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Review

Key Viral Adaptations Preceding the AIDS Pandemic

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HIV, the causative agent of AIDS, has a complex evolutionary history involving several cross-species transmissions and recombination events as well as changes in the repertoire and function of its accessory genes. Understanding these events and the adaptations to new host species provides key insights into innate defense mechanisms, viral dependencies on cellular factors, and prerequisites for the emergence of the AIDS pandemic. In addition, understanding the factors and adaptations required for the spread of HIV in the human population helps to better assess the risk of future lentiviral zoonoses and provides clues to how improved control of viral replication can be achieved. Here, we summarize our current knowledge on viral features and adaptations preceding the AIDS pandemic. We aim at providing a viral point of view, focusing on known key hurdles of each cross-species transmission and the mechanisms that HIV and its simian precursors evolved to overcome them.

Introduction

Since the discovery that acquired immune deficiency syndrome (AIDS) is caused by a retrovirus (Barre-Sinoussi et al., 1983), the origin of human immunodeficiency virus (HIV) has been intensively studied. It soon became clear that there are two different types of HIV, termed HIV-1 and HIV-2. These share the same morphology and tropism for CD4+ T cells but are genetically and antigenically distinct (Clavel et al., 1986). A related virus was first identified in captive macaques suffering from AIDS-like symptoms (Daniel et al., 1985). Subsequently, simian immunodeficiency viruses (SIVs) closely related to HIV-1 and HIV-2 were detected in chimpanzees and sooty mangabeys, respectively (Gao et al., 1999; Hirsch et al., 1989). It also became clear that macaques are not a natural host of SIV but were infected by accidental cross-species transmission of SIVsmm from sooty mangabeys at U.S. primate centers (Apetrei et al., 2005). Notably, SIV infection of macaques is associated with rapid development of AIDS-like disease and commonly used as a model for HIV pathogenesis and vaccine development. Follow-up studies revealed that SIVs are present in more than 40 non-human primate species from sub-Saharan Africa (Bell and Bedford, 2017; Sharp and Hahn, 2011). Nonetheless, to our current knowledge, only three primate species (chimpanzees, gorillas, and sooty mangabeys) have transmitted their viruses to humans (Figure 1A). Four independent transmission events of SIVcpz and SIVgor from chimpanzees and gorillas to humans gave rise to HIV-1 groups M, N, O, and P (Sharp and Hahn, 2011). HIV-2 groups A through I originated from nine zoonotic transmissions of SIVsmm infecting sooty mangabeys (Ayouba et al., 2013). Importantly, only HIV-1 group M is pandemic, accounting for >98% of all human infections (Sharp and Hahn, 2011). More and more studies show that successful zoonotic transmission of a virus is difficult, depending on a variety of viral, cellular, and environmental factors (Figure 1B). For example, the precursors of HIV-1 had to overcome numerous hurdles to cross the species barriers from monkeys to great apes and ultimately to humans. Here, we discuss the evolutionary history of HIV with a focus on the adaptations preceding the emergence of pandemic HIV-1 M strains and their potential consequences for viral transmission fitness and pathogenicity.

SIVs in African Monkeys

The apparently sudden emergence of HIV-1 and initial phylogenetic analyses of HIV and SIV suggested that primate lentiviruses might have a recent origin, just a few hundred years ago (Wertheim and Worobey, 2009). However, while the extremely high mutation rates of these viruses facilitate the reconstruction of recent events, such as the emergence of HIV-1, they preclude a reliable analysis of their distant evolutionary history (Holmes, 2001; Sharp et al., 2000). Studies of monkeys on Bioko, a geographically isolated island off the Cameroonian west coast, show that SIVs have infected non-human primate species for at least 32,000 years but most likely much longer (Worobey et al., 2010). In fact, the presence of endogenous "prosimian" viruses in lemurs suggests that lentiviruses have been infecting primates for millions of years (Gifford et al., 2008; Gilbert et al., 2009). Moreover, selection and evolution of host genes, due to pressure exerted by pathogenic lentiviruses, indicate that primate lentiviruses have been present in African species for 5–10 million years (Compton and Emerman, 2013; Compton et al., 2013; McCarthy et al., 2015). To date, primate lentiviruses have only been detected in African non-human primate species, suggesting that SIVs invaded them after the divergence of African and Asian monkeys.

Primate lentiviruses show high sequence divergence, but all share a set of at least eight genes: *gag*, *pol*, and *env*, encoding structural and enzymatic proteins; *tat* and *rev*, encoding essential regulatory proteins; and three so-called accessory genes, *vif*, *vpr*, and *nef*. Of the latter, *vif* is the evolutionarily most ancient gene and is also present in the genomes of the bovine, feline, and ovine-caprine groups of lentiviruses (Gifford, 2012). HIV-1 and its closest simian counterparts contain an additional gene encoding the viral protein U (Vpu) (Figure 2). The origin of *vpu* is unclear but it was most likely acquired by a common ancestor of SIVgsn, SIVmon, and SIVmus infecting greater spot-nosed, mona, and

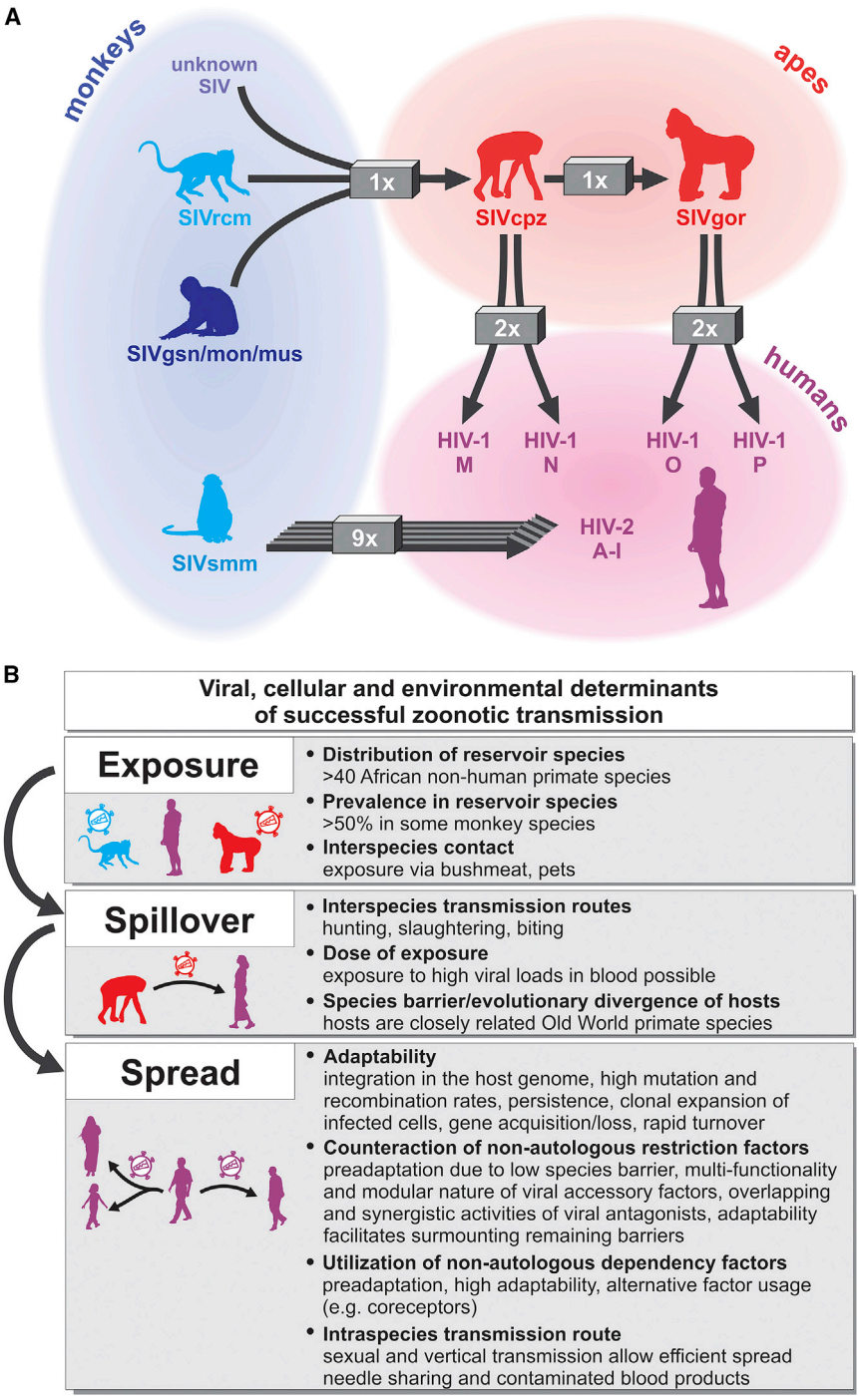

Figure 1. Cross-Species Transmission Events Preceding the Emergence of HIV-1 and HIV-2 and Determinants of Cross-Species Viral Transmission

(A) SIVcpz in chimpanzees is the result of recombination events between three different SIV strains. Besides an unknown SIV strain, recombination involved a precursor of today's SIVgsn/mon/mus clade infecting *Cercopithecus* monkeys and possibly a precursor of today's SIVrcm from red-capped mangabeys. The chimpanzee virus was subsequently transmitted to gorillas and humans, giving rise to SIVgor and HIV-1 groups M and N, respectively. HIV-1 groups O and P are the result of two zoonotic transmission events of SIVgor, while SIVsmm infecting sooty mangabeys was transmitted to humans on at least nine occasions, resulting in the emergence of HIV-2 groups A through I.

(B) The boxes summarize determinants of successful primate lentiviral cross-species transmission.

SIV replication and transmission in their natural hosts is largely unknown.

Phylogenetic analyses support long-term coevolution of SIVs with some of their respective hosts, and host-specific clustering suggests that many SIV transmissions occur among members of the same species. However, there is also evidence for at least 14 cross-species transmissions and 13 recombination events between different lineages of SIV (Bell and Bedford, 2017). Notably, the ability of primate lentiviruses to cross species barriers seems to vary. For example, SIVcol infecting colobus monkeys is evolutionarily isolated, whereas SIVs from African green monkeys seem to frequently cross species borders (Ayouba et al., 2015; Bell and Bedford, 2017). In general, however, cross-species transmissions are relatively rare, although the enormous variability of primate lentiviruses, their ability to integrate into the host genome, and the acquisition of versatile modular tools to counteract antiviral factors are powerful means facilitating successful cross-species transmission.

SIVs are currently widespread in sub-Saharan Africa and found in more than half of all African ape and monkey species. Their prevalence varies enormously, ranging from $\leq$1% for SIVgsn/mus/mon infecting closely related *Cercopithecus* species to $\geq$50% for SIVsmm, SIVtan, SIVlst, SIVsun, and SIVblu found in sooty mangabeys, tantalus monkeys, L'Hoest's monkeys, sun-tailed monkeys, and blue monkeys, respectively (Aghokeng et al., 2006, 2010; Beer et al., 2000; Santiago et al., 2005). Importantly, it is thought that most SIVs replicate to high levels in their natural simian hosts without causing disease (Chahroudi et al., 2012). However, experimental

mustached monkeys, respectively (Bailes et al., 2003; Takeuchi et al., 2015). Some SIVs infecting mangabeys, drills, and mandrills (i.e., the *Papionini* tribe of monkeys) as well as HIV-2 contain a *vpx* gene. *Vpx* is structurally related to Vpr and most likely originated from the acquisition of a heterologous *vpr* gene by recombination (Etienne et al., 2013; Sharp et al., 1996). The mechanisms underlying the function of the accessory viral factors have been studied in detail, but their relevance for

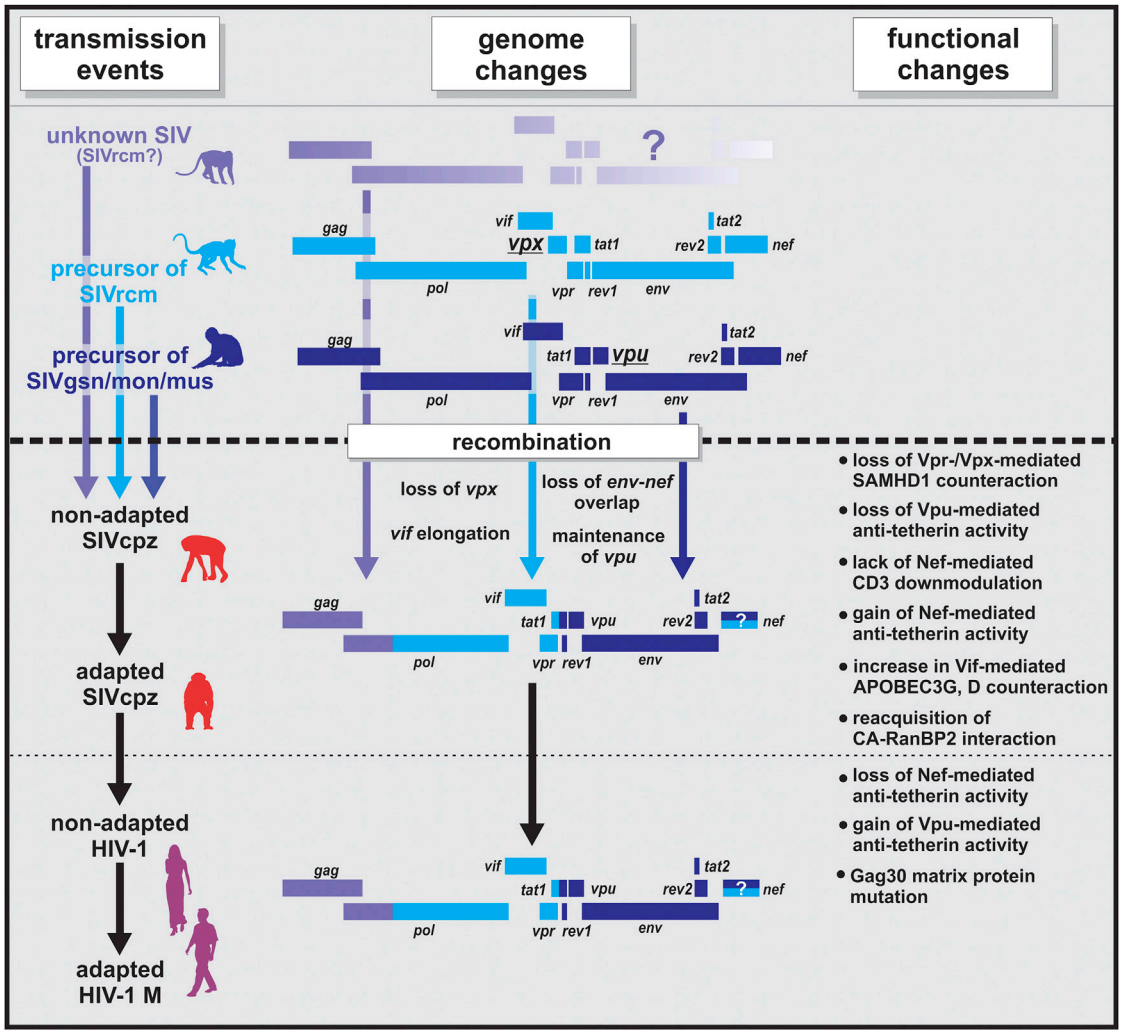

Figure 2. Genomic and Functional Changes during the Evolution of Pandemic HIV-1 M
Several transmission events (left), genome rearrangements (middle), and functional changes (right) preceded the emergence of HIV-1. For example, the tripartite genome structure of HIV-1 is the result of recombination events that coincided with loss of the accessory gene *vpx*, elongation of the *vif* coding sequence, and loss of the *env-nef* overlap. These genome alterations were associated with host-specific adaptations to virus-dependency factors and restriction factors that enabled successful replication and spread upon cross-species transmission of the virus.

evidence mainly comes from studies of SIVsmm, SIVagm, and SIVmnd, and some fitness effects of SIVs on wild animals cannot be ruled out. Most notably, it has been shown that SIVcpz causes AIDS-like disease in wild chimpanzees (Keele et al., 2006, 2009). Moreover, signatures of positive selection in antiviral host genes imply that, at least in the past, primate lentiviruses had negative fitness effects on their hosts (Compton et al., 2012, 2013).

Acquisition of SIV by Chimpanzees

One prerequisite for cross-species transmission is exposure of the new host to virus-contaminated body fluids or tissues of the original host. Chimpanzees cooperatively hunt various monkey species and have most likely been exposed to SIVs numerous times throughout their evolution (Leendertz et al., 2011; Mitani and Watts, 1999). It has been proposed that SIVcpz resulted from a recombination between a *vpu*-containing ancestor of SIVs, nowadays found in *Cercopithecus* monkeys (SIVgsn/mon/mus), and the precursor of an SIV found in red-capped mangabeys (*Cercocebus torquatus*) (Bailes et al., 2003). More recent phylogenetic analyses suggested that SIVrcm was also transmitted from red-capped mangabeys to mandrills (Bell and Bedford, 2017). Thus, it is unclear whether parts of the SIVcpz genome were acquired from SIVrcm or from SIVmnd2. The ancestry of SIVcpz may even be tripartite, indicating that chimpanzees were infected with SIVs from at least three monkey species, although the possibility that recombination events occurred in SIV infected monkeys prior to transmission of a hybrid virus to chimpanzees cannot be ruled out (Bell and Bedford, 2017) (Figure 2). It may seem surprising that distinct monkey SIVs were apparently capable of coinfecting the same chimpanzee cell to recombine to SIVcpz (Figure 2) since they were presumably poorly adapted and not very fit for replication in the new host. However, efficient recombination of attenuated SIVs has been demonstrated: injection of two

different SIVmac mutants (*nef*- or *vpx/vpr*-deleted) into separate legs of rhesus macaques resulted in rapid outgrowth of the wild-type virus (Wooley et al., 1997).

Although present-day SIVcpz strains show high sequence diversity, their hybrid genomes seem to share the same breakpoints, suggesting a common ancestor (Bailes et al., 2003; Bell and Bedford, 2017) (Figure 2). In addition, no other SIVs have been detected in chimpanzees, although, e.g., SIVwrc is highly prevalent in western red colobus monkeys, a common prey of chimpanzees (Leendertz et al., 2011). Thus, despite frequent exposure to SIVs, only a single hybrid virus has spread in chimpanzees. Notably, SIVcpz has only been detected in two of four subspecies of chimpanzees, i.e., SIVcpz*Ptt* in *Pan troglodytes troglodytes* and SIVcpz*Pts* in *Pan troglodytes schweinfurthii* (Santiago et al., 2002). Thus, SIVcpz likely emerged after chimpanzee subspeciation and before the split between central and eastern common chimpanzees, i.e., 0.1–0.5 million years ago (Hey, 2010). In agreement with a more recent evolutionary origin than SIVs in old world monkeys, SIVcpz is not optimally adapted to its chimpanzee host since it causes disease and shows an uneven focal distribution in wild chimpanzee populations (Keele et al., 2006, 2009). Crossing the species barrier from monkeys to chimpanzees was certainly not easy for SIV since genome-wide screens indicate that lentiviruses may need to hijack hundreds of cellular virus-dependency factors, although the overlap between these and other studies is minimal and further studies are required to verify their significance (König et al., 2008; Zhou et al., 2008). In addition, primate lentiviruses need to evade or counteract a variety of intrinsic antiviral restriction factors targeting essentially every step of the viral replication cycle (e.g. viral entry, reverse transcription, uncoating, nuclear import, integration, transcription, translation, assembly, and release) in order to spread efficiently (Kluge et al., 2015; Simon et al., 2015). Restriction factors are under high selection pressure for adaptive changes due to the arms race between viruses and their hosts and often act in a species-specific manner (Pyndiah et al., 2015). Genetically, chimpanzees are more closely related to humans (~98.8% DNA sequence identity) than to small monkeys. Thus, the genetic barrier for transmission of SIVs from monkeys to chimpanzees was high. We are far from completely understanding the events and adaptations required for generation of a hybrid virus capable of all obligatory interactions and evasion or counteraction mechanisms required for spread in chimpanzees. However, recent studies provide some insights on how SIVcpz mastered some main hurdles. One of the first restriction factors encountered after viral entry is TRIM5α, which targets incoming viral capsids in a species-dependent manner and induces their untimely uncoating (Stremlau et al., 2004). However, TRIM5α most likely did not constitute a significant barrier against monkey-ape transmission since chimpanzee TRIM5α does not restrict many SIVs infecting small monkeys, including present-day SIVgsn strains (Kratovac et al., 2008) (Figure 3). For efficient nuclear import of the viral genome, the viral capsid needs to bind to nuclear pore protein RanBP2/Nup358 (Ocwieja et al., 2011). Recent data support that transmission of SIV from monkeys to chimpanzees coincided with changes in Gag, restoring this interaction in the new host species (Meyerson et al., 2018).

For efficient replication, *in vivo* primate lentiviruses must counteract the cytidine deaminase APOBEC3G that is otherwise incorporated into viral particles, introducing lethal hypermutations in the viral genome (Sheehy et al., 2002). Analyses of primate genomes suggest that Vif has driven the evolution of primate APOBEC3G proteins for millions of years (Compton and Emerman, 2013). The APOBEC family of DNA cytosine deaminases has numerous members, and APOBEC3D, APOBEC3F, and APOBEC3H may also restrict viral replication (Desimmie et al., 2014). Most SIV Vif proteins are unable to efficiently antagonize chimpanzee APOBEC3D and G (Etienne et al., 2015). Apparently, the recombination that created SIVcpz (Figure 2) resulted in the deletion of *vpx* and generation of a unique *vif* gene that overlaps with *vpr* at its 3′ end (Etienne et al., 2013). Remarkably, the resulting unusual Vif protein counteracts chimpanzee APOBEC3D and G (Figure 3). In contrast, APOBEC3F and H did not constitute a barrier to cross-species transmission of SIVrcm to chimpanzees, as SIVrcm Vif antagonizes the chimpanzee orthologs of these restriction factors (Etienne et al., 2013). Vpx antagonizes SAMHD1, a cellular nucleotide triphosphate phosphohydrolase that restricts lentiviral replication in myeloid cells and resting T cells (Hrecka et al., 2011; Laguette et al., 2011). Vpx also targets and degrades the human silencing hub (HUSH) complex that restricts viral transcription, thus resulting in the reactivation of latent proviruses (Chougui et al., 2018). Thus, acquisition of anti-APOBEC activity was achieved at the cost of SAMHD1 and HUSH complex antagonism, presumably affecting the ability of SIVcpz and its descendants—including HIV-1—to infect myeloid cells and resting T cells and to generate latent viral reservoirs.

At the late stage of their replication cycle, primate lentiviruses need to counteract additional restriction factors, including tetherin for efficient viral release and SERINC5 for high virion infectivity. SERINC5 is incorporated into assembling virions and subsequently prevents virus fusion. In contrast to other restriction factors, SERINC5 is evolutionarily highly conserved and not interferon (IFN)-inducible, indicating a yet to be determined important physiological function. Consequently, SERINC5 did not constitute a significant barrier since it is counteracted by HIV and SIV Nef proteins in a species-independent manner (Heigele et al., 2016). In contrast, chimpanzee tetherin, which retains nascent virions at the cell surface, was most likely not efficiently counteracted after cross-species transmission because Vpu and Nef antagonize this factor in a species-dependent manner (Sauter et al., 2009; Zhang et al., 2009). To our current knowledge, SIVcpz obtained its *vpu* gene from the ancestor of the SIVgsn/mus/mon lineage. Vpu proteins of these SIVs counteract monkey, but not chimpanzee, tetherin (Sauter et al., 2009). The origin of the SIVcpz *nef* gene is less clear, but phylogenetic analyses suggest that it might be derived from the SIVrcm lineage (Kobayashi et al., 2014; Schindler et al., 2006) or an as yet unknown SIV (Bell and Bedford, 2017) (Figures 2 and 3). During adaptation to chimpanzees, SIVcpz evolved Nef and not Vpu as an effective tetherin antagonist (Sauter et al., 2009). However, SIVcpz Vpu proteins maintained other activities, such as degradation of CD4.

The recombination of SIVs preceding viral emergence in chimpanzees resulted in characteristic features of SIVcpz and consequently HIV-1. In addition to the loss of *vpx*, maintenance of *vpu*, and generation of a unique *vif*, recombination to the hybrid

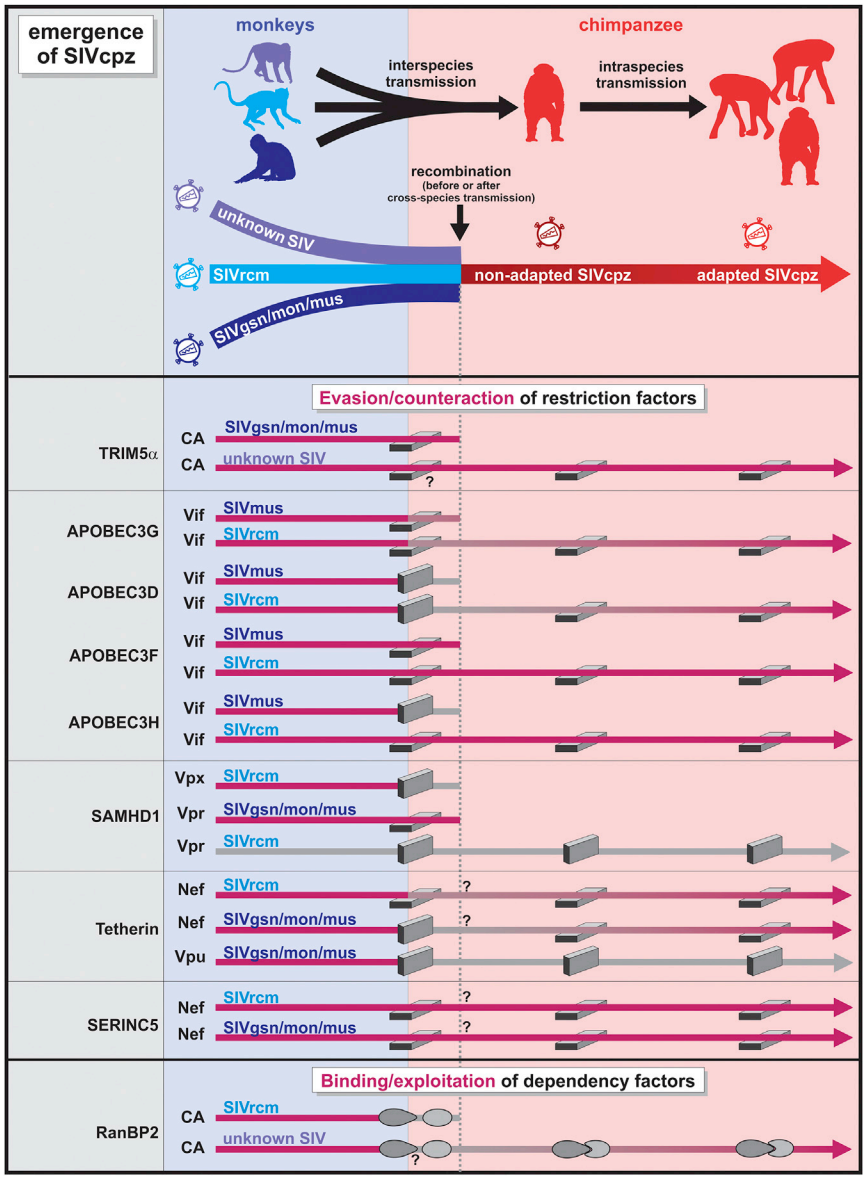

Figure 3. Emergence of SIVcpz
The upper panel shows the cross-species transmissions and recombination events of three different SIV strains that gave rise to SIVcpz. The lower panel illustrates the adaptation of viral accessory proteins (Vif, Vpx, Vpr, Nef, and Vpu) and capsid (CA) to cellular restriction factors (TRIM5α, APOBEC3s, SAMHD1, Tetherin, and SERINCs) and the dependency factor RanBP2. Counteraction of a restriction factor or evasion thereof is highlighted by pink arrows and fallen walls. Likewise, pink arrows illustrate the interaction of CA with the dependency factor RanBP2. Barriers to viral replication are represented by intact walls and gray arrows. The recombination event giving rise to SIVcpz and associated gene loss events are highlighted by a vertical dotted line. Please note that it is still unknown whether the recombination occurred before and/or after cross-species transmission to chimpanzees.

precursor of SIVcpz eliminated the overlap of ~156 bp between the 3′ end of *env* and the 5′ end of the *nef* gene. The functional consequences remain largely a matter of speculation. In principle, separation of both genes should allow Env and Nef to more "freely" acquire additional functions. However, the Nef proteins of primate lentiviruses lacking the *env-nef* overlap (SIVcpz, SIVgor, and HIV-1) usually lack the ability to downmodulate the T cell coreceptor CD3 and are less active in modulating the T cell costimulatory receptor CD28 than those of other SIVs and HIV-2 (Schindler et al., 2006). Although SIVcpz has apparently been infecting chimpanzees for thousands of years, it still causes fatal disease in this species (Keele et al., 2009). It has been suggested that the unusual paucity of SIVgsn/mus/mon might also be due to a pathogenic outcome of these infections in their natural simian hosts (Schmidt et al., 2017). Whether cross-species transmission among African primate species was frequently associated with disease in new non-adapted hosts is currently unknown.

Transmission of SIVcpz to Gorillas and Humans

Genetic relatedness between host species increases the likelihood that viruses can utilize dependency factors and counteract antiviral factors and hence the chances of successful cross-species transmissions. Thus, it is not surprising that HIV-1 originated from SIVs infecting great apes, our closest non-human relatives (Figures 1 and 4). To our current knowledge, pandemic HIV-1 group M (major) strains, which have infected more than 80 million people and killed about half of them, resulted from a single transmission event from an SIVcpz-infected central chimpanzee (*Ptt*) that occurred about a century ago (Worobey et al., 2008). Chimpanzee-human transmission may have taken place in southeastern Cameroon, with initial spread in Léopoldville, renamed Kinshasa in 1966 (Faria et al., 2014; Worobey et al., 2008). HIV-1 group N strains, which have only been detected in ~20 individuals, also originated from a central chimpanzee but emerged more recently than group M viruses (Wertheim and Worobey, 2009). It came as a surprise that the closest simian relatives of the remaining two groups of HIV-1 (O and P) were detected in gorillas (Sharp and Hahn, 2011), who most likely originally acquired their virus from central chimpanzees (Takehisa et al., 2009). Gorillas usually do not eat meat and avoid interactions with chimpanzees. However, the ranges of their habitats overlap, and occasional aggressive interactions may occur. It is unknown when SIV was introduced into wild-living gorillas, but the diversity of available SIVgor sequences suggests that gorillas acquired the virus at least 100–200 years ago and possibly much earlier (Takehisa et al., 2009). To our current knowledge, most viral interactions and counteraction

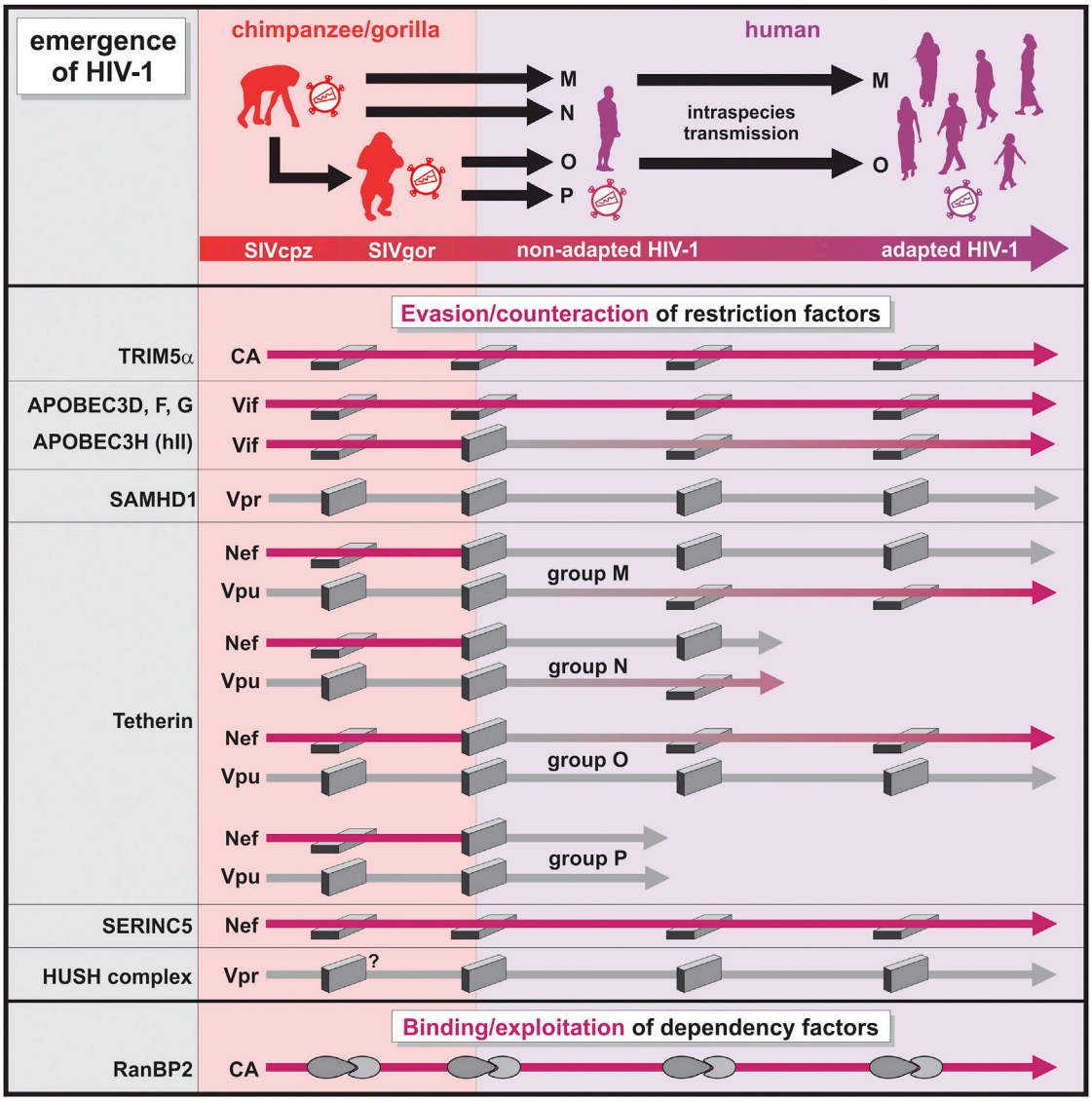

Figure 4. Emergence of HIV-1
The upper panel illustrates the transmission events from chimpanzees to gorillas and humans that ultimately gave rise to HIV-1 groups M, N, O, and P. While groups M and (to a lesser extent) O efficiently spread in the human population, group N and P strains were only identified in few individuals. The lower panel shows the adaptation of viral accessory proteins (Vif, Nef, Vpu, and Vpr) and capsid (CA) to cellular restriction factors (APOBEC3s, TRIM5α, Tetherin, SAMHD1, HUSH complex, and SERINCs) and the dependency factor RanBP2. Barriers to viral spread are represented as intact walls, while successful evasion or counteraction of restriction factors and binding to RanBP2 are illustrated by fallen walls and pink instead of gray arrows.

mechanisms required for viral replication were maintained after cross-species transmission from chimpanzees to gorillas. However, SIVcpz Nefs are poor antagonists of gorilla tetherin, and SIVgor Nef acquired some changes to counteract this restriction factor in the new host (Sauter et al., 2009). In addition, substitutions in Vif were required to overcome the APOBEC3G-mediated species barrier in gorillas (D'arc et al., 2015; Letko et al., 2013).

Viral adaptation to chimpanzees and gorillas paved the way for successful virus transmission to humans, as SIVcpz and SIVgor Vif proteins are effective antagonists of human APOBEC3D, F, and G proteins (Etienne et al., 2013; Nakano et al., 2018; Zhang et al., 2017). However, human APOBEC3H (haplotype II) is resistant to SIVcpz and SIVgor Vif (Etienne et al., 2013; Zhang et al., 2017) and may therefore hamper zoonotic transmission (Figure 4). Similarly, human tetherin contains a deletion in its cytoplasmic domain that renders it largely resistant to the accessory protein Nef used by SIVcpz and SIVgor to counteract tetherin in their respective hosts (Jia et al., 2009; Sauter et al., 2009; Zhang et al., 2009). How the four groups of HIV-1 dealt with the tetherin restriction provides a striking example of the versatility of these viruses. Pandemic HIV-1 M strains switched from Nef to Vpu (which is also the tetherin antagonist of SIVgsn/mus/mon) to counteract human tetherin after zoonotic transmission (Sauter et al., 2009). At least in some cases, only a few changes in the transmembrane domain of SIVcpz Vpu are required to render it active against human tetherin (Kluge et al., 2013; Lim et al.,

2010; Vigan and Neil, 2010). The reason for this is most likely the modular nature of the viral accessory proteins (Sauter and Kirchhoff, 2018). In the case of Vpu, interactions with ubiquitin ligase and/or adaptor protein complexes are maintained to allow degradation of host proteins such as CD4 (which is thought to facilitate virion release and prevent superinfection). Thus, only the interaction with tetherin needs to be restored. HIV-1 N Vpus acquired modest anti-tetherin activity but lost the CD4 degradation function (Sauter et al., 2012). In support of ongoing human adaptation, a group N HIV-1 strain—isolated in France in 2011—encodes a Vpu that is an effective antagonist of human tetherin (Sauter et al., 2012). In comparison, Nef proteins of HIV-1 O strains that have infected ~100,000 individuals, mainly in Cameroon and surrounding countries, evolved the ability to target a region adjacent to the protective deletion in human tetherin (Kluge et al., 2014). Finally, HIV-1 P strains that have only been detected in two individuals have apparently not (yet) evolved an effective tetherin antagonist in humans (Sauter et al., 2011; Yang et al., 2011). In agreement with a possible role in virus transmission, Vpu-mediated tetherin antagonism is important for IFN resistance of HIV-1 (Kmiec et al., 2016)—a hallmark of transmitted-founder HIV-1 strains accounting for initial infection (Iyer et al., 2017) and early replication *in vivo* in humanized mouse models (Yamada et al., 2018). It is tempting to speculate that suppression of virion release from infected cells due to ineffective tetherin antagonism may reduce the levels of infectious HIV-1 in semen and female genital fluids.

Notably, comparison of the inferred ancestral sequences of HIV-1 groups M, N, and O with 16 full-length SIVcpz sequences identified only a single amino acid residue as completely conserved among SIVcpz*Ptt* strains but altered in most HIV-1 strains. Gag30 in the *gag*-encoded matrix protein (MA) is Met or Leu in SIVcpz*Ptt* but changed to Arg or Lys in HIV-1 groups M, N, and O, as well as one of the two group P strains (Wain et al., 2007). Non-adapted SIVcpz strains can replicate in human CD4+ T cells (Takehisa et al., 2007), but the adaptive change in MA is required for effective replication in *ex vivo* infected human lymphoid tissues (Bibollet-Ruche et al., 2012). Why it affects viral replication fitness in a species-specific manner is unknown and might involve interaction with a yet to be determined virus-dependency or restriction factor.

Altogether, our current knowledge suggests that adaptation to the human host, including the ability to counteract IFN-inducible restriction factors and exploit cellular dependency factors, was a prerequisite for the efficient spread of pandemic HIV-1 group M strains in the human population. HIV-1 group M Vpu exerts a striking variety of additional functions including degradation of CD4, modulation of natural killer cell activation ligands, downregulation of HLA-C, and inhibition of NF-κB activity (Sandberg et al., 2012; Sauter and Kirchhoff, 2018). Much less is known about the function of SIV Vpu proteins, but some key activities such as CD4 degradation and suppression of NF-κB are conserved (Hotter et al., 2017; Sauter et al., 2009, 2015). Although Vpu exerts various activities that should be beneficial for viral replication, its acquisition also might have drawbacks for HIV-1 and its SIV counterparts. As mentioned above, the prevalence of *vpu*-containing SIVs in the wild is generally low, possibly due to viral pathogenicity (Aghokeng et al., 2010; Keele et al., 2009; Schmidt et al., 2017). SIVagm (lacking *vpu*) is highly prevalent and does not cause disease in African green monkey populations. Experimental infection of these monkeys with an HIV-1-like SIVagm variant encoding a functional Vpu and a Nef unable to suppress T cell activation via downmodulation of CD3 resulted in increased levels of chronic immune activation, yet no disease development (Joas et al., 2018). This is in agreement with the accumulating evidence that well-adapted natural hosts of SIV have evolved effective protective mechanisms, such as maintenance of critical T cell subsets and alterations in genes involved in immune sensing of viral infection (Beaumier et al., 2009; Paiardini et al., 2011; Palesch et al., 2018). It is tempting to speculate that specific viral features might be more relevant in recent hosts that have not yet evolved effective protective mechanisms to prevent SIV- and HIV-induced disease.

Origin and Human Adaptation of HIV-2

Given their close genetic relationship, it is plausible that great apes and not monkeys have transmitted their viruses to humans. However, there is one striking exception. SIVsmm of sooty mangabeys was transmitted to humans on at least nine independent occasions, giving rise to HIV-2 groups A–I (Ayouba et al., 2013; Sharp and Hahn, 2011) (Figure 1). The two major groups of HIV-2 (A and B) may be the consequence of transmission events of SIVsmm from sooty mangabeys living in the Taï forest in Ivory Coast (Santiago et al., 2005). In contrast, none of the other SIVs infecting numerous monkey species in sub-Saharan Africa has been detected in humans. The reasons for these striking differences in the number of zoonotic transmissions to humans may be multi-factorial. Sooty mangabeys show a high prevalence for SIVsmm and are kept as household pets or hunted for bushmeat, suggesting frequent viral exposure of humans. SIVsmm isolates replicate in human peripheral blood mononuclear cells (Gautam et al., 2007) and seem capable of overcoming major human restriction factors without adaptation (Figure 5). For example, the SIVsmm Vif protein has broad activity against APOBEC3G from many species, including human APOBEC3G (Letko et al., 2013). Interestingly, however, HIV-2 strains show on average more APOBEC3G/F-induced hyper-mutations than HIV-1 isolates (Bertine et al., 2015; Gao et al., 1992). Similarly, it has been reported that HIV-2 capsids are more susceptible to inhibition by human TRIM5α than those of HIV-1, but only a limited number of isolates have been analyzed (Takeuchi et al., 2013; Ylinen et al., 2005). Recent data suggest that SIVsmm uses both Env and Nef to counteract tetherin in its natural hosts and that its Env is also active against human tetherin (Heusinger et al., 2018). Thus, Env-mediated tetherin antagonism may have facilitated successful zoonotic transmission (Heusinger et al., 2018; Le Tortorec and Neil, 2009). One feature that distinguishes HIV-2 from HIV-1 and many SIVs is the presence of a *vpx* gene. Vpx counteracts SAMHD1 and supports infection of myeloid cells and resting T cells *in vitro* (Hrecka et al., 2011; Laguette et al., 2011). Although primate lentiviruses frequently target SAMHD1 in a species-specific manner (Fregoso et al., 2013), SIVsmm is able to antagonize the human ortholog of this restriction factor (Laguette et al., 2012). Similarly, SIVsmm Vpx is active against the human HUSH complex (Chougui et al., 2018). Finally, human SERINC5 did not pose a barrier to zoonotic transmission, as it is counteracted by SIVsmm Nef (Heigele et al., 2016).

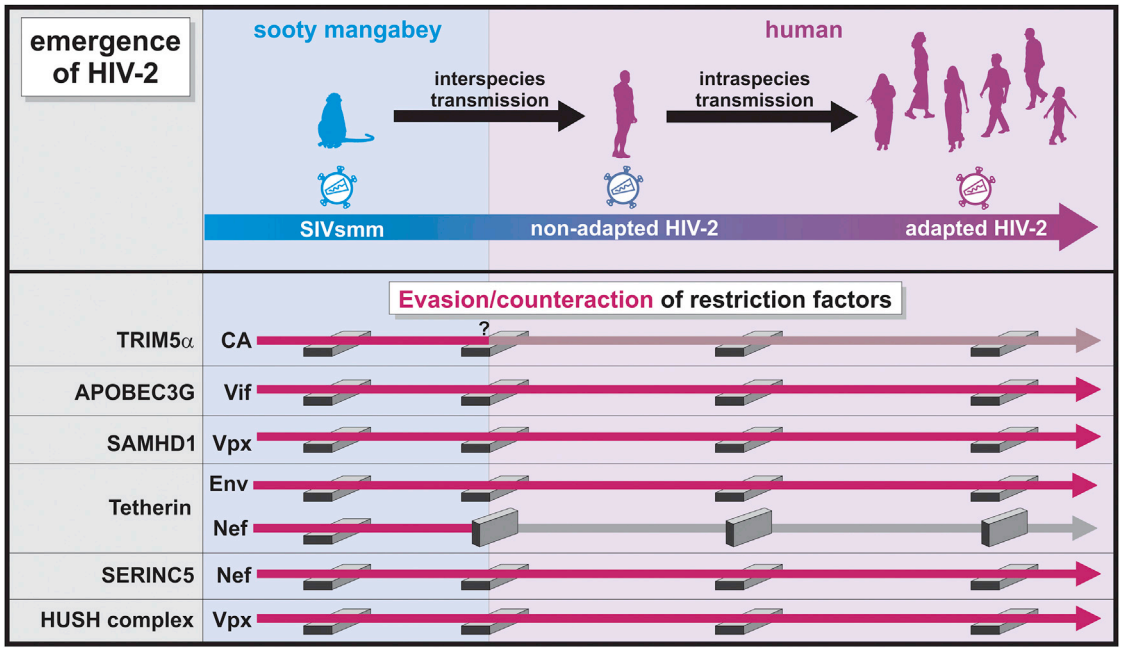

Figure 5. Emergence of HIV-2
The zoonotic transmission of SIVsmm from sooty mangabeys to humans and the emergence of HIV-2 are shown on top. Adaptation of viral accessory proteins (Vif, Nef, and Vpx), envelope (Env), and capsid (CA) to cellular restriction factors (APOBEC3s, TRIM5α, Tetherin, SAMHD1, HUSH complex, and SERINCs) are illustrated at the bottom. Restriction factors posing potential barriers to viral spread are represented as intact walls, while cleared barriers are illustrated by fallen walls and pink instead of gray arrows.

Altogether, SIVsmm accessory proteins seem to be more active against human restriction factors than those of SIVs infecting other monkey species. Nonetheless, it is evident that HIV-2 is far from being perfectly adapted to the human host. Just two of at least nine transmissions (HIV-2 group A and B) and a circulating recombinant form thereof (CRF_AB01) resulted in significant spread in humans—mainly in West Africa, where HIV-2 infects about 1–2 million people (Visseaux et al., 2016). Although HIV-2 is less pathogenic than HIV-1 (Nyamweya et al., 2013), it is less successful in spreading in the human population, and its prevalence is declining (Olesen et al., 2018). While HIV-1 usually maintains high viral loads throughout infection, HIV-2 is controlled by the immune system in most infected individuals, resulting in slow disease progression and lower transmission rates. In agreement with suboptimal adaptation, passaging experiments of SIVsmm in humanized mice identified numerous adaptive changes, particularly in the *env* and *nef* genes (Schmitt et al., 2017). Their functional relevance and potential significance for viral fitness in the human host remain to be determined.

CONCLUSIONS AND OPEN QUESTIONS

Although progress has been made, we are only beginning to understand the complex evolutionary history of HIV. It has become clear that only one of at least thirteen zoonotic lentiviral transmission events resulted in the current AIDS pandemic. Possibly, additional cross-species transmissions of SIVs occurred but went unnoticed. Indeed, there is indirect evidence of a more ancient pathogenic lentivirus in the chimpanzee lineage that may have driven the selection of its antiviral repertoire (Duggal et al., 2011; de Groot and Bontrop, 2013). Key events preceding the emergence of pandemic HIV-1 group M strains were the recombination of different SIVs in chimpanzees, which resulted in the acquisition of a *vpu* gene as well as the emergence of a functional *vif* gene at the cost of *vpx*, enabling adaptation to chimpanzees and acquisition of Vpu-mediated tetherin activity during human adaptation. Clearly, some characteristic features render retroviruses particularly fit for cross-species transmissions, i.e., integration into the cellular genome and the ability to evolve a million times faster than mammalian DNA and to combine favorable properties by recombination. In addition, primate lentiviruses express a set of three or four accessory factors. Their modular nature and multi-functionality prevent gene loss in new host species and allow efficient reacquisition of functions that are initially lost. It is also becoming evident that accessory viral proteins can compensate for one another since several switches between Vpu- and Nef-mediated tetherin antagonism preceded the emergence of pandemic HIV-1 group M strains (Sauter et al., 2009), and primate lentiviruses "toggled" between Vpx and Vpr to counteract SAMHD1 (Fregoso et al., 2013). Accumulating evidence also suggests that some characteristic features of HIV-1 did not just evolve by coincidence but as a consequence of functional interactions between different viral proteins. For example, Vpu-mediated suppression of NF-κB activity most likely facilitated the loss of the CD3 downmodulation function of Nef (Hotter et al., 2017). One interesting question is whether pandemic HIV-1 group M strains are already almost perfectly adapted to humans or still adapting. It has been proposed that different HIV-1 subtypes may vary in their biological

properties (Taylor et al., 2008). For example, subtype C HIV-1 group M strains that are responsible for almost half of all global infections may be less pathogenic and consequently better adapted to the human host than other subtypes of HIV-1 (Venner et al., 2016). However, further studies are required to clearly define potential differences in transmission fitness and pathogenicity of different subtypes of HIV-1.

It is evident that the barriers for successful zoonotic transmission of primate lentiviruses from monkeys and apes to humans are high but not insurmountable. Unfortunately, hunting and butchering of our non-human relatives is ongoing and clearly poses a significant risk for future zoonoses (Peeters et al., 2002). Notably, the IFN resistance of many transmitted-founder HIV-1 strains relative to their chronic counterparts later obtained from the same infected individuals (Iyer et al., 2017) cannot be explained by sensitivity to known antiretroviral restriction factors. Thus, significant barriers to efficient spread of primate lentiviruses in humans remain to be discovered, and their characterization will be important for a better assessment of the risk of future zoonoses.

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