



# AIDS as a Zoonosis: Scientific and Public Health Implications

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Evidence of simian immunodeficiency virus (SIV) infection has been reported for 26 different species of African nonhuman primates. Two of these viruses, SIVcpz from chimpanzees and SIVsm from sooty mangabeys, are the cause of acquired immunodeficiency syndrome (AIDS) in humans. Together, they have been transmitted to humans on at least seven occasions. The implications of human infection by a diverse set of SIVs and of exposure to a plethora of additional human immunodeficiency virus-related viruses are discussed.

Emerging infectious diseases represent substantial threats to global health (1). As such, AIDS ranks as one of the most important infectious diseases facing humankind in the 21st century. Since its initial clinical description less than two decades ago, AIDS has resulted in the deaths of more than 16 million people worldwide (2). Human immunodeficiency virus-type 1 (HIV-1), the most common cause of AIDS, has infected more than 50 million individuals (including those who have died), and the rate of new infections is estimated at nearly 6 million per year (2). Equally disturbing are the uncertainties of the epidemic to come. Although sub-Saharan Africa remains the global epicenter, rates of infection have increased in recent times in the former Soviet Union and parts of south and southeast Asia, including India and China, where literally hundreds of millions of individuals are potentially at risk. In the United States, new waves of infection have been recognized in women, minorities, and younger generations of gay men. Combination antiretroviral therapy has afforded many people clinical relief, but the costs and toxicities of treatment are substantial, and HIV-1 infection remains a fatal disease. Moreover, the vast majority of infected people worldwide do not have access to these agents. Thus, although the demographics (and, in some instances, the natural history) of AIDS have changed, the epidemic is far from over; instead, it is evolving, expanding, and posing ever greater challenges.

Like the epidemic, the viruses responsible for AIDS have proven to be more complicated and more unpredictable than first recognized. The AIDS viruses are members of the lentivirus family of retroviruses. As such, they have been amply demonstrated to exhibit the remarkable (and perplexing) properties of insidious disease induction, persistence, latency, variation, recombination, and escape from immune and drug pressures. There are two distinct types of human AIDS viruses, HIV-1 and HIV-2, which are distinguished on the basis of their genome organizations and phylogenetic (i.e., evolutionary) relationships with other primate lentiviruses. Both have been further subclassified on the basis of phylogenetic criteria. Current data indicate that HIV-1 comprises three distinct virus groups (termed M, N, and O), with the predominant M group consisting of 11 clades denoted subtypes A through K (3). Similarly, HIV-2 strains infecting humans have been found to comprise six distinct phylogenetic lineages, subtypes A through F (3). Reconstruction of the phylogenetic relationships among the many strains of HIV-1 and HIV-2, as well as related viruses from African primates, has made possible the elucidation of the simian origins of AIDS as well as circumstances and factors contributing to the initiation of the epidemic.

Current evidence indicates that the SIV counterparts of HIV-1 and HIV-2 were introduced into the human population no fewer than seven times, and possibly more (4–7). Yet the HIV-1 group M viruses, which are responsible for the great majority of all HIV infections worldwide, appear to have arisen from just one such cross-species transmission event (4). We discuss the scientific and public health implications of human infection by a genetically diverse set of SIVs and of human exposure to a plethora of additional HIV-related viruses now known to infect African primates.

## Phylogeny of Primate Lentiviruses

Humans are not the natural hosts of either HIV-1 or HIV-2. Instead, these viruses have entered the human population as a result of zoonotic, or cross-species, transmission. We now know of at least 18 distinct primate lentiviruses that naturally infect different African primates (Table 1).

Although these simian lentiviruses are termed immunodeficiency viruses because of their genetic and structural similarities to the human AIDS viruses, the simian viruses have not been observed to cause disease in their natural hosts. SIV infections of 20 different primate species have thus far been identified and confirmed by molecular analyses, and six additional species have been found to harbor SIV-specific antibodies (Table 1). In most instances, the infected primate species represents the natural reservoir of the virus, and the virus is so designated (e.g., simian immunodeficiency virus of sooty mangabeys, or SIVsm). Less frequently, primates experience incidental infection after exposure to viruses whose natural host is a member of a different primate species; examples include SIVagm infections of a patas monkey, a yellow baboon, and a chacma baboon (Table 1). It is thus clear that African primates represent an extremely large reservoir of lentiviruses with the potential for infecting other species (including humans) in their natural habitats.

The primate lentiviruses for which full-length genomic sequences are available fall into five major, approximately equidistant, phylogenetic lineages (Fig. 1). These five viral lineages are represented by (i) SIVcpz from chimpanzees (*Pan troglodytes*), together with HIV-1; (ii) SIVsm from sooty mangabeys (*Cercocebus atys*), together with HIV-2 and SIVmac from macaques (genus *Macaca*); (iii) SIVagm from four species of African green monkeys (genus *Chlorocebus*); (iv) SIVsyk from Sykes' monkeys (*Cercopithecus albogularis*); and (v) SIVlhoest from l'Hoest monkeys (*Cercopithecus lhoesti*), SIVsun from sun-tailed monkeys (*Cercopithecus solatus*), and SIVmnd from a mandrill (*Mandrillus sphinx*). The phylogenetic positions of the other viruses listed in Table 1, including those infecting *C. mitis*, *C. hamlyni*, *C. neglectus*, *C. campbelli*, *C. wolfei*, *C. torquatus*, *M. talapoin*, *C. guereza*, and *M. leucophaeus*, remain to be fully resolved.

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# Host-Dependent Evolution of Primate Lentiviruses

Much can be learned about the evolutionary origins and transmission patterns of primate lentiviruses, including HIV-1 and HIV-2, from their positions in phylogenetic trees. The primary observation is that all viruses from any one (nonhuman) primate species are generally much more closely related to one another than to viruses from another species. That is, the SIVs form host-specific clusters within the evolutionary tree, which implies that they have been infecting their respective primate hosts for a relatively long period of time. This conclusion is substantially reinforced by instances where SIVs appear to have undergone "host-dependent" evolution, meaning that the divergence (or splitting) of

viral lineages reflects, and was most likely caused by, the divergence of host lineages. For example, African green monkeys comprise four major species: *Chlorocebus sabaeus* (common name, sabaeus monkey) in west Africa, *C. tantalus* (tantalus monkey) in central Africa, *C. pygerythrus* (grivet monkey) in east Africa, and *C. aethiops* (vervet monkey) in east to south Africa. The natural ranges of the four species are largely non-overlapping, and each is infected by SIVagm at high prevalence (8, 9). Viruses from each of the four different green monkey species form four distinct monophyletic clusters, which in turn are more closely related to each other than to other SIVs. A limited example of this is shown in Fig. 1 for three vervet viruses that form a clade and, in turn, cluster

with grivet and tantalus viruses; more extensive trees comprising many more (partial) SIVagm sequences exhibit the same species-specific virus radiations (8, 9). This clustering is clearly host-specific and not geographically based, because vervet viruses from east Africa are much more closely related to other vervet viruses from south Africa than to grivet viruses from nearby sites in east Africa (9).

These observations are best explained by assuming that the common ancestor of the African green monkey species was infected with the common ancestor of the SIVagm lineages, followed by coevolution of virus and host. Alternatively, it could be posited that an SIVagm ancestor infected one of the green monkey species at some time after their

**Table 1.** African nonhuman primates infected with SIV.

Genus	Species/subspecies	Virus	Extent of characterization	Reference
Guenons ( <i>Cercopithecus</i> )	Sykes' monkey ( <i>C. albogularis</i> )	SIVsyk	Full-length sequence of single strain	(53)
	Blue monkey ( <i>C. mitis</i> )	SIVblu	Partial sequence of single strain	(14)
	L'Hoest monkey ( <i>C. lhoesti</i> )	SIVlhoest	Full-length sequence of multiple strains	(49)
	Sun-tailed monkey ( <i>C. solatus</i> )	SIVsun	Full-length and partial sequences of multiple strains	(24)
	Hamlyn's monkey ( <i>C. hamlyni</i> )	SIV?	Serology*	(54)
	De Brazza monkey ( <i>C. neglectus</i> )	SIVdeb	Partial sequence of multiple strains	(14)
	Campbell's mona ( <i>C. campbelli</i> )	SIVmon	Partial sequence of single strain	(14)
	Wolf's mona ( <i>C. wolffi</i> )	SIV?	Serology*	(54)
African green monkeys ( <i>Chlorocebus</i> )	Vervet monkey ( <i>C. pygerythrus</i> )	SIVagmVer	Full-length and partial sequences of multiple strains	(8, 55)
	Grivet monkey ( <i>C. aethiops</i> )	SIVagmGri	Full-length and partial sequences of multiple strains	(8, 56)
	Green monkey ( <i>C. sabaeus</i> )	SIVagmSab	Full-length and partial sequences of multiple strains	(8, 9)
	Tantalus monkey ( <i>C. tantalus</i> )	SIVagmTan	Full-length and partial sequences of multiple strains	(8, 57)
White-eyelid mangabeys ( <i>Cercocebus</i> )	Sooty mangabey ( <i>C. atys</i> )	SIVsm	Full-length and partial sequences of multiple strains	(3, 6, 15)
	Red-capped mangabey ( <i>C. torquatus</i> )	SIVrcm	Full-length and partial sequences of multiple strains	(20, 21)
Talapoin ( <i>Miopithecus</i> )	Angolan talapoin ( <i>M. talapoin</i> )	SIVtal	Partial sequence of single strain	(58)
Black and white colobus ( <i>Colobus</i> )	Mantled guereza ( <i>C. guereza</i> )	SIVcol	Partial sequence of single strain	(59)
Mandrills ( <i>Mandrillus</i> )	Mandrill ( <i>M. sphinx</i> )	SIVmnd/SIVmnd2	Full-length and partial sequences of multiple strains†	(22, 23)
	Drill ( <i>M. leucophaeus</i> )	SIVdrl	Partial sequence of single strain	(60)
Chimpanzee ( <i>Pan</i> )	Western chimpanzee ( <i>P. troglodytes troglodytes</i> )	SIVcpz(P.t.t.)	Full-length sequences of multiple strains	(4, 11, 27, 28)
	Eastern chimpanzee ( <i>P. troglodytes schweinfurthii</i> )	SIVcpz(P.t.s.)	Full-length sequence of single strain	(12)
Patas monkeys ( <i>Erythrocebus</i> )	Patas monkey ( <i>E. patas</i> )	SIVagmSab	Partial sequence of single strain	(17)
Baboons ( <i>Papio</i> )	Yellow baboon ( <i>P. cynocephalus</i> )	SIVagmVer	Partial sequence of single strain	(18)
	Chacma baboon ( <i>P. ursinus</i> )	SIVagmVer	Partial sequence of single strain	(19)

\*Confirmed by Western blot analysis. Members of four additional species (*C. diana*, *C. nictitans*, *C. cephus*, and *A. nigroviridis*) have been reported to have ELISA-reactive antibodies (61). †A second virus (SIVmnd2) highly divergent from SIVmnd has recently been found in wild-living mandrills (22).

speciation, and soon thereafter underwent a series of sequential transmissions to each of the three other species. Although the opportunities for such cross-species transmissions would almost certainly have existed, this latter explanation would require that such transmissions were in each case successful only once, which seems unlikely. In either event, the relationships among known examples of SIVagm indicate that their evolution reflects a long-standing virus-host relationship.

Another instance of host-dependent virus evolution appears to have occurred in chimpanzees. The common chimpanzee (*Pan troglodytes*) has been classified on the basis of mitochondrial DNA analyses into four distinct subspecies (10): the western *P. t. verus*, the Nigerian *P. t. vellerosus*, the central *P. t. troglodytes*, and the eastern *P. t. schweinfurthii*. Thus far, only members of the latter two subspecies have been found to harbor SIVcpz apparently contracted in the wild (4, 11). Of six known natural SIVcpz infections, five (GAB1, GAB2, US, CAM3, and CAM5) have been found in members of the *P. t. troglodytes* subspecies, whereas the remaining virus (ANT) was identified in a *P. t. schweinfurthii* animal (4, 11). All of these chimpanzee viruses form a clade distinct from any other simian lentiviruses (Fig. 1), and furthermore, the five strains derived from

*P. t. troglodytes* animals cluster together separately from the *P. t. schweinfurthii* virus (SIVcpzANT) (Figs. 1 and 2) (4, 11, 12). Again, these observations are consistent with the common ancestor of the SIVcpz strains having infected the common ancestor of *P. troglodytes*, followed by host-dependent viral diversification.

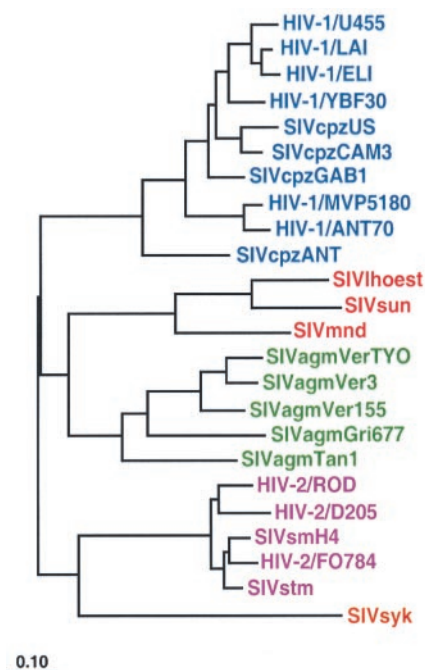
A third probable example of host-dependent evolution involves viruses infecting l'Hoest (*C. lhoesti*) and sun-tailed (*C. solatus*) monkeys. These two species have been classified by some primatologists as belonging to the same superspecies (13), and preliminary analyses of nuclear gene sequences confirm that l'Hoest and sun-tailed monkeys, along with Preuss's monkeys (*C. preussi*), form a tightly knit clade distinct from other *Cercopithecus* species (14). The viruses infecting l'Hoest and sun-tailed monkeys (SIVlhoest and SIVsun) are more closely related to one another than to any other SIV (Fig. 1), consistent with host-dependent evolution.

It is quite likely that further evidence of long-term coevolution of SIV and host lineages will emerge as viruses from more species are fully characterized. The examples so far seem compelling and strongly suggest that lentiviruses have infected these hosts for long periods of time. However, there is one caveat: Taken at face value, these examples of host-dependent evolution would imply that lentiviruses have infected primates for possibly hundreds of thousands or even millions of years, whereas analyses of the extent of genetic divergence among these viruses so far have yielded estimates of divergence times that are more recent (7).

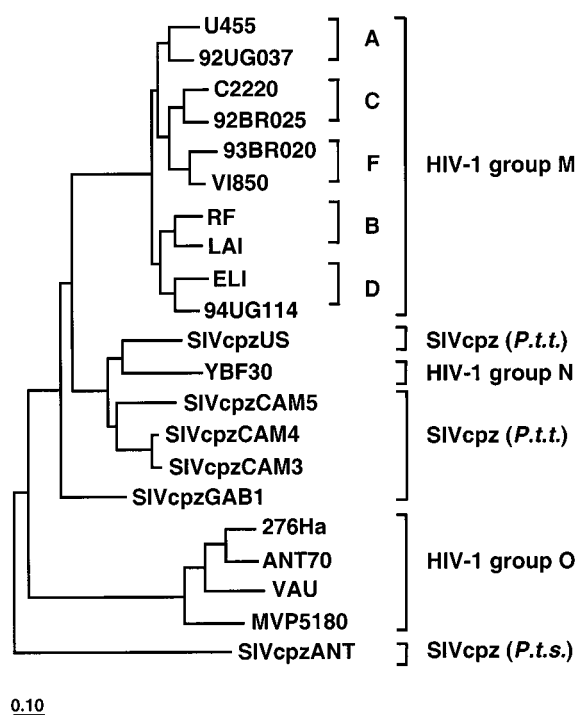
## Cross-Species Transmission of Primate Lentiviruses

The observation that SIV infection in wild-living primates has generally been host-specific serves to highlight those instances where these viruses have jumped between species. Cross-species transmission of primate lentiviruses can have a variety of outcomes in the new host, ranging from incidental infection to epidemic spread, and examples of each have been documented. Transmissions of SIVsm from captive sooty mangabeys to stump-tailed macaques (Fig. 1), rhesus macaques, and pig-tailed macaques represent three well-known examples (15, 16). In each instance, viral infection of the new (unnatural) host resulted in pathology, and SIVsm infection of macaques now serves as a valuable animal model of HIV disease (16). In the wild, transmissions of the local forms of SIVagm to a patas monkey in west Africa (17), to a yellow baboon in Tanzania (18), and to a chacma baboon in South Africa (19) have been reported (Table 1). In none of these cases is it known whether the viruses spread further or whether they caused disease in the new host species.

In cases where the recipients of the cross-species transmission event are already infected by a lentivirus, superinfection by viruses of different lineages has the potential for generating recombinant viruses of considerable genetic complexity. Evidence for such cross-species transmission and recombination events has come from the investigation of viruses infecting west African sabaeus monkeys (SIVagmSab) and red-capped mangabeys (SIVrcm). In each case, phylogenetic analyses revealed signifi-



**Fig. 1.** Evolutionary relationships of primate lentiviruses based on maximum-likelihood phylogenetic analysis of full-length Pol protein sequences (52). The five major lineages are color-coded. SIVs have subscripts denoting their species of origin (defined in Table 1). The scale bar indicates 0.1 amino acid replacement per site after correction for multiple hits (52).



**Fig. 2.** Evolutionary relationships of members of the HIV-1/SIVcpz lineage based on maximum-likelihood phylogenetic analysis of full-length Env protein sequences (52). The three groups of HIV-1 (M, N, and O) are indicated by brackets at the right, as are five representative subtypes of the M group (A through F). The SIVcpz strains were isolated from either *P. t. troglodytes* (*P.t.t.*) or *P. t. schweinfurthii* (*P.t.s.*) animals. The scale bar indicates 0.1 amino acid replacement per site after correction for multiple hits (52).



cantly discordant branching patterns for different parts of the viral genome (9, 20, 21). That is, one part of the viral genome clusters with one viral lineage, whereas another part of the genome clusters with a different viral lineage. This genetic mosaicism indicates that recombination between distinct viral lineages must have occurred at some point during the ancestry of both SIVagmSab and SIVrcm (9, 20). Such recombination events can only take place when animals are coinfecting with divergent viruses. SIVagmSab and SIVrcm are widely distributed in their respective hosts (9, 17, 21) and thus represent examples of cross-species transmissions that resulted in successful virus adaptation and widespread dissemination.

Finally, the fact that SIVmnd falls within the same major lentivirus lineage as SIVlhoest and SIVsun (Fig. 1) is clearly at odds with the evolutionary relationships of these three host species. That is, although l'Hoest and sun-tailed monkeys (both members of the genus *Cerco-pithecus*) are closely related to each other, they are only very distantly related to mandrills (genus *Mandrillus*). Indeed, mandrills have recently been found to harbor a second type of SIV (22) that is highly divergent from the SIVmnd strain shown in Fig. 1 (23). These data support the conclusion that the SIVmnd strain depicted in Fig. 1 is likely the result of a cross-species transmission event. In this case, the primate source is not known but may have been a species closely related to l'Hoest and sun-tailed monkeys, such as Preuss's monkeys (24).

In summary, although host-specific virus evolution of SIVs is generally the rule, there are clear-cut examples of simian-to-simian cross-species transmission in both captive and free-living animals. The frequency of such events and their impact on the primate lentiviral ecosystem are only beginning to be understood.

### Origin of HIV-2

HIV infections have also resulted from cross-species transmission events. Five lines of evidence have been used to substantiate the zoonotic origins of these viruses (4): (i) similarities in viral genome organization, (ii) phylogenetic relatedness, (iii) prevalence in the natural host, (iv) geographic coincidence, and (v) plausible routes of transmission.

HIV-2 was the first human lentiviral infection for which these criteria were satisfied and the simian source of the virus identified (namely, sooty mangabeys). In this case, the five criteria were met as follows: (i) HIV-2 and SIVsm share an identical genome structure, with each virus encoding an accessory protein, termed Vpx, that has not been found in any other primate lentivirus (15). (ii) SIVsm and HIV-2 strains are phylogenetically closely related and cannot be separated into distinct phylogenetic lineages according to their species of origin (Fig. 1). In trees of partial *gag* sequences

from many additional viruses, it has even been possible to find evidence of phylogenetic and geographic linkage of HIV-2 and SIVsm strains at a local level (6). That is, SIVsm and HIV-2 sequences derived from animals and humans from the same immediate geographical area were found to be most related, which implicates hunting or other local activities as the route of transmission. (iii) Sooty mangabeys are numerous in many west African countries and are infected with SIVsm at substantial frequency (22% in some troops) in the wild (6). (iv) There is geographic coincidence between the natural habitat of the sooty mangabey and the areas where HIV-2 is endemic. The historical range of the sooty mangabey is coastal west Africa from south of the Casamance River in Senegal to the Sassandra River in Côte d'Ivoire. This range is in close proximity to the epicenters of the HIV-2 epidemic in Senegal, Guinea-Bissau, Guinea "Conakry," and Côte d'Ivoire, and it overlaps Sierra Leone and Liberia, where the most divergent HIV-2 strains have been identified (5, 6, 25, 26). (v) Sooty mangabeys are frequently hunted for food, and orphans are kept as pets (6). Thus, there is the opportunity for frequent human contact with infected animals.

### Origin of HIV-1

Elucidating the origin of HIV-1 has proven to be more difficult. The same criteria that were used to establish zoonotic transmission of SIVsm to humans have been applied to SIVcpz (4). Early on, SIVcpz and HIV-1 were found to be identical in genomic organization, containing a particular gene, *vpu*, not present in other lentiviruses (27). This similarity in genome organization made SIVcpz a strong candidate for the origin of HIV-1, but other characteristics of the virus raised doubts as to its legitimacy as the immediate precursor to HIV-1. These characteristics included an unexpectedly distant relationship between one isolate of SIVcpz (ANT) and HIV-1 (Fig. 1) (12), seemingly low prevalence of SIVcpz infection in wild-living chimpanzees (28), uncertain geographic coincidence between chimpanzee habitats and early AIDS cases (10, 29), and questions concerning plausible routes of transmission.

In a recent publication (4), we described a new SIVcpz sequence (SIVcpzUS) and, on the basis of its analysis along with other data, concluded that the HIV-1 epidemic had arisen as a consequence of SIVcpz transmission from a particular chimpanzee subspecies, *P. t. troglodytes*, to humans. In that report, we demonstrated HIV-1 to be most closely related at a phylogenetic level to SIVcpz from *P. t. troglodytes*, presented indirect evidence for a higher prevalence of natural SIVcpz infection based on the discovery of viral recombination between SIVcpz viruses of different lineages, described

geographic coincidence for all groups of HIV-1 (M, N, and O) and SIVcpz from *P. t. troglodytes*, and proposed hunting and field-dressing of chimpanzees (a common practice in west central Africa) as a plausible route of zoonotic transmission.

Since that report, further evidence from another group (11) has emerged that substantially bolsters and extends these conclusions. Those investigators screened 29 captive chimpanzees from Cameroon for evidence of SIVcpz infection and identified three animals (CAM3, CAM4, CAM5) as seropositive. Two of these animals had acquired their infection in the wild, whereas the remaining one represented a cage transmission. The two animals (CAM3 and CAM5) presumed to be naturally infected were found to be members of the *P. t. troglodytes* subspecies, and their viruses fell within the SIVcpz(*P.t.t.*) radiation (Figs. 1 and 2). Moreover, in the *env* region, the new Cameroonian chimpanzee viruses were significantly more closely related to SIVcpzUS and YBF30 (the single full-length representative of HIV-1 group N) than to any other virus within the HIV-1/SIVcpz(*P.t.t.*) radiation (Fig. 2). These data thus revealed a close geographical linkage of human and chimpanzee viruses and suggested that the cross-species transmission event that gave rise to HIV-1 group N occurred in Cameroon or its immediate vicinity (11, 30). Molecular viral epidemiological data showing that all known HIV-1 group N infections are restricted to Cameroon further support this hypothesis (30).

In summary, it seems clear that HIV-1 arose as a consequence of SIVcpz transmission from chimpanzees to humans and that the *P. t. troglodytes* subspecies represents a natural host and reservoir for this virus.

### The AIDS Pandemic: Where, When, How, and Why

But where, when, and how did the HIV-1 epidemic begin, and why did it first appear in the late 20th century and not before? The seeds of the HIV-1 epidemic appear to have been planted in west equatorial Africa in the region encompassing Gabon, Equatorial Guinea, Cameroon, and the Republic of Congo (Congo-Brazzaville). It is only here that HIV-1 groups M, N, and O cocirculate in human populations and where chimpanzees (*P. t. troglodytes*) have been found to be infected with genetically closely related viruses (4, 30, 31). It is also within west equatorial Africa that the greatest diversity of HIV-1 group M viruses has been found (32). In addition, chimpanzee and group N human viruses from Cameroon form a unique subcluster in phylogenetic trees of *Env* and *Nef* regions (Fig. 2), implicating this particular geographic region as the site of origin for HIV-1 group N. The precise geographical origins of HIV-1 groups M and O are not known, but further screening and analysis of SIVcpz strains from chimpanzees

within and outside of west equatorial Africa will likely be revealing. In this context, it will be important to look for SIVcpz strains that are particularly closely related to groups M and O. It will also be important to identify and to phylogenetically characterize SIVcpz strains from *P. t. schweinfurthii* animals to confirm that this subspecies is naturally infected, to assess whether the extent of genetic diversity of SIVcpz (*P.t.s.*) is comparable to that of SIVcpz (*P.t.t.*), and to determine whether SIVcpz has indeed evolved in a host-dependent manner.

The timing of SIVcpz transmission to humans, leading ultimately to the HIV-1 pandemic, has been a challenging question. We know from analyses of stored samples that humans in west central Africa had been infected with HIV-1 group M viruses by 1959 (33) and with group O viruses by 1963 (34). But how much earlier were these viruses introduced into the human population? Again, phylogenetic analyses have been informative. The interspersing of HIV-1 group M, N, and O sequences between different SIVcpz (*P.t.t.*) lineages (Figs. 2 and 3A) implies—indeed necessitates—that HIV-1 viruses from groups M, N, and O resulted from no fewer than three separate SIVcpz transmission events. Similarly, in the case of HIV-2, there is interspersing of human and simian sequences that necessitates at least four separate introductions of SIVsm into the human population (Fig. 3B).

Given the limited sampling of naturally occurring SIVsm strains and the extent of diversity between HIV-2 subtypes A, B, and C, it is possible that further studies will reveal that each of the six HIV-2 subtypes arose from separate cross-species transmission events. Conversely, the phylogeny exemplified by HIV-1 group M viruses (i.e., absence of interspersed SIVcpz sequences) implies just the opposite—that the HIV-1 group M pandemic arose as a consequence of a single SIVcpz transmission event, followed by a “starburst” radiation of numerous viral lineages (HIV-1 group M subtypes A through K) in the new host. If this interpretation of the data is correct, then a number of predictions follow. First, current and subsequently identified SIVcpz sequences cannot fall within group M. This prediction has been supported by analyses of all bona fide SIVcpz sequences obtained to date. Second, it should be possible to estimate the timing of the onset of the pandemic by calculating the date of the last common ancestor of HIV-1 group M. The partial characterization of an HIV-1 “fossil” from a plasma sample obtained in Leopoldville (now Kinshasa) in 1959 revealed that this virus fell well within the M group radiation, implying that the M group originated years or even decades earlier (33). These data contradicted earlier timing estimates that had placed the origin of group M around 1960 (35). More recently, a far greater number of well-characterized group M viral sequences has become available for

analysis (3). This has made possible the development of more sophisticated molecular clocks, founded on more realistic models, which take into consideration the peculiarities of HIV sequence evolution (7). A first attempt to use such a clock derived an estimate for the last common ancestor of group M viruses at about 1940, but with wide confidence limits (36). More recent studies have pushed this date back even further, to around 1930, with confidence intervals of  $\pm 20$  years (37). Thus, the introduction of SIVcpz into humans, giving rise to HIV-1 group M, most likely occurred in the early part of the 20th century.

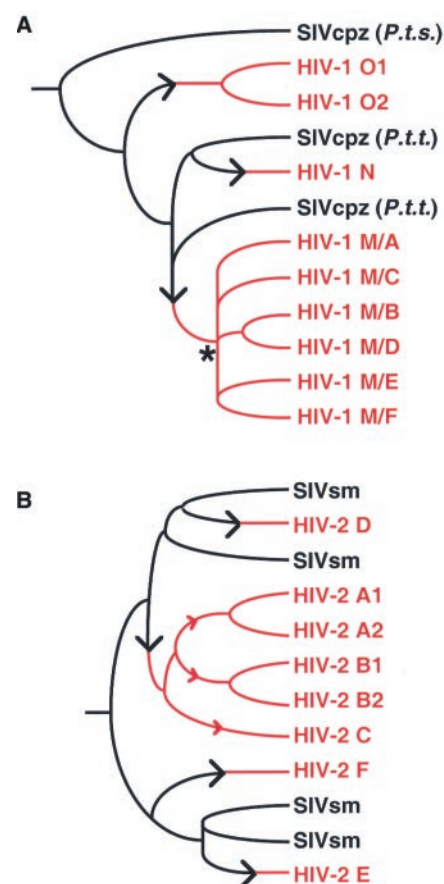
How the AIDS epidemic actually began, what the contributing factors were, and why it appeared in the mid- to late 20th century (and not before) are not known. Whatever the final answers are, they must account for (i) at least seven separate introductions of SIVcpz and SIVsm viruses into humans; (ii) the fact that the HIV-1 group M, N, and O viruses are significantly more closely related to SIVcpz viruses from *P. t. troglodytes* than to the single SIVcpz isolate from *P. t. schweinfurthii*; and (iii) the estimation of 1930 (range 1910 to 1950) as the timing of the last common ancestor of the HIV-1 group M viruses.

Two competing hypotheses have sought to explain the AIDS outbreaks. One, favored by our group, suggests that SIVcpz and SIVsm have been transmitted to humans as a result of cutaneous or mucous membrane exposure to infected animal blood (4). Among wild-living primates, biting and predation represent the most likely means of infection (17–19). In humans, direct exposure to animal blood and secretions as a result of hunting, butchering, or other activities (such as consumption of uncooked contaminated meat) provides a plausible explanation for the transmission of lentiviruses from primates to humans. Figure 4 is an example of the kind of exposure to animal blood regularly experienced by hunters and food handlers. There is precedent for direct blood and virus contact leading to human infection by HIV-1 and SIVsm in health care and primate center workers (38).

If direct exposure to primate blood (by hunting or other means) is the principal mechanism of SIV transmission to humans, zoonotic transfers of lentiviruses must have occurred repeatedly over the ages. In this context, a distinction must be made between the initial transmission of a virus between members of two species and the many additional factors required for subsequent epidemic spread. To account for the appearance of AIDS as an epidemic in the 20th century, and not before, a combination of various contributing factors has been proposed: social disruption, enslavement, urbanization, prostitution, and other sociobehavioral changes not yet fully understood (39). In addition, the use of nonsterilized needles for parenteral injections

and vaccinations could have resulted in rapid serial passage of viruses in humans, thereby facilitating viral adaptation to the new host (39).

It is notable that although SIVcpz (*P.t.t.*) and SIVsm strains have each been transmitted on multiple occasions, their subsequent spread within the human population has been quite variable, for reasons that remain speculative (40). For example, in the case of HIV-2, only two of the six lineages (subtypes A and B) appear to have infected substantial numbers of



**Fig. 3.** Schematic trees illustrating multiple independent zoonotic transmissions of SIVcpz and SIVsm to humans. The phylogenetic relationships shown are derived from many other analyses [see, for example, Figs. 1 and 2 and (4–7, 11)]. Branches in black indicate evolution of SIV within its natural hosts, black arrows indicate points of cross-species transmission, and branches in red indicate subsequent evolution within human hosts. **(A)** SIVcpz (from chimpanzees) and HIV-1. The three known groups of HIV-1 (M, N, and O) are interspersed among SIVcpz strains from *P. t. troglodytes* (*P.t.t.*) and *P. t. schweinfurthii* (*P.t.s.*). The multiple subtypes of group M derive from a common ancestor indicated by a black asterisk. **(B)** SIVsm (from sooty mangabeys) and HIV-2. The six subtypes of HIV-2 (A through F) are interspersed among SIVsm lineages. Further characterization of SIVsm diversity may reveal that subtypes A, B, and C also arose through separate cross-species transmissions (indicated by the red arrows). For HIV-2, multiple isolates have been found only for subtypes A and B.



individuals (5, 6). The other four seem to represent “dead-end” or limited transmissions with no demonstrable spread. In the case of HIV-1, infections with groups O and N have been largely limited to persons from Gabon and Cameroon, and on a global scale have accounted for only a very small fraction of AIDS cases (30, 31). By contrast, HIV-1 group M has infected millions of people worldwide and has spread to virtually every country on the globe (3). These observations illustrate the classic maxim that the epidemiology of an infectious disease reflects complex interactions between the infectious agent, the host, and the environment. Differences in the basic reproductive rates of HIV-1 and HIV-2 (i.e., the average numbers of secondary cases generated by any one primary case) reflect a combination of the rate of partner change, the transmissibility of the infection, and the duration of infectiousness (25, 41). In summary, we subscribe to the hypothesis that direct human contact with infected chimpanzee and sooty mangabey blood resulted in zoonotic transmission of SIVcpz and SIVsm to humans, and that particular social, economic, and behavioral changes that occurred in the early and mid-20th century provided the circumstances whereby these viruses could expand and reach epidemic proportions.

A competing hypothesis (42) suggests that attenuated oral poliovirus (OPV) vaccination trials carried out in the Belgian Congo in the late 1950s were responsible for the cross-species transmission of SIVcpz that initiated the HIV-1 group M epidemic, and that similar OPV trials in west central and west Africa were responsible for the origin of HIV-1 groups N and O and HIV-2, respectively. These ideas rely on the supposition that chimpanzee and sooty mangabey kidneys were used in vaccine preparation, although there is no direct evidence to support this contention. Furthermore, the OPV hypothesis is not consistent with the evidence reviewed above. First, the animals used for polio vaccine safety testing in the Belgian Congo and whose kidneys are speculated to have been used in vaccine preparation were *P. t. schweinfurthii* and *P. paniscus* (bonobos), whereas all of the viruses most closely related to HIV-1 have been isolated from *P. t. troglodytes*. Second, the M group of HIV-1 has been estimated to have originated 10 to 50 years before the OPV vaccine trials were conducted.

It is possible to construct a scenario in which the radiation of the lineages currently constituting HIV-1 group M occurred before the chimpanzee-to-human transmission event, and that humans subsequently became infected by multiple descendant SIVcpz lineages. However, this seems quite implausible. In particular, it would require that the group M subtypes resulted from independent transmissions of at least 10 different, and genetically equidistant, chimpanzee viruses.



Fig. 4. Human exposure to primate blood during food preparation. [Photograph courtesy of Karl Ammann]

In turn, these viruses either would have had to come from different animals, or must represent diverse members of a quasispecies from a single animal. Under the former scenario, equidistant subtypes would not be expected, given the clear phylogenetic substructure seen within the radiation of SIVcpz (Fig. 2) and indeed seen among SIVs naturally infecting other species such as sooty mangabeys (6) or vervets (Fig. 2). Under the latter scenario, no clear virus subtypes would be expected at all, given that recombination among members of the quasispecies (43) would blur the distinction between lineages. In contrast, the starburst radiation at the origin of the group M subtypes (Fig. 2) is best explained by a rapid expansion of virus population size, as has been seen with other epidemically spreading pathogens (44, 45). Thus, it is far more parsimonious to assume that the last common ancestor of group M infected a human rather than a chimpanzee, and that the AIDS pandemic began to spread decades before the OPV trials were conducted.

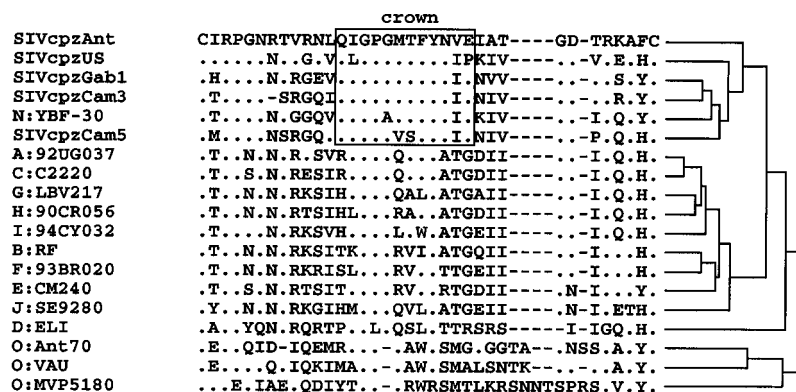
#### Scientific and Public Health Implications

The demonstration of zoonotic transfer of SIV to humans on no fewer than seven occasions has important scientific and public health implications. The fact that two very different primate species—the chimpanzee and the sooty mangabey monkey—are able to serve as the natural host and reservoir for human pathogens that have spread epidemically is especially sobering, given that some 24 additional primate species are known or believed to be infected with related viruses (Table 1). Priority should be given to the full molecular and biological characterization of each of these SIV lineages as well as a search for additional ones. At the same time, phylogenetic analyses should be performed so as to characterize the evolutionary history of

these viruses and to determine the frequency with which they cross primate species barriers. The clear public health implication here is that additional virus strains not detectable by current blood tests for HIV-1 or HIV-2 could infect humans and initially go unrecognized, potentially leading to other disease epidemics.

Because two different chimpanzee subspecies are already known to carry divergent SIVcpz lineages, a concerted effort should be made to identify and phylogenetically characterize SIV viruses that might infect wild-living *P. t. verus* and *P. t. vellerosus* as well as *P. t. schweinfurthii* and *P. t. troglodytes* animals. This approach is feasible now that noninvasive methods have been developed that can detect SIVcpz-specific antibodies and viral RNA in chimpanzee fecal and urine samples (46). Such studies should, once and for all, clarify which chimpanzee subspecies serve as natural SIVcpz reservoirs and which have transmitted their viruses to humans. These analyses should also provide insight into current risks for human exposure to SIVcpz.

Carefully orchestrated studies of SIVcpz in its natural host will provide an opportunity to begin to examine more thoroughly the natural history and pathogenesis of SIVcpz infection in chimpanzees as compared with HIV-1 infection in humans. Comparative analyses of the human and simian viruses may have already thrown some light on this issue. Figure 5 shows an alignment of envelope V3 loop sequences from examples of the major human and chimpanzee viral lineages. Among HIV-1 group M viruses, this V3 region is known to be extraordinarily variable and to play a role in cell tropism and entry (3). Several findings of interest are shown in Fig. 5: (i) Despite marked phylogenetic difference between SIVcpzANT (from *P. t. schweinfurthii*) and the other SIVcpz strains (from *P. t. troglodytes*), there is extraordinary conservation within V3, especially in its 12–



**Fig. 5.** Comparison of V3 loop sequences from SIVcpz and from representative HIV-1 strains belonging to groups N and O and to different subtypes within group M. Sequences are compared to SIVcpzANT with dots indicating amino acid identity and dashes indicating gaps introduced for alignment. The crown motif (boxed) in the central region of V3 is highly conserved among all SIVcpz strains and YBF30 (HIV-1 group N) but highly divergent among members of HIV-1 groups M and O. The phenetic similarities among the V3 loop sequences are indicated at the right. Single-letter abbreviations for amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

amino acid crown sequence; (ii) the HIV-1 group N virus (YBF-30) is far more similar to the chimpanzee viruses than to any human virus, both in the V3 crown and in the extended loop sequence; and (iii) in the same V3 region where chimpanzee viruses are the most conserved, human viruses are most divergent. These data suggest biologically important selective pressures on the V3 region of *env*, conserving the sequence in chimpanzees but promoting change in humans. The unique similarity of the HIV-1 group N virus (YBF-30) to chimpanzee viruses may indicate that the chimpanzee-to-human transmission giving rise to group N occurred

only recently. Alternatively, the apparent scarcity of group N infections in humans may reflect a lack of adaptation to the new host.

Studies are also needed to determine whether transmission of simian lentiviruses other than SIVcpz and SIVsm to humans is now occurring in regions where infections of nonhuman primates are most prevalent. This will require the development of diagnostic assays capable of recognizing a wide range of lentiviral infections. It will also require systematic clinical and virological surveillance of HIV-1- and HIV-2-negative persons with AIDS-like illnesses and of individuals with unusual serological profiles.

Because the clinical case definition for AIDS is limited both in sensitivity and specificity, and because most HIV-negative persons with symptoms typical of AIDS have other medical illnesses, such an undertaking will be labor intensive (47). Nevertheless, several viral variants, including HIV-2, were first recognized in persons with AIDS-like illness who displayed atypical serological profiles.

Risk groups in which exposure to SIV would be expected to be highest include individuals involved in the hunting and butchering of primates and in their capture and trade as pets. In this regard, it is notable that commercial logging of tropical forests represents an expanding industry in several African countries, in turn resulting in road construction into remote areas and the development of social and economic networks supporting this industry (48). As a consequence, the hunting and consumption of wild animals as a food source, traditionally a subsistence activity, has been transformed into a commercial enterprise termed the "bushmeat" trade (Fig. 6) (48). In west central Africa, for example, colobus, sun-tailed, and DeBrazza monkeys as well as mandrills, drills, and red-capped mangabeys are regularly hunted along with chimpanzees. Many of the SIVs known to infect these animals exhibit biological properties that render them at least candidates for natural transmission to humans, such as the ability to replicate efficiently in primary human lymphocytes (20, 49). Thus, the potential for human exposure to a wide range of different SIVs has increased substantially in the past two decades, as have conditions that would be expected to facilitate their widespread dissemination.



**Fig. 6.** Bushmeat market in west central Africa. A chimpanzee (separated into skull, rib cage, limbs, and various internal organs) is shown in the middle of the photo, along with other smoked or fresh meat, including two blue duikers and a spot-nosed guenon in the upper right corner. [Photograph courtesy of Karl Ammann]



Finally, the potential for recombination between currently circulating HIVs and newly introduced SIVs, possibly generating viruses with significantly altered biological properties, must be considered. Many examples of recombinant human and simian lentiviruses have been described (3, 50). The majority of these have been reported for HIV-1 group M, primarily between members of different subtypes. Some of these recombinants have demonstrated their biological fitness by becoming major circulating forms of epidemiological significance (3). Examples include HIV-1 A/E and A/G recombinants that circulate epidemically throughout south-east Asia and Africa, respectively (3). Other examples include recombinant SIVsm (6), SIVagmSab (9), SIVrcm (20, 21), and HIV-2 (5, 50). Together, these viruses highlight the fact that recombination is not a rare event in nature.

The public health implications of virus recombination derive from the potential for rapid acquisition of different biological properties, including drug resistance, altered tropism, and enhanced virulence. In particular, the discovery of viruses that are mosaics of different HIV-1 group M subtypes, or even of highly divergent lineages such as members of HIV-1 groups M and O (51), highlights the possibility that such viruses could evade serologic detection and may not be susceptible to vaccines that are based on a particular virus subtype or group (50).

## Conclusions

Although the first public health priority worldwide must be HIV-1 prevention, ongoing exposure of humans to simian lentiviruses and the potential for additional lentiviral epidemics should not be dismissed. Ultimately, a satisfactory understanding of the pathogenesis of HIVs and of the risks of further zoonoses can only come from a full appreciation of the biology, natural history, and evolution of SIVs in primates. Along the way, it is likely that biological insights will be obtained that are relevant to some of the most pressing concerns facing AIDS investigators, not the least being the development of an effective AIDS vaccine and a mechanistic understanding of HIV-1 persistence, pathogenesis, and immunity. Such work cannot be accomplished, nor such gains achieved, without a keen sensitivity on the part of scientists and policy-makers to endangered species, environmental pressures, social stigma, resource allocation, and a host of factors unique to the African setting. These difficulties notwithstanding, the study of human and simian lentiviral infections should remain a high scientific priority.

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