMs than PTMs (Pandrea et al., 2012a) (Figure 1).

Considering the extremely high prevalence of SIV infection in the wild, it is apparent that reduction in overall target cell availability in the gut does not coincide with protection of natural hosts from either transmission or $CD4^+$ depletion in the gut associated lymphatic tissue (GALT, see 5.5), though it may render them more resistant to infection (Pandrea et al., 2012a). Therefore, it can be assumed that there may be an alternative effect of this reduction on the course of infection. One possible explanation is that, as CCR5 is a chemokine receptor, reduced expression of CCR5 by the $CD4^+$ T-cells of natural hosts might decrease homing of effector memory cells to the gut, which in turn could reduce immune activation and inflammation (Pandrea and Apetrei, 2010).

3.3. A genetic bottleneck is imposed by the mucosal epithelium on the number of transmitted SIV variants

It has been demonstrated that the mucosal barrier actually acts as a significant obstacle to both SIV and HIV transmission, being difficult to cross, particularly in the vagina, where much of the mucosa is covered by durable stratified layers of squamous cell. However, a recent RM-based study demonstrated that transmission is possible at any location along the female reproductive tract (Stieh et al., 2014). On the other hand, the lower intestinal tract mucosa is formed by a simple columnar epithelium shaped into straight tubular crypts, being much thinner than vaginal mucosa and making the target cells more accessible to the virus. Due to these architectural features, the virus can cross the intestinal mucosa more easily than the vaginal mucosa.

There is also a stochastic barrier to infection at the mucosa, as the overall number of target cells initially available to infect is quite low in RMs and even lower in natural hosts. One consequence of these steep impediments to transmission is a ‘mucosal bottleneck’, where only a small number of transmitted viruses are actually able to go on to establish infection (Haase, 2011; Pandrea et al., 2007a, 2008b).

This genetic bottleneck imposed on transmitted viruses has been documented during mucosal transmission of HIV and SIVmac (Keele et al., 2008, 2009b). The same bottleneck was also reported in AGMs, both in the wild and in captivity (Ma et al., 2014; Pandrea et al., 2012a). In a study of AGMs in captivity, following both intravaginal and intrarectal inoculations with SIVagm, only 1–2 viruses were found to have been transmitted and then establish infection in each animal (Pandrea et al., 2012a). This agrees with the finding of a more recent study, which found that only a single transmitted viral variant established infection in multiple AGMs in the wild (Ma et al., 2014). The similarity of the mucosal bottleneck observed in both natural and nonnatural hosts implies that there is little difference in the way the mucosal epithelium restricts viral transmission.

4. Characteristics of horizontal and vertical transmission through the oral mucosa in natural hosts

4.1. Oral mucosal transmission is generally similar to transmission at other mucosal sites

Several studies in RMs have shown that SIV transmission across the oral mucosa is similar to transmission across other mucosal sites, such as the gut and the vagina (see 3.1). In these studies, both infant and adult RMs were shown to become infected after atraumatic oral inoculation (though a larger dosage of virus was necessary to infect adult RMs versus neonates) (Chenine et al., 2005; Milush et al., 2004). SIVmac was detectable in $CD4^+$ T-cells and macrophages within 4 days post inoculation, with SIV replication being most concentrated in the oral mucosa, esophagus, tonsils and draining LNs. This approximates what was seen in the vaginal transmission studies, with establishment of viral replication at mucosal sites and virus dissemination into the draining lymphatics (Wood et al., 2013). Additionally, a pro-inflammatory response at the mucosa has been reported during oral SIVmac transmission in RMs, which may facilitate target cell recruitment to the site of infection to support early virus replication (Giavedoni et al., 2013).

4.2. Horizontal transmission through the oral mucosa is common in natural hosts, while vertical transmission by the same route is not

As previously mentioned, SIV transmission via the oral mucosa is a far more common route of transmission in wild NHPs than humans. Grooming and biting have been well documented as routes of horizontal transmission in natural hosts, both in captivity and in the wild (Cooper et al., 1989; Estaquier et al., 1991; Etienne et al., 2012; Keele et al., 2009a; Ma et al., 2013; Otsyula et al., 1995; Phillips-Conroy et al., 1994; Rudicell et al., 2011; Santiago et al., 2005; Souquière et al., 2001). This indicates that the oral mucosa is a portal of entry for SIV (through exposure to infectious blood, see 2.5), as well as an active site of viral replication and shedding in natural host. Nevertheless, MTIT during breastfeeding is very rare in natural hosts (see 2.6). Given the fact that the VLs in breast milk in chronically

infected natural hosts are very high (between 10^4–10^6 SIV RNA copies/mL) (Gnanadurai et al., 2010; Ho et al., 2013; Wilks et al., 2011) significantly higher than what is typically seen in the breast milk of HIV-infected humans (Pillay et al., 2000), the very low levels of breastfeeding transmission may appear paradoxical (Permar et al., 2010a; Pillay et al., 2000; Salazar-Gonzalez et al., 2011). However, as discussed below, natural hosts have evolved a number of adaptions that protect them from MTIT, despite massive exposure of the oral mucosa to the virus through breast milk.

4.3. Protection from MTIT and oral transmission during breastfeeding correlates with age in natural hosts

Extensive research has revealed that apart from general resistance to disease progression, natural hosts are also characterized by even greater resistance to SIV infection until they reach the age of sexual maturity (Pandrea et al., 2012a) (Figure 1). This protection is observed both *in utero*, at delivery and during breastfeeding, which is one of the reasons that rates of MTIT remain so low in natural hosts (though high rates of miscarriage were observed in SIV-infected wild mandrills, which might be linked to SIV exposure *in utero)* (Pandrea, unpublished).

A correlation between age and susceptibility to infection was actually shown in one of the very first studies to examine prevalence and routes of transmission in natural hosts. Testing for SIV in wild grivets captured in the Awash National Park in Ethiopia established correlations between serological status for SIV antibodies, age and sex. Both male and female monkeys were seronegative for SIVgri until the age of sexual maturity (Phillips-Conroy et al., 1994). A follow-up study looked at samples collected over a period of two decades from a completely separate group of Ethiopian grivets and reported that, in that particular population, SIV was predominately transmitted by sexual contact, only occasionally by trauma and almost never by MTIT (Jolly et al., 1996). In a similar study examining the SIVgri serostatus in offspring born to SIVgri-infected dams, all the tested infants were seropositive for anti-SIV antibodies at birth, consistent with passive antibody transfer from the mother. However, postnatal antibody titers declined to low levels by 6 months and then to complete negativity by 1 year. As had been observed in the previous studies, the grivets remained seronegative until they reached the age of sexual maturity (Otsyula et al., 1995).

More recent studies looked at wild-caught vervets from multiple locations in South Africa and sabaeus from Gambia (Ma et al., 2013, 2014). These studies not only confirmed that prevalence of SIVagm-infection increased at the age of sexual maturity, but also found that the majority of acute infections (Fiebig Stage II, SIV seronegative animals with VLs above 10^6 RNA copies/mL plasma (Fiebig et al., 2003)) were in juvenile females at the age of the beginning of sexual activity. Of the infant AGMs tested, only 4–7% were found to be SIV-positive. This rate is very low, particularly in light of the fact that over 72% of lactating female dams tested SIVagm-positive and 44% of the infants had passively transferred anti-SIV antibodies (Ma et al., 2013). However, phylogenetic analysis showed that the viruses from the infected infants and juveniles were closely related to those found in adult females, strongly indicating vertical transmission through MTIT (Ma et al., 2013).

SIV prevalence has also been linked to age in wild populations of several other natural host species, including mandrills infected with SIVmnd-1 (Souquière et al., 2001) and SIVsmm-infected SMs (Chen et al., 1996; Fultz et al., 1990; Santiago et al., 2005; VandeWoude and Apetrei, 2006). These studies all demonstrated an age-related increase in SIV prevalence (VandeWoude and Apetrei, 2006). The same was found to hold true in captive animals, as studies of natural hosts housed in various Primate Centers confirmed a very low incidence of vertical transmission, supporting the findings of the surveys of animals in the wild (Chahroudi et al., 2011; Fouchet et al., 2012; Fultz et al., 1990; Ogino et al., 2013; Pandrea et al., 2008b).

Despite the numerous observational studies, to date, there has only been a single study that experimentally tested rates of SIV MTIT transmission in natural hosts (Pandrea et al., 2008b). In this study, mandrill dams were infected on the day of delivery and then allowed to nurse their offspring throughout the lactation period. Infecting the dams immediately after birth precluded any interference from passively transferred maternal antibodies. High VLs were confirmed in the milk and plasma of the dams, particularly during the acute phase of infection, yet none of the breastfed infants became infected. This observation is in contrast to similar studies of postnatal infection of RM dams, where 62–71% of infants became infected during breastfeeding (Amedee et al., 2003, 2004).

While it might be rare, MTIT does occur occasionally in natural hosts in the wild. As mentioned, the vervet study found 4–7% of infants to be SIV-positive. Also, observations of mandrills from Gabon revealed that SIVmnd transmission was more frequent within the same family of animals. While many infections were characteristic of horizontal transmission, possibly through grooming, wound care, or premastication of food, several were shown to be MTIT (Fouchet et al., 2012).

4.4. Oral transmission during breastfeeding in natural hosts does not correlate with virus shedding

It was initially suggested that a relatively low cell-associated VL in breast milk might be responsible for lower MTIT in natural hosts, but further studies in SMs showed little to no difference between SM and RM in milk VLs (Chahroudi et al., 2014; Wilks et al., 2011). It was later shown that while the VLs in breast milk in RMs and humans tends to be 1–2 log lower than plasma VLs, in AGMs plasma and milk VLs are similar (Permar et al., 2010a; Pillay et al., 2000; Salazar-Gonzalez et al., 2011). The aforementioned study of experimentally infected mandrill dames also demonstrated a lack of correlation between viral shedding in breast milk and rates of MTIT, despite the high VLs in breast milk (Pandrea et al., 2008b).

Interestingly, in nonnatural hosts (humans and RMs), plasma and milk virus are genetically similar, whereas in natural hosts milk virus is more compartmentalized and genetically distinct from plasma viral variants (Ho et al., 2013; Permar et al., 2010a; Salazar-Gonzalez et al., 2011; Wilks et al., 2011). This implies that the origin and replication of the virus in plasma *vs.* breast milk might be divergent in natural and nonnatural hosts; however, it is still unclear what implication this has for MTIT.

4.5. Factors in breast milk inhibit oral transmission, but are not unique to natural hosts

Human breast milk contains many factors that have been shown to inhibit HIV infection *in vitro* or are associated with lower rates of MTIT (Philippe Van de Perre, 2012). The long-standing question has been whether natural hosts exhibit additional factors in breast milk that could impair MTIT even more. Recent *in vitro* experiments with TZM-b1 cells showed that both SM and RM milk inhibits SIV infection, though the milk from SMs had a greater impact on the rate of infection. However, the results were somewhat confounded by the fact that SM breast milk contained more of the pro-inflammatory cytokine IL-8, which enhances cell-associated HIV infection. Additionally, there was no significant difference in the levels of antiviral factors, such as IFN-α, IFN-γ, TNF-α, MIP-1α, MIP-1β, RANTES and MDCs, in the milk of natural and nonnatural hosts (Chahroudi et al., 2014).

Besides cytokines and chemokines, antibodies are another factor postulated to play an important role in protecting natural hosts from MTIT. Anti-SIV IgG levels are 1–2 logs lower in the breast milk of SMs and AGMs than in macaques. While this might suggest that antibodies do not influence the rates of MTIT, breast milk IgA concentrations in the SMs and AGMs were shown to be roughly the same as the plasma IgA concentration, whereas milk IgA tends to be 0.5–1 log lower than plasma IgA in RMs and humans (Mabuka et al., 2012; Permar et al., 2010b; Rychert and Amedee, 2005). Interestingly, this trend parallels overall VLs in plasma vs. milk, suggesting that IgA levels might be correlated with virus levels. Furthermore, an SIV neutralizing IgG response was observed in the breast milk of AGMs that was not detected in RMs or humans (Amos et al., 2013; Fouda et al., 2011; Permar et al., 2010b; Wilks et al., 2011). As such, the impact of these milk factors (i.e., cytokines, chemokines and antibodies) on MTIT transmission in natural hosts remains uncertain.

4.6. Reduced target cell availability may protect natural hosts from oral transmission

As natural hosts have reduced availability of $CD4^+$ $CCR5^+$ T-cells (i.e., target cells) at the mucosal sites (see 5.4), target cell restriction at the oral mucosa has been proposed as a mechanism of protection from MTIT (Pandrea et al., 2008b). Infant RMs initially have low populations of $CD4^+$ $CCR5^+$ T-cells at their mucosal sites, but these levels increase dramatically to nearly the levels seen in adult RMs within the first 6 months postpartum (Pandrea et al., 2008b). This supports the observation that the virus challenge needed to infect newborn RM infants was 10-fold higher than the dose needed to infect older infants (Chenine et al., 2005). However, such an increase in $CD4^+$ $CCR5^+$ T-cells could not be observed in AGM infants or juveniles less than 3 years old (Ma et al., 2014; Pandrea et al., 2008b).

A recent study experimentally demonstrated the importance of $CCR5^+$ availability to oral SIV transmission in AGMs. Infant AGMs were orally exposed to high concentrations of SIVsab, while juvenile and adult AGMs were intrarectally inoculated with the same dosage of virus. Following inoculation, none of the infant AGMs became infected, while half of the juveniles and all of the adults were infected. The juveniles that did not become infected were found to have lower levels of $CD4^+$ $CCR5^+$ T-cells in blood and mucosal sites than those that did become infected (Pandrea et al., 2012a).

No study has yet been able to measure the presence of $CD4^+$ $CCR5^+$ T-cells at the oral mucosa in wild natural hosts, given the difficulty of invasive sampling in the field. However, in the recent study of wild AGMs in Gambia, the highest frequency of circulating $CD4^+$ T-cells expressing CCR5 among the infants tested was observed in the blood of the single infant AGM that was infected with SIVagm (Ma et al., 2014).

In the rare instances of MTIT in SMs, the SM infants infected through MTIT exhibited VLs 2 logs lower than those seen in adults, suggesting that only a low number of $CD4^+$ $CCR5^+$ T-cells support viral replication (Chahroudi et al., 2011). This is in contrast to what has been previously observed in human infants, where VLs are very high, sometimes exceeding those seen in adults (Chahroudi et al., 2011). Such an age-related difference in the levels of viral replication was not observed in AGMs (Ma et al., 2014). These results strongly suggest that target cell restriction at the oral mucosa does act to protect natural hosts from MTIT during breastfeeding and possibly until the age of sexual maturity, when the overall counts of mucosal $CD4^+$ $CCR5^+$ cells increase (Pandrea et al., 2008b) (Figure 1).

5. Post-transmission features that may impact SIV pathogenesis in natural hosts

5.1. Natural hosts sustain high levels of viral replication without disease progression

There are a number of features that distinguish natural, nonpathogenic hosts from nonnatural, pathogenic hosts, like macaques and humans (Table 1). Of these, the hallmark characteristic of all natural SIV infections are high levels of SIV replication during both the acute and chronic stages of infection (Brenchley et al., 2012; Diop et al., 2000a; Goldstein et al., 2006; Gordon et al., 2007; Gueye et al., 2004; Kouyos et al., 2010; Onanga et al., 2002, 2006; Pandrea et al., 2005, 2006a, 2008c, 2012a, 2007b; Silvestri et al., 2005; Souquière et al., 2009; Wilks et al., 2011). During the acute infection, the peaks of virus replication in natural hosts are comparable to those seen in untreated HIV-1 and SIVmac infections (Apetrei et al., 2007, 2011; Diop et al., 2000a; Goldstein et al., 2000; Gordon et al., 2007; Gueye et al., 2004; Ma et al., 2013, 2014; Milush et al., 2011; Mir et al., 2012, 2015; Onanga et al., 2002, 2006; Pandrea et al., 2003, 2006a, 2008c, 2012a, 2007b; Schmitz et al., 2012; Silvestri et al., 2005; Souquière et al., 2009; Vanderford et al., 2012). During the chronic infection, VLs in natural hosts tend to be as high or even slightly higher than the VLs seen in pathogenic infections (Pandrea et al., 2006b). Additionally, the chronic viral replication in natural hosts is remarkably stable, whereas it tends to vary widely and increase with disease progression in humans and macaques, thus being predictive of disease progression (Apetrei et al., 2007; Pandrea and Apetrei, 2010; Pandrea et al., 2003, 2008c; VandeWoude and Apetrei, 2006). As viral replication remains virtually unchanged throughout the course of chronic infection in natural hosts, it can be assumed that plasma viremia has no correlation with disease progression. However, in the rare instances where progression to AIDS has occurred in natural hosts, the levels of chronic viral replication were significantly higher (1–2 logs) than normally seen in the majority of naturally SIV-infected animals (Pandrea and Apetrei, 2010; Pandrea et al., 2009).

Though many studies have examined SIV replication in natural hosts in captivity, very limited information is available regarding the levels of viral replication in the wild. The most comprehensive studies to date on virus replication in the wild was performed using samples collected from several hundred wild-caught vervets from South Africa and sabaeus from Gambia (Ma et al., 2013, 2014). In these animals, plasma viremia ranged between 10^4–10^7 copies of SIVagm RNA copies/mL. Note that these numbers represents an average, as the VLs in bulk of the animals tested were fairly consistent, measuring between 10^4–10^5 RNA copies/mL. In both AGM species, approximately 10% of animals tested presented with VLs that were significantly higher (10^6–10^8 RNA copies/mL plasma). The plasma of these animals also tested seronegative for SIV-specific antibodies, suggesting that they were in the Fiebig Stage II of acute SIV infection (Fiebig et al., 2003), particularly since the levels of viral replication were in the same range of the VLs observed during acute infection in captive, experimentally infected AGMs (Ma et al., 2013).

Based on the findings of these studies and on data derived from studies of natural hosts in captivity, it can be reasonably inferred that there is no significant difference in viral replication between wild and captive natural hosts (Pandrea et al., 2006b). One may argue that high levels of viral replication observed may be due to a low virus turnover and not necessarily to high levels of virus replication. However, previous experimental studies have shown that virus turnover is high in SIV-infected AGMs and SMs, higher even than in SIVmac infection (Gordon et al., 2008; Pandrea et al., 2008c).

The higher levels of chronic viral replication observed in the wild AGMs compared to HIV-1 patients (Ma et al., 2013; Pandrea et al., 2003; Sharp and Hahn, 2011), may significantly impact viral transmission in the wild. A plasma viremia of around 1500 RNA copies/mL or higher is associated with significant increase in rates of sexual transmission in humans (Watkins et al., 2008). This is lower than either the average acute or chronic VLs in natural hosts. Assuming that similar virus shedding occurs in the body fluids of humans and NHPs, this would support mucosal exposure through sexual contact as the primary route of transmission in the wild (Ansari and Silvestri, 2014).

5.2. SIV primarily targets $CD4^+$ $CCR5^+$ T-cells during mucosal transmission in natural hosts

For most SIVs, the primary viral binding receptor is CD4, while chemokine receptors such as CCR5 serve as coreceptors (Chen et al., 1997; Gautam et al., 2007; Moore et al., 2004; Zhang et al., 2000). This shared receptor and coreceptor usage indicates that, like HIV, the primary target cells of SIV are $CD4^+$ $CCR5^+$ T-cells (Chen et al., 1997, 1998a; Moore et al., 2004; Pandrea et al., 2007a; VandeWoude and Apetrei, 2006; Veazey et al., 2000). However, while HIV can utilize both CCR5 and CXCR4, most SIVs are limited to only CCR5 as a coreceptor. There are some exceptions to this, as several SIV isolates were reported to also use CXCR4, including SIVmnd-1, SIVsab and several SIVsmm strains (Owen et al., 2000; Pandrea et al., 2005; Schols and De Clercq, 1998). Very recently, SIVsmm and SIVagm strains were reported to utilize CXCR6 as a coreceptor (Elliott et al., 2015; Riddick et al., 2016). It has also been reported that CCR6 and CRK-L3, a natural isoform of CCR6, can act as a coreceptor for both primary HIV and SIVsmm isolates (Islam et al., 2013, 2014). This

suggests that some SIVs may have an expanded cell tropism besides $CD4^+$ $CCR5^+$ T-cells or an expanded range of potential target cells (Elliott et al., 2015; Riddick et al., 2016).

One of the major exceptions to the usage of $CCR5^+$ as a coreceptor by SIVs is SIVrcm, which uses CCR2b as a coreceptor instead of CCR5. This appears to be an evolutionary feature born from necessity, as the majority of red-capped mangabeys (RCMs), the natural hosts of SIVrcm, lack CCR5 entirely. This is because approximately 83% of RCMs have a Δ24 deletion that silences transcription of their *CCR5* gene, making them resistant to viral entry using CCR5 as a coreceptor. This is very similar to the situation in humans, where a small number of people exhibit a Δ32 mutation of their *CCR5* gene that renders them resistant to HIV infection (Samson et al., 1996). Consequently, SIVrcm has adapted to use CCR2 or CCR4 to ensure its continued dissemination throughout the RCM population or persistence upon cross-species transmission (Chen et al., 1998b; Gautam et al., 2009). The usage of CXCR4, CXCR6 and CCR6 coreceptors by some SIVagm and SIVsmm lineages suggests that there might have been similar adaption by these viruses to overcome the naturally low availability of $CD4^+$ $CCR5^+$ target cells in natural hosts (see 5.4).

5.3. Natural hosts maintain peripheral T-cell populations and T-cell function

Despite the high levels of ongoing viral replication during both the acute and chronic infection, another defining feature of SIV-infection of natural hosts is the preservation of peripheral $CD4^+$ T-cell populations during chronic infection (Apetrei et al., 2007; Broussard et al., 2001; Diop et al., 2000b; Gordon et al., 2007; Kornfeld et al., 2005; Ma et al., 2014; Onanga et al., 2002, 2006; Pandrea et al., 2003, 2005, 2006a, 2012a; Silvestri et al., 2003). This is in contrast to pathogenic HIV/SIV infections, where chronic peripheral $CD4^+$ T-cell depletion is associated with disease progression and the development of AIDS (Rodríguez B et al., 2006). However, $CD4^+$ T-cells are depleted during the acute infection in both SIV-infection of natural hosts and HIV/SIVmac infection, with partial restoration of $CD4^+$ T-cell populations by chronic infection (see 5.5) (Li et al., 2005; Mattapallil et al., 2005; Mehandru et al., 2004, 2007; Pandrea and Apetrei, 2010; VandeWoude and Apetrei, 2006; Veazey et al., 1998).

The fact that natural hosts can undergo even a partial depletion of $CD4^+$ T-cells and then maintain high levels of viral replication calls into question how they are able to maintain T-cell function. One possible explanation was derived from studies in SMs, where $CD4^+$ T-cell depletion can occur down to AIDS-associated levels without any clinical consequences (Apetrei et al., 2007; Gordon et al., 2007; Milush et al., 2007, 2011; Sumpter et al., 2007). This preservation of immune function was reported to be due to populations of $CD4^{neg}$ $CD8^{neg}$ T-cells that perform helper cell-like functions following SIV-induced $CD4^+$ depletion (Milush et al., 2011). These double negative T-cells arise through down-regulation of CD4 expression by memory T-cells as they enter the memory pool. The double negative T-cells were shown to be able to carry out a variety of $CD4^+$ T-cell associated functions (production of IL-2 and IL-17, FoxP3 and CD40 ligand expression, MHCII restriction) and are resistant to SIV infection (Beaumier et al., 2009; Vinton et al., 2011). In HIV patients, $CD4^{neg}$ $CD8^{neg}$ cells can also arise from down-regulation, but remain susceptible to infection (Kaiser et al., 2007).

5.4. Natural hosts of SIVs exhibit reduced expression of CCR5 and lower total numbers of $CD4^+$ $CCR5^+$ T-cells at mucosal sites

Another defining characteristic of natural hosts of SIV is the low expression levels of the viral coreceptor CCR5 on $CD4^+$ T-cells, particularly on those residing in the gut. In comparison, nonnatural hosts have high numbers of $CD4^+$ $CCR5^+$ T-cells in the gut and other mucosal sites (Pandrea et al., 2007a, 2008b) (Figure 1). This down-regulation of CCR5 expression specifically occurs for $CD4^+$ T-cells, as CCR5 expression on $CD8^+$ T-cells remains in the same range as in pathogenic hosts (Pandrea et al., 2007a). This low levels of expression of CCR5 by the memory $CD4^+$ T- cells occurs even in the absence of SIV-infection in the natural hosts of SIVs (Pandrea et al., 2007a).

In addition to low expression levels of CCR5, some natural hosts also exhibit an general reduction in the overall $CD4^+$ T-cell counts. While this decrease applies to all tissue compartments, it is even more pronounced at mucosal sites, such as the gut (Pandrea et al., 2006a, 2007a, 2008b, 2012a). This trend only holds true for some species of African guenons (tribe Cercopithecini), i.e., AGMs, patas and sun-tailed monkeys (Pandrea et al., 2006a). SMs and mandrills (tribe Papionini) have been reported to have higher $CD4^+$ T-cell counts, similar to those seen in RMs (Pandrea and Apetrei, 2010).

The observation that natural hosts can have high levels of viral replication, but low levels of $CD4^+$ $CCR5^+$ target cells available to support that replication is one of the major paradoxes of SIV infection in natural hosts. One possible explanation for this is that the level of CCR5 expression by $CD4^+$ T-cells does increase in response to infection in natural hosts, but the effect is masked by simultaneous SIV-induced depletion (Pandrea and Apetrei, 2010). Another potential explanation is that there are other target cells in natural hosts apart from $CD4^+$ $CCR5^+$ T-cells, such as macrophages (Pandrea and Apetrei, 2010). This is somewhat supported by the observation that SIVsab and other SIVs are dual-tropic for CCR5 and CXCR4 (see 5.2). The occurance of giant cell disease in the rare cases of AIDS in natural hosts also supports the infection of monocytes/macrophages during natural infection (Pandrea et al., 2009). However, during acute infection, $CD4^+$ T-cells are most depleted in the gut, where they more frequently express CCR5. The depletion is more limited in blood and LNs, where a higher fraction of $CD4^+$ T-cells express CXCR4. This holds true for infections by both natural (AGMs) and nonnatural (RMs and PTMs) hosts, as well as for HIV infections (Kornfeld et al., 2005; Pandrea and Apetrei, 2010; Pandrea et al., 2007b), strongly suggesting that even in cases where SIVs can employ other coreceptors for infection, $CD4^+$ T lymphocytes will be preferentially targeted.

Apart from their obvious depletion, $CD4^+$ T-cells have been implicated as the major cell type supporting SIV replication by *in situ* hybridization studies showing that SIV RNA colocalizes mostly with $CD3^+$ cells and infrequently with macrophages (Gordon et al., 2008; Pandrea et al., 2008c; Perelson, 2002). Furthermore, when natural hosts experimentally receive ART, the viral decay suggests that the cells predominantly supporting viral replication are short lived, implicating lymphocytes as the principal target cell (Gordon et al., 2008; Pandrea et al., 2008c; Perelson, 2002). Additionally, in a study where $CD4^+$ T-cells were experimentally depleted in naturally SIVsmm-infected SMs using humanized anti-CD4 mAb, VLs decreased sharply in blood, rectal biopsies and bronchoalveolar

lavages, and returned to baseline levels after the $CD4^+$ populations were replenished (Klatt et al., 2008). Conversely, the $CD4^+$ depletion had no effect on macrophages, T regulatory cell or $CD8^+$ T-cell populations, indicating that $CD4^+$ T-cells were the primary cell type supporting viral replication (Klatt et al., 2008). Yet, when $CD4^+$ T cells are depleted or are resistant to the virus (such as cells defective for CCR5 expression, like in RCMs), SIVs will infect macrophages in both progressive and nonprogressive hosts (Avalos et al., 2016; Bernard-Stoecklin et al., 2013; Li et al., 2015; Mir et al., 2015). This is best demonstrated by the fact that both progressive and natural hosts that develop AIDS exhibit giant cell disease, a condition characterized by heavy infiltration of tissues by SIV-infected macrophages (Li et al., 1991; Ling et al., 2004; Pandrea et al., 2009). Macrophage tropism of SIVs is not surprising, since lentiviruses first emerged as macrophage-tropic viruses, as is still the case for lentiviruses infecting other mammal species (Maedi-Visna, equine infectious anemia virus or caprine arthritic encephalitis virus) (VandeWoude and Apetrei, 2006).

5.5. Following depletion, peripheral but not the mucosal $CD4^+$ T-cell populations are restored to near preinfection levels in natural hosts

Both natural and nonnatural hosts undergo a similar massive depletion of mucosal $CD4^+$ T-cells during the acute stage of infection. The primary site of $CD4^+$ T-cell depletion is the gut, specifically the GALT and depletion mainly occurs during the acute stage of infection (Brenchley et al., 2004; Gordon et al., 2007; Li et al., 2005; Mattapallil et al., 2005; Mehandru et al., 2004, 2007; Pandrea et al., 2007b; Smit-McBride et al., 1998; Veazey et al., 1998). Natural hosts experience this depletion in spite of the reduced level of CCR5 expression or lower total number of $CD4^+$ cells (see 5.4) (Pandrea et al., 2007a, 2008b).

What sets natural and nonnatural hosts apart are the immunological events following depletion of mucosal $CD4^+$ T-cells (Table 2). In untreated HIV patients and pathogenic SIV infections, the peripheral $CD4^+$ T-cell populations will eventually decline without intervention, leading to the development of AIDS. The scenario in natural hosts is quite different, with recovery of the peripheral $CD4^+$ T-cells population to nearly baseline levels by the chronic infection. Additionally, the GALT-associated $CD4^+$ T-cells partially recover, despite the robust chronic viral replication, though GALT $CD4^+$ T-cells populations never recover fully to preinfection levels (Chahroudi et al., 2012; Haase, 2010; Pandrea and Apetrei, 2010; Sodora et al., 2009). Most of this recovery following acute infection consists of restoration of central memory and naïve T-cells, while effector memory T-cells remain depleted (Pandrea et al., 2007b). This partial recovery is possible in natural hosts because of the control of immune activation and apoptosis (see 5.6), which prevents excessive depletion of the overall $CD4^+$ T-cells population, with the loss due to viral replication being compensated by a normal production of cells (Pandrea and Apetrei, 2010).

After their restoration, $CD4^+$ central memory cells (T_{CM}) are lost in SIVsmm-infected SMs at rates 20 times slower than those of SIV-infected RMs (McGary et al., 2014). This translates to a half-life of total T_{CM} populations <16 months for RMs, but >17 years for SMs, which is in agreement with the rare cases of AIDS in natural hosts in very old animals. Also, SM $CD4^+$ T_{CM} proliferation levels are lower than in RMs and the RM T_{CM} proliferation correlates with viral replication (McGary et al., 2014). Yet, a recent study of

mandrills in Gabon found a significant decrease in memory T-cells populations that was correlated with the duration of infection (Greenwood et al., 2014). However, other studies of the same mandrill cohort did not find similar features (Apetrei et al., 2011).

Besides central memory T-cells, other cell types are also preserved in natural hosts and show divergent dynamics between SIV-infected RMs and SMs. Notably, memory $CD4^+$ T-cells with stem cell-like properties (T_{SCM}) undergo depletion and exhibit increased rates of proliferation and high levels of virus infection in RMs. Conversely, SMs $CD4^+$ T_{SCM} cell populations remained stable, showed no marked increase in proliferation, and had very low rates of direct infection. As T_{SCM} are known to be able to differentiate into central, effector and naïve T-cells, their homeostasis could be crucial to restoration of T-cell populations following depletion in natural hosts (Cartwright et al., 2014; Chahroudi et al., 2015).

5.6. Natural hosts control chronic immune activation, proliferation, and interferon production

One of the most striking features of the SIV infection in natural hosts is their ability to control their levels of chronic immune cell activation. This is reflected by the expression of HLA-DR and CD69 (both markers of immune cell activation) on T-cells, predominately $CD8^+$ T-cells, in natural hosts, which increase slightly during acute infection and returns to baseline levels by chronic infection. In pathogenic infections, the expression levels of these activation markers by T-cells rise dramatically during the acute infection and are never resolved during the chronic infection, being correlated with disease progression (Diop et al., 2000b; Gordon et al., 2007; Kornfeld et al., 2005; Milush et al., 2007; Onanga et al., 2006; Pandrea et al., 2003, 2005, 2006a, 2008c, 2007b; Ploquin et al., 2006; Silvestri et al., 2003; Souquière et al., 2009). Also, expression of PD-1, a cell surface protein that acts as a negative regulator of the immune activation, was found to be rapidly induced in the lymphatic tissue in SMs in response to SIV-infection. This was associated with resolution of acute immune activation and the preservation of $CD4^+$ populations and lymphatic tissue structure (Estes et al., 2008). Resolution of this aberrant, persistent immune activation during the transition from acute-to-chronic infection is therefore thought to be the major mechanism by which natural hosts avoid progression to AIDS (Bosinger et al., 2009, 2011; Estes et al., 2008; Harris et al., 2010; Jacquelin et al., 2009; Pandrea et al., 2007b). However, it should be noted that suppression of the control of immune activation at the transition from acute-to-chronic infection and maintenance of high levels of immune activation throughout the first six months of infection did not result in major alterations of the later stages of chronic infection (Pandrea and Apetrei, unpublished).

Similar to immune cell activation, T-cell proliferation increases only during the acute infection in natural hosts (Gordon et al., 2007; Milush et al., 2007; Muthukumar et al., 2005; Pandrea et al., 2007b; Silvestri et al., 2005). By the chronic phase of infection, proliferation levels return to near their preinfection state (Chakrabarti et al., 2000; Kaur et al., 2008; Muthukumar et al., 2005). This can be observed as a transient increase in expression of the proliferation marker Ki-67 during the acute infection and early chronic infection in AGMs, with return to baseline by late chronic infection (Li et al., 2005; Pandrea et al., 2007b). Conversely, in pathogenic infections, T-cell proliferation continues to increase to the point of

excessive cell turnover, likely in an attempt to recover from the depletion of $CD4^+$ T-cells (Grossman et al., 2006; Picker et al., 2004).

Another point of divergence between natural and nonnatural hosts during SIV infection is seen in the production of interferons. A strong and sustained Th1-mediated type I and type II interferon response was observed in the LNs of pigtailed macaques (PTMs) infected with SIVsab, which is pathogenic in PTMs. In contrast, only a transient type I interferon response occurred in SIVsab-infected AGMs, which was resolved after peak viral replication (Lederer et al., 2009). Furthermore, experimental administration of high concentrations of the type I IFN-α to acutely infected AGMs had no impact on immune activation (Jacquelin et al., 2014). Taken together, natural hosts seem to possess the ability to maintain homeostasis of their immune cell populations and resolve immune activation, proliferation and IFN production after the acute SIV infection.

5.7. $CD8^+$ T-cells do not contribute significantly to the prevention of disease progression

The current data indicates that the general $CD8^+$ T-cell populations and their SIV-specific responses are comparable in both infected and uninfected AGMs and RMs (Reina et al., 2009; Schmitz et al., 2009; Zahn et al., 2008, 2010). However, the role that $CD8^+$ T-cells play in different natural host species becomes unclear when looking at the dynamics of viral replication following experimental depletion of $CD8^+$ T-cells. In chronically SIVmac-infected RMs, experimental $CD8^+$ cell depletion results in a 1–3 log increase in plasma viremia (Jin et al., 1999; Schmitz et al., 1999). In contrast, $CD8^+$ depletion in chronically SIVsmm-infected SMs seem to have very little impact on viral replication, though one study did show an increase in VLs following $CD8^+$ depletion (Barry et al., 2007; Wang et al., 2006). Similarly, $CD8^+$ T-cell depletion during acute infection did not increase the peak VLs in AGMs, but it did lead to a plateau of viral replication following peak infection until the $CD8^+$ populations were restored. These findings, along with those of other studies on cellular immune responses in natural hosts, indicate that $CD8^+$ T-cells do play a role in controlling viral replication to some extent (Kaur et al., 2001; Wang et al., 2006; Zahn et al., 2008). However, none of the *in vivo* depletion experiments had any effect on the actual state of disease progression (Barry et al., 2007; Gaufin et al., 2010). This is in contrast to $CD8^+$ depletion in RMs, which results in increased $CD4^+$ T-cell proliferation and rapid disease progression (Okoye et al., 2009). Consequently, it remains unclear what impact, if any, $CD8^+$ T-cells play in preventing disease progression in natural hosts.

5.8. Natural hosts maintain function of immune cell populations

Apart from the changes in $CD4^+$ and $CD8^+$ T-cell populations, natural hosts also maintain normal populations and functions of a variety of other immune cell subsets, such as NK cells, Th17 T-cells, regulatory T-cells (Tregs), γδ T-cells and mDCs. In contrast, disturbances in these cell populations have been described during pathogenic HIV and SIV infections (Barratt-Boyes and Wijewardana, 2011; Brenchley et al., 2006a, 2008; Favre et al., 2009; Grossman et al., 2006; Wijewardana et al., 2013; Xu et al., 2014). Preservation of these secondary immune cell populations could impact protection from disease progression in natural hosts in a number of ways. For instance, there is evidence to support that maintenance of the Th-17/Treg ratio may be crucial to preventing disease progression and

maintaining the integrity of the mucosal barrier during acute infection (Brenchley et al., 2008; Favre et al., 2009). Moreover, preserving Treg homeostasis might confer protection through production of anti-inflammatory cytokines, such as IL-10, or by prevention of excess $CD4^+$ T-cell proliferation following the initial $CD4^+$ depletion in the gut (Pandrea and Apetrei, 2010). Expression of the Treg marker FoxP3 was reported to increase along with anti-inflammatory cytokine production, suggesting that Tregs might play an important role in establishing the anti-inflammatory response (Kornfeld et al., 2005). Tregs are rapidly depleted in the intestines of neonatal RMs infected with SIVmac, supporting the role of the loss of Tregs in pathogenic disease progression (Wang et al., 2015).

In addition to maintaining the homeostasis of Tregs, preventing dysfunction of γδ T-cells may play a crucial role in averting disease progression, as apart from cytokine production, γδ T-cells also perform a variety of other functions, including regulation of tissue healing (Kosub et al., 2008; Vantourout and Hayday, 2013). In HIV infection, it has been shown that γδ T-cells become anergic and can no longer migrate in response to pro-inflammatory cytokines (Martini et al., 2002; Poggi et al., 2004). In contrast, γδ T-cells remain fully functional in SMs (Brenchley et al., 2006a; Milush et al., 2007). It was also shown that γδ T-cells in SMs retain their ability to produce the Th1 cytokines TNF-α and INF-γ postinfection, while this capacity was reduced in γδ T-cells from HIV-infected subjects, along with the overall numbers of γδ T-cells (Kosub et al., 2008). Given the importance of controlling inflammation during primary infection (see 5.10 and 5.11), preservation of regulatory cell populations like Tregs and γδ T-cells likely plays an important role in the prevention of disease progression in natural hosts.

5.9. The humoral response plays little to no role in controlling viral replication following mucosal transmission

The humoral response in SIV-infected natural hosts has been shown to be similar to or lower than what has been reported in pathogenic infections (Gaufin et al., 2009; Gicheru et al., 1999; Hirsch, 2004; Souquière et al., 2009). However, a paucity of SIV Gag-specific antibodies is a shared feature of SIV-infected natural hosts. Oddly, the T-cell response to Gag in natural hosts is comparable to those seen in pathogenic infections, meaning that the absence of anti-Gag antibodies is not due to a lack of Gag-specific T-cells (Reina et al., 2009). Furthermore, some SIVs, like several SIVsmm strains, are actually resistant to antibody neutralization, making it unclear what effect antibodies might have on SIVs (Gautam et al., 2007). Further complicating the situation, experimental depletion of $CD20^+$ B-cells had no effect on either viral replication or disease progression in AGMs, even after the depletion was maintained in our studies for over 6 months (Gaufin et al., 2009; Schmitz et al., 2009). Similarly, in a pair of studies that sought to suppress the adaptive immune response through simultaneous depletion of $CD8^+$ and $CD20^+$ cells during primary SIV infection, the depletion caused no alteration in the state of disease progression in AGMs. In contrast, SIVagm-infected PTMs rapidly progressed to AIDS when both $CD8^+$ and $CD20^+$ populations were depleted (Schmitz et al., 2009; Zahn et al., 2010). In summation, these results strongly suggest that the role of the adaptive immune response in natural hosts is minimal at best and likely has little to do with preventing disease progression.

5.10. Damage to the gut epithelium occurs in both natural and nonnatural hosts, but is quickly resolved in natural hosts

Perhaps one of the most important differences between SIV infection in natural and nonnatural SIV hosts and the one that might play the biggest role in avoiding persistent immune activation is the lack of chronic damage to the gut epithelium in natural hosts. In nonnatural, pathogenic hosts (i.e., humans and RMs), this damage is a consequence of early viral replication, which causes disruption of the gut epithelium and dysregulation of epithelial cell homeostasis (Mohan et al., 2013). The result is damage to the gut epithelium, which allows leakage of microbes and microbial products from the gut lumen into the surrounding tissue, a process known as microbial translocation (MT). Once outside the lumen, microbial antigens bind to Toll-like receptors, stimulating chronic aberrant immune activation. This, in turn, not only creates more available target cells for the virus, but also functionally exhausts the immune system and its capacity for regeneration (Brenchley and Douek, 2012; Brenchley et al., 2006b, 2006b; Gordon et al., 2007; Pandrea et al., 2007b).

It is important to note that natural hosts do sustain some damage to their gut epithelium during the early stages of SIV infection. However, this damage is transient and is rapidly reversed, with no leakage from the lumen of the gut. This is reflected by the absence of bacterial lipopolysaccharide (LPS) in the plasma during both the acute and chronic stages of SIV infection in AGMs (Pandrea et al., 2007b). The importance of avoiding MT was highlighted by two studies where experimentally administration of LPS to AGMs induced general immune activation followed by $CD4^+$ T-cell depletion and an increase in VLs (though there was ultimately no impact on disease progression) (Pandrea et al., 2008d, 2012b). In another study, we administered dextran sulphate, a drug that is directly toxic to intestinal epithelial cells and is known to impair the integrity of the mucosal barrier, to AGMs. This resulted in increases in plasma SIV RNA, sCD14 (see below), CRP and LPS levels, along with loss of mucosal $CD4^+$ T-cells (Hao et al., 2015). Conversely, when acutely SIV-infected PTMs were treated with sevelamer, an LPS chelator, in the gut, the treatment resulted in a dramatic reduction in both inflammation and immune activation, directly demonstrating the significance of MT on SIV pathogenesis (Kristoff et al., 2014).

As the bulk of data regarding MT in natural hosts was derived from studies of animals in captivity, a recent study sought to examine whether or not natural hosts were able to avoid MT in the wild. Because direct measurement of mucosal integrity in wild natural hosts would have been virtually impossible, the sCD14 protein was used as a surrogate marker for MT. CD14 is a coreceptor for LPS expressed by peripheral blood monocytes and tissue macrophages. After LPS stimulation, $CD14^+$ monocytes/macrophages secrete sCD14 and shed surface CD14, which then bind to LPS (Brenchley and Douek, 2012). We did not find any difference in plasma sCD14 levels between wild SIV-positive and SIV-negative vervets and sabaeus (Ma et al., 2013, 2014). These results are in agreement with studies of experimentally infected AGMs, where sCD14 levels remained stable following infection (Pandrea et al., 2006b, 2012a, 2012a, 2007b). A separate study of semi-wild mandrills in Gabon confirmed these results by showing that plasma levels of sCD14 remained unchanged following SIVmnd1-infection (Greenwood et al., 2014).

5.11. Resolution of damage to the gut and prevention of MT primarily hinges on control of apoptosis and establishment of a rapid anti-inflammatory response

The precise means by which natural hosts avoid chronic damage to their gut and the associated MT is still somewhat uncertain. $CD4^+$ T-cell apoptosis levels in natural hosts do not increase significantly during acute or chronic infection (Cumont et al., 2008; Estaquier et al., 1994; Hurtrel et al., 2005; Meythaler et al., 2009; Pandrea et al., 2007b; Silvestri et al., 2003). However, transient $CD8^+$ apoptosis occurs in both natural host and pathogenic hosts (Meythaler et al., 2009). Lack of increased apoptosis of both gut lymphocytes and epithelial cells may contribute to the preservation of the integrity of the gut epithelium (Pandrea and Apetrei, 2010).

Another important mechanism reported to contribute to the preservation of the integrity of the gut epithelium is the establishment of an anti-inflammatory milieu early during infection that represses the effects of pro-inflammatory cytokines. Both natural and nonnatural hosts exhibit increased expression levels of pro-inflammatory cytokines (IFN-γ,TNF-α, IL-1β, IL-12) following infection, albeit at a somewhat lower level in natural hosts. These cytokines are produced by both immune and epithelial cells as part of the innate immune response to viral replication following transmission (Diop et al., 2008; Hirao et al., 2014; Lu et al., 2014; Mandl et al., 2008; Pandrea and Apetrei, 2010). However, this increase is only transient in natural hosts; following acute infection, expression of pro-inflammatory cytokines return to preinfection levels. In HIV-infected patients and SIVmac-infected RMs, pro-inflammatory cytokine production persists into chronic infection, stimulating chronic inflammation and, in turn, immune activation (Kornfeld et al., 2005; Milush et al., 2007; Ploquin et al., 2006). Resolution of this initial pro-inflammatory response to the virus seems to depend on establishment of the anti-inflammatory milieu early during infection of the natural host. This is reflected in a rapid increase in expression of the anti-inflammatory cytokines TGF-β and IL-10 following SIVagm infection of AGMs (Kornfeld et al., 2005). Furthermore, a recent study in RMs established a correlation with internalization of the IL-10 receptor (i.e., lowered responsiveness to IL-10) by mucosal lymphocytes in the gut epithelium with increased levels of apoptosis (Pan et al., 2014).

6. Conclusions

The study of SIV infection in African NHPs that are natural hosts of SIVs has already dramatically contributed to the new paradigm of the pathogenesis of HIV infection; namely, that control of chronic immune activation and inflammation could significantly improve the prognostic, survival and quality of life of chronically HIV-infected patients. But there are many other lessons that can be learned from the study of natural SIV infection in natural hosts, notably with regards to control of virus transmission. In this environment of high rates of SIV transmission despite target cell restriction at the mucosal sites of entry, control of virus transmission to the offspring is remarkable and needs to be investigated to design and implement new strategies for preventing MTIT in humans.

Perhaps the most important lesson that the study of SIV infection in natural hosts should teach us is that it might be more productive to shift our focus from preventing infection to preventing the deleterious consequences of infection. Millions of year of coevolution drove

virus-host coadaptation in natural hosts in this direction. Instead of attempting to overcome transmission (which is a Catch-22, where any increase in immune cell effectors results in increases of target cells and consequently fuels transmission), natural hosts developed a tempered ignorance of the virus in which multiple pathways and mechanisms lead to a nonprogressive, albeit very active, “Well-Tempered SIV infection”. Similar to its musical counterpart, “The Well-Tempered Clavier”, SIV infection in the natural hosts is a masterpiece of evolution that is perfectly tuned, and designed to last forever.

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Abbreviations

AGMs	African green monkeys
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
GALT	gut associated lymphatic tissue
HIV	human immunodeficiency virus
LPS	lipopolysaccharide
MT	microbial translocation
MTIT	mother-to-infant transmission
NHPs	nonhuman primates
PTMs	pig-tailed macaques
RCM	red-capped mangabeys
RMs	rhesus macaques
SIV	simian immunodeficiency virus
SMs	sooty mangabeys
T_{CM}	central memory T cells
Tregs	regulatory T cells

T_{SCM}	memory T-cells with stem cell-like properties
TLRs	Toll-like receptors
VL	viral loads

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Highlights

- Over 40 species of African nonhuman primates carry species-specific SIVs
- SIV prevalence in the wild is very high in most of the natural host species
- SIV horizontal transmission is efficient in spite of low levels of mucosal target cells
- Maternal-to-infant transmission is rare in spite of massive offspring exposure to SIV
- Natural hosts of SIVs generally do not progress to AIDS
- Control of immune activation is the key factor behind lack of disease progression

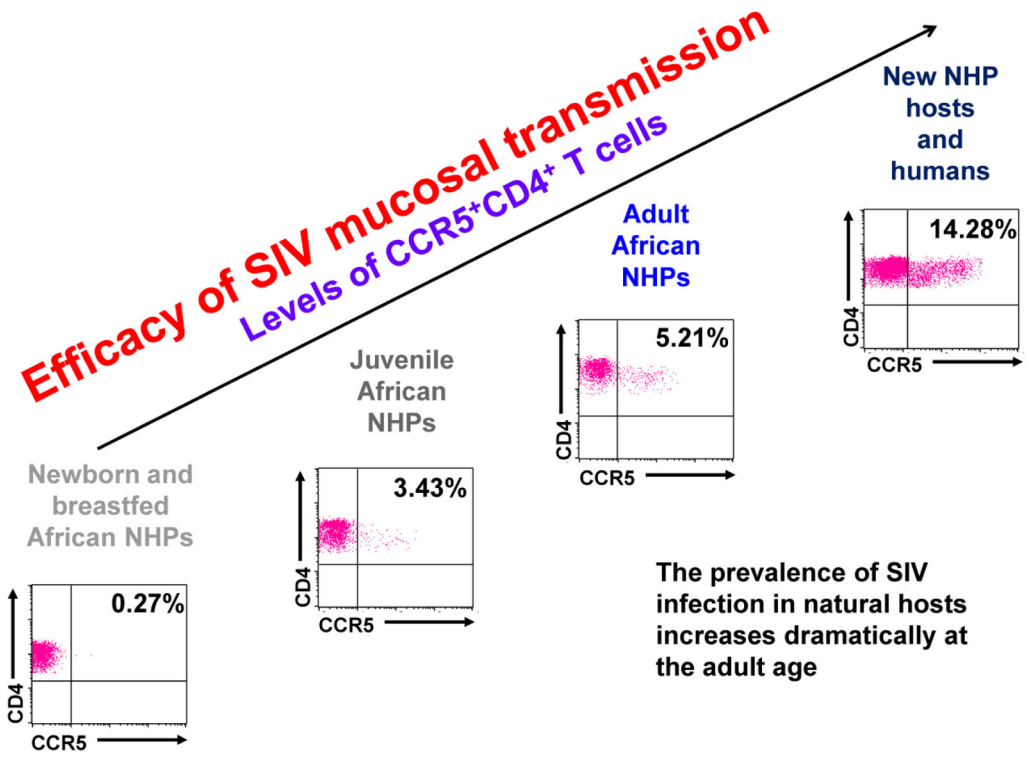

Figure 1. Studies in natural hosts of SIVs lead to the hypothesis that susceptibility to SIV/HIV transmission is proportional to the levels of $CD4^+$ T-cells expressing $CCR5^+$ at the mucosal sites, which are higher in nonnatural hosts than natural hosts and are also correlated with age

Each separate graphic represents flow cytometry gating for total gut $CD4^+$ $CCR5^+$ T-cells in the respective hosts, with the total percent population of the $CD4^+$ $CCR5^+$ T-cells given in the right hand corner.

Table 1

Comparative Pathogenesis Features with Impact on SIV/HIV Transmission in Natural versus Pathogenic Hosts

Feature	Natural Hosts	Asian NHPs	Humans
Horizontal Transmission	Frequent	Frequent	Frequent
Vertical Transmission	Rare	Frequent	Frequent
Genetic bottleneck at transmission	Yes	Yes	Yes
Acute plasma viremia	+++	+++	+++
Chronic plasma viremia	High, stable	Progressive	Progressive
Primary target cells	$CCR5^+$ $CD4^+$ T cells	$CCR5^+$ $CD4^+$ T cells	$CCR5^+$ $CD4^+$ T cells
CCR5 expression on $CD4^+$ T cells (periphery)	+	+++	+++
CCR5 expression on $CD4^+$ T cells (mucosal)	+	+++	+++
Maturation of CCR5 expression on $CD4^+$ T cells	Adult age	6–9 months	5–6 years
Breast milk VLs	+++	++	++
Inhibitory breast milk factors	Yes	Yes	Yes

Table 2

Pathological and Immunological Features of Lentiviral Infections in Natural versus Pathogenic Hosts

Feature	Natural Hosts	Asian NHPs	Humans
Progression to AIDS	No	Yes	Yes
Hypercoagulability	No	Yes	Yes
Comorbidities	Rare	Yes	Yes
Virus cytopathy	Yes	Yes	Yes
Acute damage to gut epithelium	Yes	Yes	Yes
Microbial translocation	No	Yes	Yes
Acute immune activation	Yes	Yes	Yes
Acute anti-inflammatory milieu	Yes	No	No
Interferon response	Acute only	Yes	Yes
T-cell proliferation	Acute only	Yes	Yes
Chronic immune activation	No	Yes	Yes
Chronic inflammation	No	Yes	Yes
Peripheral $CD4^+$ T-cell depletion	Acute only	+++	+++
Mucosal $CD4^+$ T-cell depletion	++	+++	+++
$CD4^{neg}CD8^{neg}$ resistance to infection	Yes	No	No
$CD4^+$ Th17-cell depletion	No	Yes	Yes
T_{scm} depletion	No	Yes	Yes
$CD8^+$ T-cell response	Yes	Yes	Yes
$CD20^+$ B-cell response	Yes	Yes	Yes
Treg homeostasis	Yes	No	No
γδ T-cell anergy	No	Yes	Yes