26 Origin and Emergence of HIV/AIDS

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26.1 History of AIDS

Acquired immunodeficiency syndrome (AIDS) was first recognized between 1979 and 1981 among men having sex with men (MSM) who presented with pneumonia caused by *Pneumocystiis carinii* and/or with symptoms of Kaposi sarcoma in New York, Los Angeles, or San Francisco (CDC 1981) (Figure 26.1). Subsequently patients with similar symptoms were seen among intravenous drug users (IDUs), hemophiliacs, Haitians, and Africans in Europe. In May 1983, the etiologic agent of AIDS, the human immunodeficiency virus (HIV), was identified (Barre-Sinoussi et al., 1983). In 1984, several authors reported AIDS cases in women and men in hospitals from sub-Saharan Africa, suggesting also a heterosexual epidemic (Ellrodt et al., 1984; Piot et al., 1984; Van de Perre et al., 1984). Sero-epidemiological studies showed subsequently that a significant proportion of the population in certain regions of Africa was infected with HIV. In the early 1990s, the epidemic exploded in south and eastern Africa, where in certain urban areas 25% of pregnant women were HIV positive (Buve et al., 2002) (Figure 26.1).

Molecular epidemiological studies revealed that the epicenter of the HIV pandemic is situated in Central Africa, and more precisely the area of Kinshasa, the capital city of the Democratic Republic of Congo (DRC) (Vidal et al., 2000; Worobey et al., 2008). The virus has been introduced from Africa in Haiti in the 1960s (most recent common ancestor MRCA 1966) before it started to circulate in North America (MRCA, 1969) about 12 years before the discovery and description of the first AIDS cases (Low-Beer, 2001; Gilbert et al., 2007). Today, more than 33 million people all over the world are infected with HIV (Figure 26.1) and about 70% of HIV-infected persons live in sub-Saharan Africa. With more than 25 million people already deceased, HIV/AIDS continues to be one of the most serious public health threats in the twenty-first century (http://www.unaids.org). It is thus important to identify where this virus came from, to understand how it has been

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Genetics and Evolution of Infectious Diseases. DOI: 10.1016/B978-0-12-384890-1.00026-1

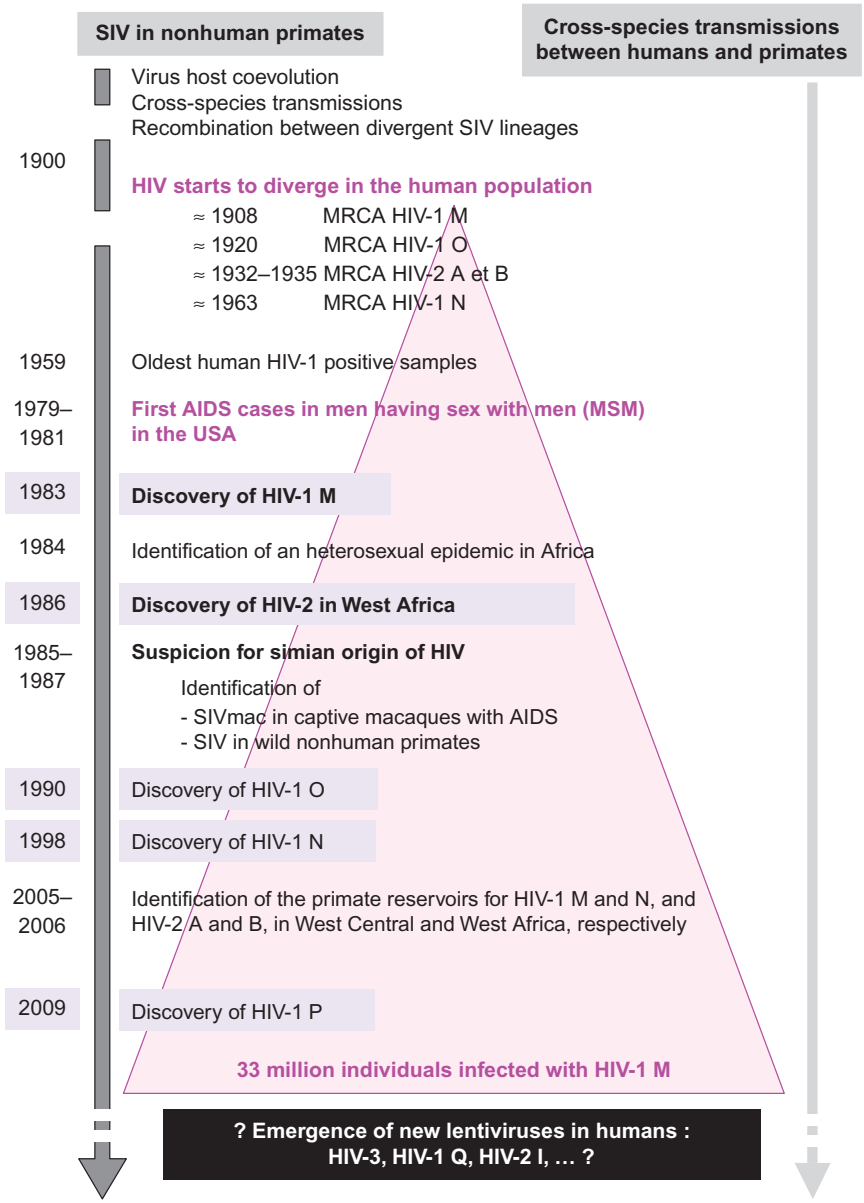

Figure 26.1 History of the AIDS epidemic: past and future events. Dates referring to events in the history of the HIV epidemic in humans are shown at the left, major events are highlighted in pink, boxes indicate subsequent discoveries of the different HIV-1 groups. The number of persons living with HIV increases overtime as illustrated by the pink triangle. Gray arrows represent a schematic timescale of the different events. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this book.)

introduced into the human population and to determine which factors are associated with host adaptation and epidemic spread.

26.2 HIV Is Closely Related to Simian Immunodeficiency Viruses (SIV) from Nonhuman Primates

Although HIV-1 has been identified in 1983, another closely related virus, HIV-2, has been described in 1986 in France among west Africans with AIDS (Clavel et al., 1986). HIV belongs to the Lentivirus genus of the Retroviridae family where five serogroups are recognized, each reflecting the vertebrate hosts with which they are associated (primates, sheep and goats, horses, cats, and cattle). Both, HIV-1 and HIV-2, are most closely related to the lentiviruses from primates, called simian immunodeficiency viruses (SIVs) and are thus most likely the result of cross-species transmissions of SIVs from African primates.

26.2.1 Discovery of the First SIV

Shortly after the identification of HIV-1 as the cause of AIDS in 1983, the first SIV, SIVmac, was isolated from rhesus macaques (*Macaca mulatta*) with immune deficiency and clinical symptoms similar to AIDS at the New England Regional Primate Research Center (NERPRC) (Henrickson et al., 1983; Daniel et al., 1985). Retrospective studies revealed that SIVmac was introduced at NERPRC by other rhesus monkeys, previously housed at the California National Primate Research Center (CNPRC), where they survived an earlier disease outbreak (late 1960s), characterized by immune suppression and opportunistic infections (Mansfield et al., 1995). A decade after the first outbreak, stump-tailed macaques (*Macaca arctoides*) developed a similar disease in the same settings and a lentivirus called SIVstm was isolated from frozen tissue from one of these monkeys (Lowenstine et al., 1986). In both cases, the infected macaques had been in contact with healthy, but retrospectively shown, SIVsmm seropositive sooty mangabeys at the CNPRC (Lowenstine et al., 1986). The close phylogenetic relationship between SIVmac, SIVstm, and SIVsmm identified mangabeys as the plausible source of SIV in macaques.

Since SIVmac induced a disease in rhesus macaques with remarkable similarity to human AIDS, a simian origin of HIV was soon suspected. The discovery in 1986 of HIV-2, the agent of AIDS in West Africa, and the remarkable high relatedness of HIV-2 with SIVsmm, naturally occurring in sooty mangabeys in West Africa, reinforced this hypothesis.

26.2.2 SIVs in African Nonhuman Primates

Currently, serological evidence of SIV infection has been shown for more than 40 different primate species and SIV infection has been confirmed by viral sequence analysis in the majority (Table 26.1 and Figure 26.2). A high genetic diversity is

Table 26.1 SIV Infections in Old World Monkeys and Apes in Africa

Genus	Species Subspecies	Common Name	SIV
Pan	***troglodytes troglodytes***	**Central chimpanzee**	**SIVcpz*Ptt***
	troglodytes schweinfurthii	East African chimpanzee	SIVcpz*Pts*
Gorilla	***gorilla gorilla***	**Western gorilla**	**SIVgor**
Colobus	*guereza*	Mantled guereza	SIVcol
Piliocolobus	*badius badius*	Western red colobus	SIVwrc*Pbb*
	badius temminckii	Temminck's Red Colobus	SIVwrc*Pbt*
	tholloni	Thollon's Red Colobus	SIVtrc*
	rufomitratus tephrosceles	Ugandan Red Colobus	SIVkrc*
Procolobus	*verus*	Olive colobus	SIVolc
Lophocebus	*albigena*	Gray-cheeked mangabey	
	aterrimus	Black crested mangabey	SIVbkm*
Papio	*anubis*	Olive baboon	
	cynocephalus	Yellow baboon	SIVagm-Ver*
	ursinus	Chacma baboon	SIVagm-Ver*
Cercocebus	***atys***	**Sooty mangabey**	**SIVsmm**
	torquatus	Red capped mangabey	SIVrcm
	agilis	agile mangabey	SIVagi
Mandrillus	*sphinx*	Mandrill	SIVmnd-1,-2
	leucophaeus	Drill	SIVdrl
Allenopithecus	*nigroviridis*	Allen's swamp monkey	
Miopithecus	*talapoin*	Angolan or southern talapoin	SIVtal*
	ogouensis	Gabon or northern talapoin	SIVtal
Erythrocebus	*patas*	Patas monkey	SIVagm-sab*
Chlorocebus	*sabaeus*	Green monkey	SIVagm-Sab
	aethiops	Grivet monkey	SIVagm-Gri
	tantalus	tantalus monkey	SIVagm-Ver
Cercopithecus	*diana*	Diana monkey	
	nictitans	Greater spot nosed monkey	SIVgsn
	mitis	Bleu monkey	SIVblu
	albogularis	Sykes' monkey	SIVsyk
	mona	Mona monkey	SIVmon
	lowei	Lowe's mona monkey	
	campbelli	Campbells mona monkey	
	pogonias	Crested mona monkey	
	denti	Dent's mona monkey	SIVden
	wolfi	Wolf's mona monkey	SIVwol*
	cephus	mustached monkey	SIVmus1,-2
	erythrotis	Red-eared monkey	SIVery
	ascanius	Red-tailed monkey	SIVasc*
	lhoest	l'Hoest monkey	SIVlho
	solatus	Sun-tailed monkey	SIVsun
	preussi	Preuss's monkey	SIVpre*
	hamlyni	Owl-faced monkey	
	neglectus	de Brazza's monkey	SIVdeb

For each species the genus, species, and subspecies (if applicable) are given. Species representing a reservoir for HIV-1 and 2 are highlighted in bold, species with only serological evidence for SIV infection are shown in gray, species with SIV infection confirmed by sequence analysis are shown in black and an asterisks indicates that only partial sequences are currently available. The following references were used for the table: Bibollet-Ruche et al. (2004), Takemura et al. (2005), Van Heuverswyn et al. (2006), VandeWoude and Apetrei (2006), Goldberg et al. (2009), Liégeois et al. (2009), Ahuka-Mundeke et al. (2010).

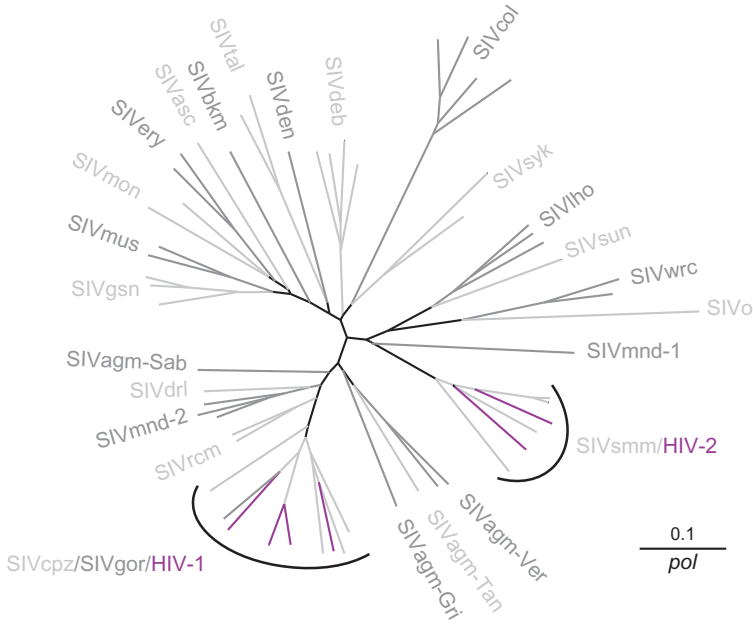

Figure 26.2 Genetic diversity and evolutionary history of the different HIV/SIV lineages. Phylogenetic tree analysis using the neighbor-joining method on a 512 bp fragment from the *pol* gene of different SIVs infecting nonhuman primates and HIVs infecting humans. Branch lengths are drawn to scale (the scale bar indicates 0.1 substitutions per site). The different gray colors are used for clarity to discriminate the different SIV lineages. The different HIV-1 and HIV-2 lineages, which are interspersed with the SIVcpz/SIVgor and SIVsmm lineages respectively, are indicated in pink. The correspondence between the SIV lineages and their natural hosts are shown in Table 26.1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this book.)

observed among the different SIVs, but generally each primate species is infected with a species-specific virus, which forms monophyletic lineages in phylogenetic trees. These species-specific SIVs are generally identified by a lower case three-letter code, which corresponds to the initial letters of the common species name, such as for African green monkeys, SIVcpz for chimpanzees. When different subspecies of the same species are infected, an abbreviation referring to the name of the subspecies is added to the virus designation, such as SIVcpz*Ptt* and SIVcpz*Pts* to differentiate between the two chimpanzee subspecies, *Pan troglodytes troglodytes* and *P. t. schweinfurthii*, respectively, in Table 26.1 and Figure 26.2.

Importantly, the number of African primates infected with SIV is most probably underestimated, since 30 species of the 73 recognized Old World monkey and ape species in sub-Saharan Africa have not been tested yet or only very few individuals. Knowing that the vast majority (90%) of the primate species tested is SIV infected, many of the remaining species can be expected to harbor SIV infections.

In addition, all major SIV lineages known to date were discovered as a consequence of primate hosts' antibodies, which cross-reacted with HIV-1 or HIV-2 antigens. Because the extent of this cross-reactivity is not known, SIV infection can be underestimated.

Interestingly, only old world primates are infected with SIVs, and only those from the African continent. No SIVs have been identified in Asian primate species.

26.2.3 Pathogenicity of SIVs in their Natural Hosts

Although SIVs are called immune deficiency viruses, these viruses generally do not induce an AIDS-like disease in their natural hosts, suggesting that they have been associated and evolved with their hosts over an extended period of time (Silvestri et al., 2007). This absence of pathogenicity has been extensively studied among naturally infected captive sooty mangabeys and African green monkeys. Their life span as well as their immunological system do not seem to be affected by SIV (Silvestri et al., 2003; Keele et al., 2009a; Liovat et al., 2009). However, some cases of AIDS have been described among captive monkeys, but mainly at an age which is not reached in their natural habitats (Ling et al., 2004). Nevertheless, the paradigm of nonpathogenicity has been challenged recently by observations on wild chimpanzees (*P. t. schweinfurthii*) in Tanzania where SIVcpz*Pt*s infection seems to have a negative impact on life span and reproduction (Keele et al., 2009b). Moreover, retrospective analysis on tissues conserved from dead SIVcpz*Pts* infected animals showed that they have also symptoms of immune deficiency similar to what is observed in humans with AIDS. More studies are needed to confirm these observations, especially in other chimpanzee communities and in the central African subspecies, *P. t. troglodytes,* infected with SIVcpz*Ptt*.

26.2.4 Evolution and Phylogeny of SIVs

The genetic diversity among nonhuman primate lentiviruses is extremely complex. There are many examples of coevolution between viruses and their hosts, but recombination between distant SIVs does not seem exceptional and one species can even harbor two different SIVs. Although it seems now clear that a simple co-divergence between viruses and their hosts is not common, phylogenies for some SIVs and their hosts suggest coevolution over long time periods, like SIVagm in the different African green monkey species (*Chlorocebus* sp.) or SIVs in arboreal *Cercopithecus* species (Charleston et al., 2002; Wertheim et al., 2007). However, cross-species transmissions could give erroneous impressions of coevolution, especially when chances for efficient host switch are higher among genetically closely related species (Charleston et al., 2002). There are numerous examples of cross-species transmissions of SIVs between primates living in the same habitats or in polyspecific associations. For example, SIVagm from African green monkeys has been transmitted to Patas monkeys in West Africa (Bibollet-Ruche et al., 1996) and to yellow and chacma baboons in South Africa (Jin et al., 1994; van Rensburg et al., 1998). There are also more complex examples of cross-species transmissions

of SIVs between greater spot nosed monkeys (SIVgsn) and mustached monkeys (SIVmus), followed by recombination as seen for SIVmus-2 in mustached monkeys in Cameroon (Aghokeng et al., 2007) (Table 26.1). One of the most striking examples of cross-species transmission, followed by recombination is SIVcpz in chimpanzees. The 5′ region of SIVcpz is most similar to SIVrcm from red capped mangabeys, and the 3′ region is found to be closely related to SIVgsn from greater spot nosed monkeys (Bailes et al., 2003). Chimpanzees are known to hunt monkeys for food. Most probably, the recombination of these monkey viruses occurred within chimpanzees and gave rise to the common ancestor of today's SIVcpz lineages, which on their turn were subsequently transmitted to gorillas (Van Heuverswyn et al., 2006; Takehisa et al., 2009).

As numerous cross-species transmissions among different primate species occurred, both HIV-1 and HIV-2 in humans are also the result of cross-species transmissions of SIVs from African primates (Hahn et al., 2000). The closest simian relatives of HIV-1 are SIVcpz and SIVgor, in chimpanzees (*Pan troglodytes troglodytes*) and gorillas (*Gorilla gorilla*), respectively, from west-central Africa, and SIVsmm in sooty mangabeys (*Cercocebus atys*) from West Africa are the closest relatives of HIV-2.

26.3 HIV-1 Is Derived from SIVs Circulating among African Apes

Based on phylogenetic analyses of numerous isolates obtained from diverse geographic origins, HIV-1 is classified into four groups, M, N, O, and P (Figure 26.1). Group M (for Major), discovered in 1983 (Barre-Sinoussi et al., 1983), represents the vast majority of HIV-1 strains found worldwide and is responsible for the global pandemic. Group O (for Outlier), described in 1990 (De Leys et al., 1990), remained restricted to west-central Africa, and represents currently 1% of HIV-1 infections in Cameroon. Groups N and P, described in 1998 and 2009, respectively (Simon et al., 1998; Plantier et al., 2009), have only been observed in a handful of Cameroonian patients. Each HIV-1 group corresponds to an independent cross-species transmission from SIVs from apes to humans.

26.3.1 SIVs from Chimpanzees and Gorillas Are the Ancestors of HIV-1 in Humans

The first SIVcpz strains have been isolated from two captive wild-born chimpanzees in Gabon more than 20 years ago, SIVcpzGab1 and SIVcpzGab2 (Peeters et al., 1989). Genetic analysis of the SIVcpzGab1 genome revealed the presence of the accessory gene, *vpu*, also identified in HIV-1. Furthermore, phylogenetic analysis showed that SIVcpzGab1 was more closely related to HIV-1 than to any other SIV (Huet et al., 1990). Characterization of a third SIVcpz, SIVcpzANT, showed an unexpected high degree of divergence among the chimpanzee viruses (Peeters

et al., 1992; Vanden Haesevelde et al., 1996). Subsequent subspecies identification of the chimpanzee hosts revealed that the SIVcpzANT strain was isolated from a member of the *P. t. schweinfurthii* subspecies, whereas the other chimpanzees belonged to the *P. t. troglodytes* subspecies (Gao et al., 1999). These findings suggested two distinct SIVcpz lineages according to the host subspecies: SIVcpz*Ptt* and SIVcpz*Pts* from central (*P. t. troglodytes)* and eastern chimpanzees (*P. t. schweinfurthii)*, respectively. All HIV-1 groups were more closely related to SIVcpz*Ptt* than to SIVcpz*Pts* (Figure 26.3). Although these data pointed already to the west-central African chimpanzees (*P. t. troglodytes*) as the natural reservoir of the ancestors of HIV-1, the SIVcpz reservoirs in wild living apes that are at the origin of HIV in humans still needed to be identified. The major issue in studying SIVcpz infection in wild chimpanzees is their endangered status and the fact that they live in isolated forest regions. In addition, all previously studied chimpanzees were wild-caught, but they were capture as infants, which do not reflect true prevalences among wild living adult animals. The recent development of noninvasive methods to detect and characterize SIVcpz in fecal and urine samples boosted the search for new SIVcpz strains in wild ape populations in the vast tropical forest of central Africa (Santiago et al., 2002; Santiago et al., 2003a). The first full-length SIVcpz sequence from a wild infected chimpanzee, SIVcpzTan1, was obtained from a fecal sample from a *P. t. schweinfurthii* chimpanzee in Gombe National Park, Tanzania. Subsequently, additional cases of SIVcpz*Pts* infections were documented in Tanzania and the DRC (Santiago et al., 2003b; Worobey et al., 2004; Li et al., 2010). All the new SIVcpz*Pts* viruses formed phylogeographic clusters according to their geographic origin, but formed a separate lineage with the initially described SIVcpzANT strain indicating thus that the SIVcpz*Pts* strains are not at the origin of HIV-1 (Figure 26.3).

Recent molecular epidemiological studies on SIVcpz*Ptt* in central chimpanzees (*P. t. troglodytes*) allowed to trace the ancestors of the HIV-1 group M and N strains to distinct chimpanzee communities in south-east and south-central Cameroon (Keele et al., 2006) (Figure 26.3). Overall, SIVcpz*Ptt* viruses exhibited also a significant geographic clustering and SIVcpz*Ptt* is widely present in Central chimpanzees with an overall prevalence of 5.9%, although not all chimpanzee communities are infected and prevalences can range from 0% to 32% (Van Heuverswyn et al., 2007).

Despite testing of numerous samples, no SIV infection has been detected yet in the two other chimpanzee subspecies, *P. t. elioti* (previously *P. t. vellerosus*) and *P. t. verus* (Switzer et al., 2005; Van Heuverswyn et al., 2007).

While the reservoirs of the ancestors of HIV-1 M and N were identified in 2006, the reservoirs of group O and P remained unknown. In 2006, SIV infection was described for the first time in western gorillas (*Gorilla gorilla gorilla*) in Cameroon. Surprisingly, the newly characterized gorilla viruses, termed SIVgor, formed a monophyletic group within the HIV-1/SIVcpz*Ptt* radiation, but in contrast to SIVcpz*Ptt*, they were most closely related to the HIV-1 group O and P lineages (Figure 26.3) (Van Heuverswyn et al., 2006; Takehisa et al., 2009). However, the phylogenetic relationships between SIVcpz, SIVgor, and HIV-1 indicate that chimpanzees represent the original reservoir of SIVs now found in chimpanzees, gorillas

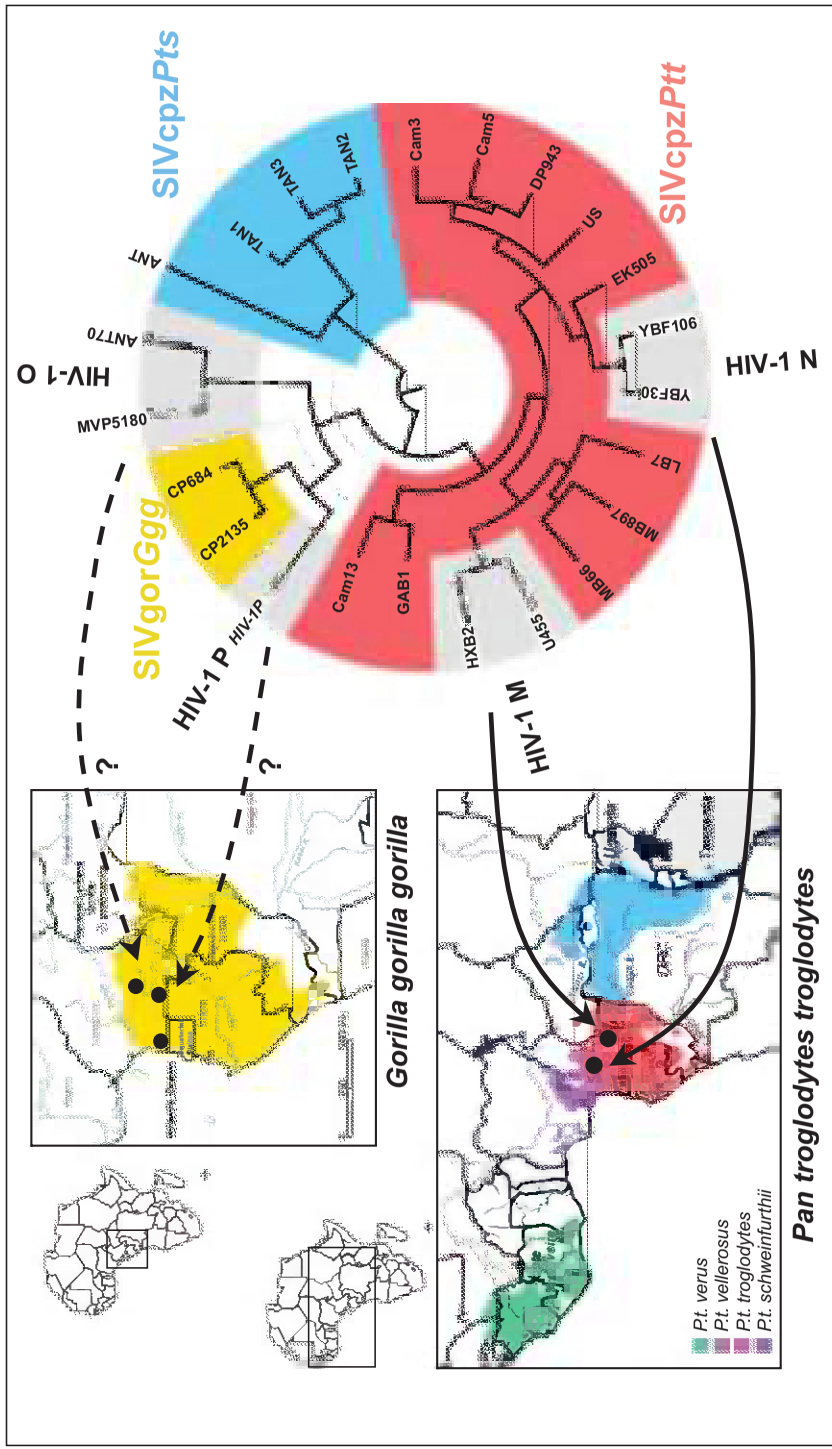

Figure 26.3 *(Continued)*

and humans (Figure 26.3). Given the herbivorous diet of gorillas and their peaceful coexistence with other primate species, especially chimpanzees, it remains a mystery by which route gorillas acquired SIVgor. A large molecular epidemiological survey among more than 2200 fecal samples from wild gorillas collected in 21 sites across southern Cameroon showed a global prevalence of 1.6% ranging from 0% to 4.6% in gorillas, which is three times less than the overall prevalence observed in chimpanzees in the same areas (Neel et al., 2010).

The close phylogenetic relationship of the recently discovered HIV-1 group P and SIVgor, suggested that group P is derived from a gorilla lentivirus (Plantier et al., 2009). However, no SIVgor strain sufficiently close to HIV-1 P has been identified yet to be the direct ancestor of HIV-1 group P or O found in humans (Figure 26.3).

It is now clear that central chimpanzees (*P. t. troglodytes*) are the reservoirs for the pandemic HIV-1 group M strain and also for HIV-1 N. However, more studies are still needed to identify the direct ancestors of HIV-1 O and P in gorillas and/or chimpanzees in other areas in Cameroon and in neighboring countries. These studies will also help to clarify the origin of SIVgor in gorillas, whether gorillas and/or chimpanzees transmitted group O and P to humans, and whether the ancestors of SIVgor, HIV-1 O and P still circulate among chimpanzees.

Importantly, the finding that SIVcpz strains from east African chimpanzees, including those from Kisangani in DRC, are more distantly related to HIV-1 provides also evidence that the oral polio vaccine (OPV), which was largely distributed in this part of Africa at the end of the 50s, is not at the origin of the HIV-1 epidemic. It has been suggested that tissues derived from SIVcpz-infected chimpanzees, captured in the northeastern part of DRC were used for the OPV production. However, this geographical region is situated in the middle of the *P. t. schweinfurthii* range and the characterization of SIVcpz*Pts* from wild chimpanzees in DRC proved once more the inconsistency of the OPV theory (Worobey et al., 2004) (Figure 26.3).

26.3.2 The Cross-species Transmissions Resulting in HIV-1 Viruses in Humans Occurred in West-Central Africa

Since the four groups of HIV-1 fall within the HIV-1/SIVcpz*Ptt*/SIVgor radiation, the cross-species transmissions giving rise to HIV-1 most likely occurred in

Figure 26.3 *(Cont.)* HIV-1 is derived from SIVs circulating in chimpanzees and/or gorillas from West Central Africa. Evolutionary relationship of SIVcpz*Pts* (blue), SIVcpz*Ptt* (red), SIVgor (yellow), and HIV-1 group M, N, O, and P (gray) strains based on maximum likelihood phylogenetic analysis of partial Env (gp41) sequences. Horizontal branch lengths are drawn to scale (the scale bar indicates 0.2 substitutions per site). Maps represent the geographical range of *G. g. gorilla* (upper map) and the four chimpanzee subspecies (lower map). Arrows between the phylogenetic tree and maps indicate the ape reservoirs with the ancestors or most closely related strains to the different HIV groups. Dotted arrows indicate that the direct reservoirs for HIV-1 groups O and P are not yet identified. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this book.)

western equatorial Africa, the home of *P. t. troglodytes* chimpanzees and western gorillas. Furthermore, no human counterpart is found for SIVcpz*Pts* from *P. t. schweinfurthii*. The recent studies in wild chimpanzee communities in Cameroon, not only strengthen the evidence of the west-central African origin of HIV-1, but also indicate that HIV-1 groups M and N arose from geographically distinct chimpanzee populations in south Cameroon (Figure 26.3). This coincides with the geographical area of group N infections, which remain actually restricted to Cameroon. HV-1 groups O and P are also mainly restricted to Cameroon (Brennan et al., 2008; Vessiere et al., 2010), coinciding with the geographical ranges of central chimpanzees and western gorillas.

The four HIV-1 groups have thus their seeds in west-central Africa, but only one, HIV-1 group M, has spread across Africa and all the other continents. Moreover, the reservoir of the ancestors of HIV-1 M has been identified at almost 1000 km distance from the epicenter of the HIV-1 epidemic in DRC (Vidal et al., 2000; Worobey et al., 2008). A combination of several factors (viral, host, socioeconomic, demographic, etc.) are thus most likely involved in the subsequent efficient spread of HIV-1 M. It has also to be noted that nowadays no data are available on SIV infection in wild chimpanzee and gorilla populations living between southern Cameroon and Kinshasa, DRC, and it cannot be excluded that in this area other chimpanzee populations exist that are infected with viruses also closely related to HIV-1 M.

26.3.3 HIV-1 Started to Diverge in the Human Population at the Beginning of the Twentieth Century

As mentioned above, the SIVcpz*Ptt* ancestors of group M have been identified in Cameroon, but the highest genetic diversity of HIV-1 M, in number of co circulating subtypes and intrasubtype diversity, has been observed in the western part of DRC, suggesting that this region may be the epicenter of HIV-1 group M (Vidal et al., 2000). Retrospective studies showed that 20 years before the AIDS epidemic was recognized in the United States, HIV-1 M (subtypes A and D) infection was already circulating in humans in Kinshasa (i.e., HIV-1 was identified in a serum from 1959) (Zhu et al., 1998) and a biopsy from 1960 (Worobey et al., 2008). Molecular clock analyses estimated the date of the most recent common ancestor of HIV-1 group M around 1908 with a confidence interval of 1884–1924 (Wertheim et al., 2009). A similar time frame is estimated for the origin of the HIV-1 group O radiation; 1920 with a range from 1890–1940 (Wertheim et al., 2009). Since the first identification of HIV-1 group N in 1998, less than 10 group N infections have been described, and all were from Cameroonian patients. The intragroup genetic diversity is significantly lower for group N than for group M or O, which suggest a more recent introduction of the HIV-1 N lineage into the human population and the most recent common ancestor of HIV-1 group N is estimated around 1963 with a confidence interval of 1948–1977 (Wertheim et al., 2009).

26.3.4 SIVs Are Transmitted to Humans by Exposure to Infected Primates

Although the conditions and circumstances of cross-species from SIVs from primates to humans remain unknown, human exposure to blood or other secretions of infected primates, through hunting and butchering of primate bushmeat, represents the most plausible source for human infection. Also bites and other injuries caused by primates, kept as pet animals can favor a possible viral transmission. However, factors associated with single cross-species transmission have to be differentiated from those associated with epidemic spread, the latter being a combination of multiple factors.

26.4 Origin of HIV-2: An Other Emergence, an Other Epidemic

Two independent studies in 1989 and 1992 confirmed the homologies between HIV-2 and SIVsmm infecting sooty mangabeys in West Africa (Hirsch et al., 1989; Gao et al., 1992). Sooty mangabeys are home to West Africa, from Senegal to Ivory Coast, coinciding with the endemic center of HIV-2 (Figure 26.4). In contrast to HIV-1, HIV-2 remained restricted to West Africa and HIV-2 prevalences are even decreasing, since HIV-1 M is now also predominating in West Africa (de Silva et al., 2008; van Tienen et al., 2009). The highest HIV-2 prevalences have been observed in Guinea-Bissau and southern Senegal (Casamance area). Overall, HIV-2 is less pathogenic, less transmissible with almost absence of mother to child transmission, and less-efficient sexual transmission most likely related to lower viral loads (Gottlieb et al., 2006; Hawes et al., 2008). However, a high genetic diversity is seen among HIV-2 strains, eight groups (A−H) of HIV-2 have been described so far (Damond et al., 2004) (Figure 26.4), each corresponding to a cross-species transmission. Only groups A and B are largely represented in the HIV-2 epidemic, with group A circulating in the western part of West Africa (Senegal, Guinea-Bissau) and group B being predominant in Ivory Coast. The ancestors of the HIV-2 group A and B viruses have been identified in wild sooty mangabey populations in the Tai forest in Ivory Coast, close to the border with Liberia (Santiago et al., 2005). The other HIV-2 groups have been documented in one or few individuals only. Except for groups G and H, groups C, D, E, and F were isolated in rural areas in Sierra Leone and Liberia, and these viruses are more closely related to the SIVsmm strains obtained from sooty mangabeys found in the same area than to any other HIV-2 strain. Molecular clock analyses traced the origin of the epidemic HIV-2 groups A and B to be around 1932 (1906−1955) and 1935 (1907−1961), respectively (Wertheim et al., 2009). These dates seem to coincide with a political unstable period in Guinea-Bissau, and it has been suggested that civil wars at that time amplified the rapid spread of HIV-2 into the human population (Lemey et al., 2003) (Figure 26.4).

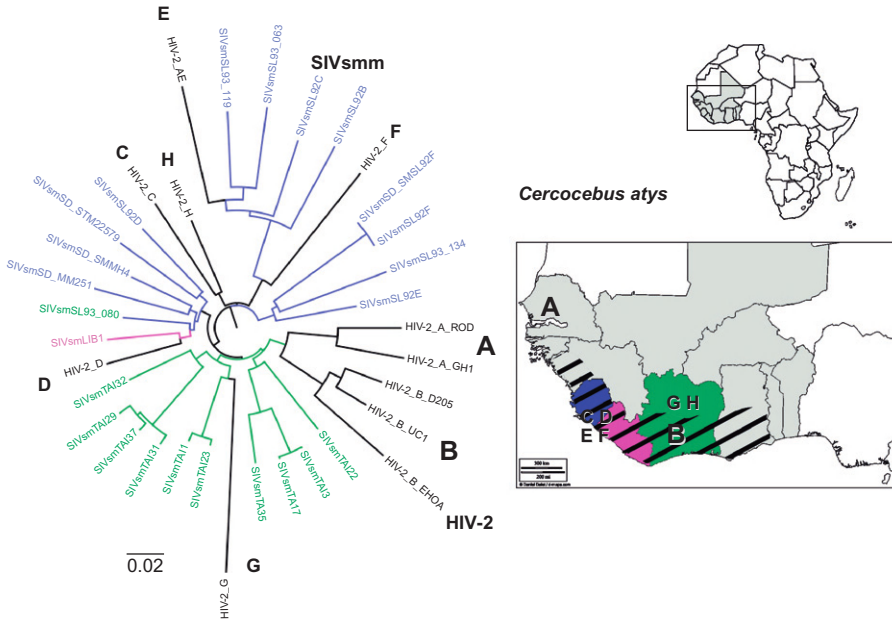

Figure 26.4 HIV-2 is derived from SIVs circulating in sooty mangabeys from West Central Africa. Evolutionary relationship of HIV-2 groups A to H (black) and SIVsmm (blue, green, and pink according to the country of origin) using the neighbor-joining method on partial *env* (741 bp) sequences. Horizontal branch lengths are drawn to scale (the scale bar indicates 0.02 substitutions per site). The map indicates the distribution of HIV-2 in the human population (gray) with letters referring to the HIV-2 groups in the different areas, capital letters refer to epidemic strains, lower cases refer to geographically isolated HIV-2 variants with no or limited spread in humans. The geographic range of sooty mangabeys (*Cercocebus atys)* is highlighted by black lines, color codes for the different SIVsmm strains in the phylogenetic tree are green for strains from Ivory Coast, pink for Liberia and blue for Sierra Leone. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this book.)

26.5 Ongoing Exposure of Humans to a Large Diversity of SIVs: Risk for a Novel HIV?

26.5.1 Exposure to SIV-Infected Primates Is Still Ongoing

Bushmeat hunting, as a source of animal proteins and income for the family, is a longstanding common component of rural households in the Congo Basin, and more generally throughout sub-Saharan Africa. However, the bushmeat trade has increased significantly during the last decades, due to the expanding logging industry and the increasing demand of bushmeat in cities (Laporte et al., 2007). Indeed, a recent study showed that in Northern Congo, the bushmeat trade increased

together with the increasing presence of logging concessions in the same area (Poulsen et al., 2009). Commercial logging has led to road constructions penetrating remote forest areas, to human migration, and the development of social and economic networks (including those of sex workers), which support this industry. Furthermore, villages around logging concessions have grown from a few hundred to several thousand inhabitants in just a few years, and the number of people entering previously inaccessible forest areas increased significantly over the last decades. Importantly, the HIV prevalences in these previous rural settings are also increasing. A high number of individuals with immune deficiency are thus potentially exposed to new viruses, and recombination between newly introduced SIVs and circulating HIVs can pose an additional risk for the outbreak of a novel HIV epidemic (Laurent et al., 2004; LeBreton et al., 2007).

Our prior studies on primate bushmeat in Cameroon showed that bushmeat hunting is not limited to chimpanzees and mangabeys, but the majority of hunted primates are represented by multiple *Cercopithecus* species, colobus monkeys, mandrills, drills, etc. Moreover, these data revealed ongoing exposure of humans to a plethora of different SIVs (Peeters et al., 2002; Aghokeng et al., 2009). Cross-species transmissions with SIV strains from other primates to humans should thus be considered. It has also to be noted that apes are not only hunted for bushmeat but also medicinal uses (Meder, 1999). The socioeconomic changes, which go together with the presence of logging or other industries in remote areas, combined with the SIV prevalence and genetic complexity in wild living primates, suggest that the magnitude of human exposure to SIV has increased, as have the social and environmental conditions that support the emergence and spread of new zoonotic infections.

26.5.2 SIV Prevalences and Cross-species Transmissions

The chances for cross-species transmissions most likely increase when frequency of exposure and SIV prevalences are high. A recent study in pet monkeys in Cameroon revealed that SIV prevalence in mandrill pets could reach 23% (Ndembi et al., 2009). We recently showed among more than 2,500 samples in Cameroon and by using SIV lineage specific Elisas that about 3% of primate bushmeat is SIV infected, but prevalences can vary from 0% to 10% depending on geographic localities, or from 0% to 40% according to species (Aghokeng et al., 2009). Interestingly, the lowest prevalences (0% to 1%) were observed among the most frequently hunted species, reducing thus the risk for cross-species transmissions. However, this situation can be different in other geographic areas, for example in the DRC a pilot study showed that 20% of the primate bushmeat are infected with the highest prevalences among the most frequently hunted monkeys (Ahuka-Mundeke et al., 2010). Our studies on wild chimpanzees in Cameroon showed also that SIVcpz prevalences in chimpanzee communities infected with the ancestors of HIV-1 M and N are among the highest (i.e., around 30%) (Keele et al., 2006; Van Heuverswyn et al., 2007).

Moreover, in West Africa, the SIVsmm prevalences of wild mangabeys are around 50%, and at least eight cross-species from mangabeys to humans occurred.

In this same region, 50% of western red colobus monkeys are also infected with SIVs and are together with mangabeys highly represented among primate bushmeat, but no SIVwrc cross-species transmission to humans has been documented yet. Western red colobus monkeys represent also 80% of animal proteins among the chimpanzee from the *P. t. verus* subspecies in the Tai forest in Ivory Coast, and again no SIVwrc infection could be identified in this chimpanzee subspecies. These data suggest that in addition to SIV prevalences, other factors like viral adaptation to the new host play also an important role.

26.5.3 Viral Adaptation

The majority of the viruses infecting wild animals are not able to cross the species barrier, adapt to a new host, and spread into the new species. The viral and molecular characteristics that allowed the ancestors of HIV-1 and HIV-2 to cross and adapt to humans are not yet identified, and more studies are needed to find out why, for example, SIVs from mangabeys and chimpanzees or gorillas have been transmitted at multiple occasions and not those of western red colobus or other monkeys. Moreover, cross-species transmissions are not always followed by efficient spread into the new populations, as illustrated by HIV-1 versus HIV-2 and among the different HIV-1 groups, and depend thus not only on the virus but also on the host and the environment (Chastel, 2000; Lloyd-Smith et al., 2009).

Actually, only limited studies showed some viral adaptation, for example at the Gag-30 position in the p17 region of the *gag* gene, methionine or leucine is present among SIVcpz/SIVgor, but in humans all HIV-1 strains harbor an arginine at this position (Wain et al., 2007) suggesting an adaptation of the virus to its new host. Sauter and colleagues showed recently that the Vpu protein of the pandemic HIV-1 M strain is able to block the human restriction factor tetherin, whereas HIV-1 O viruses do not (Sauter et al., 2009). This could have lead to a higher replication of HIV-1 M in humans, better interhuman transmission, and thus allowing a better epidemic spread of the virus in the human population (Gupta et al., 2009). Nef allows viral persistence in the host but controls also for superactivation of the immune system. However, this latter function is lost in certain SIV lineages and more precisely in the ancestors of the HIV-1/SIVcpz lineage, which could thus have resulted in higher pathogenicity in humans, in contrast to SIVsmm/HIV-2 where this adaptation is not observed and which are less pathogenic (Schindler et al., 2006). Another study showed a lower viral fitness for HIV-2 compared to HIV-1, and for HIV-1 O versus M, which could also partially explain the lower prevalence and limited spread of HIV-2 and HIV-1 O (Arien et al., 2005). However, these observations need to be confirmed by additional studies on viral factors.

26.5.4 Human Factors

Human factors also play a major role in the epidemic spread of a new virus, especially among viruses that are transmitted by blood or sexual contacts, as it is the case for HIV. The difference in the localizations of the origin of HIV-1 M (South

Cameroon) and the origin of the epidemic (DRC for HIV-1 M) illustrates the importance of human and environmental factors in the epidemic spread. The main factors involved in human-to-human spread are sexual risk behavior, high prevalences of sexually transmitted infections, absence of circumcision, and transmission through unsafe blood transfusions and nonsterile needles. These factors associated with sociodemographic factors like human density in forest areas, increasing transport between urban and rural areas, human migration, urbanization, increase in commercial sex were in favor of an epidemic spread of the virus.

26.5.5 Ongoing Cross-species Transmissions from Other Retroviruses from Primates to Humans

SFVs (simian foamy viruses) are infecting primates at high levels; 70% of primates in captivity (Hussain et al., 2003), 97% of wild western red colobus monkeys (Goldberg et al., 2009), between 44% and 100% of wild chimpanzees (Liu et al., 2008). Epidemiological studies among primate care workers in the United States showed a SFV prevalence of 25% in persons who reported ape bites (Switzer et al., 2004; Calattini et al., 2007). However, human-to-human transmission or a SFV epidemic has not been documented yet, and no pathogenicity associated with SFV infection has been observed in humans. In this example, cross-species transmissions were thus possible, but viral adaptation was insufficient to allow a spread of the virus into the new host.

Exposure to nonhuman primates allowed also the emergence of HTLV (Human T-lymphotropic virus) in humans (Wolfe et al., 2005; Switzer et al., 2009) and recent studies among hunters in central Africa showed ongoing cross-species transmissions of STLVs (Sintasath et al., 2009; Zheng et al., 2010). These T-lymphotropic viruses are thus able to cross the species barrier, and certain variants were able to spread into the human population leading to HTLV-1 and HTLV-2, which are endemic in certain parts of the world.

The ongoing transmissions of SFV and STLV highlight the risk for potential emergence of a new SIV into the human population. The recent discovery in 2009 of a new HIV-1, group P, is an additional demonstration of a zoonotic transmission.

26.6 Conclusion

Actually, we have a clear picture of the origin of HIV and the seeds of the AIDS pandemic. The current HIV-1 epidemic provides evidence for the extraordinary impact that can result from a single primate lentiviral zoonotic transmission event. Despite the fact that the first AIDS cases have been observed around 1980 in the United States, the virus circulated already early in the twentieth century in the human population in central Africa (Figure 26.1). Currently, at least 12 SIV cross-species transmissions occurred, 8 for HIV-2 and 4 for HIV-1, but most likely several others occurred in the past, which remained unrecognized since some viruses

were not able to adapt to the new host or the environment was not suitable for epidemic spread. Because humans are still exposed to a plethora of primate lentiviruses through hunting and handling of primate bushmeat, the possibility of additional cross-species transfers of primate lentiviruses from other primate species in addition to chimpanzees, gorillas, or sooty mangabeys has to be considered. One major public health implication is that these SIV strains are not always recognized by commercial HIV-1/HIV-2 screening assays. As a consequence, due to the long incubation period, human infection with such variants can go unrecognized for several years and lead to another epidemic. Identification of SIVs in wild primates can serve as sentinels by signaling which pathogens may be a risk for humans and allow the development of serological and molecular assays to detect transmissions with other SIVs in humans. While more insight is gained about the origin of the HIV-1 and HIV-2 viruses, some important questions concerning pathogenicity and epidemic spread of certain HIV/SIV variants need to be further elucidated.

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Origin and emergence of HIV/AIDS.

In : Tibayrenc Michel (ed.). Genetics and evolution of infectious diseases. Amsterdam : Elsevier, 2011, p. 689-710.

(Elsevier Insights Series). ISBN 978-0-12-384890-1