Coinfection with HIV-1 and Simian Foamy Virus in West Central Africans

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Frequent infection with zoonotic simian foamy virus (SFV) has been reported among HIV-negative primate hunters in rural Cameroon. Plasma samples obtained from urban commercial sex workers (CSWs; \( n = 139 \)), patients with sexually transmitted diseases \(( n = 41 \)) and blood donors \(( n = 179 \)) in the Democratic Republic of Congo [formerly known as Zaire] and Cameroon were tested for SFV and HIV-1 infection. One CSW and one blood donor were found to be seropositive for both SFV and HIV-1, thereby documenting what are, to our knowledge, the first reported cases of dual SFV and HIV infection. The findings of the present study suggest opportunities for bloodborne and sexual transmission of SFV and highlight the importance of defining the clinical consequences of dual infections.

Nonhuman primates (NHPs) are hosts to a plethora of microorganisms, including parasites, bacteria, and viruses. People in contact with NHPs are thus at risk for infection with primate microbes, and there is the possibility that these infections might then spread secondarily from person to person. The pandemic spread of the human immunodeficiency virus (HIV), which originated from cross-species transmissions of simian immunodeficiency viruses (SIVs) from African NHPs, is an example of the potential public health consequences of such zoonotic infections [1].

Simian foamy virus (SFV), a retrovirus in the Spumaretrovirinae subfamily, is widely prevalent in wild-caught and captive-born NHPs [2, 3]. Molecular evidence suggests that SFV has cospeciated with NHPs for millions of years [4]. Transmission of SFV readily occurs in NHPs via contact with infectious body fluids, probably through biting, grooming, and, possibly, to a lesser extent, sexual contact [2, 3]. Although highly cytopathic in vitro, SFV is apparently nonpathogenic in NHPs [2, 3]. Nonetheless, disease associations with SFV have not been systematically evaluated in any NHP species.

Increasing evidence has documented transmission of SFV to persons exposed to the blood and bodily fluids of NHPs [2, 3, 5–7]. Persistent SFV infection occurs in 1%–4% of persons reporting direct contact with NHPs at research institutions, private centers, and zoos in North America and Europe [2, 3, 5]. SFV infection also occurs frequently in natural settings, with a prevalence of 1% noted among persons exposed to NHPs in Cameroon via hunting or butchering NHPs or keeping them as pets [6]. More recently, SFV infection prevalences of 3.6%–24% were reported for persons who received severe injuries during the hunting of monkeys and apes in Cameroon [7]. A worker at a religious temple in Indonesia who was exposed to macaques was also found to be infected with SFV [2, 3]. Phylogenetic analysis demonstrated that, in these persons, zoonotic SFV infection originated from divergent ape and monkey species, including chimpanzee, gorilla, macaque, African green monkey, baboon, and mandrill [2, 3, 5–7]. Combined, these results show that persons in direct contact with NHPs in both occupational and natural settings are at increased risk for SFV infection.

The potential for SFV to cause disease in humans and to be transmitted from person to person after cross-species transmission is not fully understood and has been limited by the testing of small numbers of healthy workers and their close contacts, with little or no clinical follow-up [2, 5]. To date, neither disease nor sexual transmission has been observed after zoonotic SFV infection [2, 5, 7]. Many SFV-infected primate workers have donated blood, increasing the potential for dissemination of SFV through transfusion of contaminated blood [2, 5]. However, the risk of bloodborne transmission of SFV also has not been thoroughly examined in humans, and studies have been limited to a single study of leukocyte-reduced blood product donations from a...
Hunting and butchering NHPs and keeping them as pets are activities that are not unique to Cameroon but, instead, are common and ancient activities in many parts of the world, particularly in West Central Africa. This fact suggests that SFV may be more prevalent and widespread among humans than is currently understood. However, little is known about the geographic penetration of SFV in urban Central African populations not directly exposed to NHPs and among persons at risk for HIV-1 infection. In the present study, we examined the occurrence of dual SFV and HIV-1 infections by use of specimens obtained from commercial sex workers (CSWs), blood donors, and patients with sexually transmitted diseases (STDs) from 2 countries in West Central Africa. We also provide what is, to our knowledge, the first evidence of human coinfection with both retroviruses.

**Methods.** Archived, anonymous plasma samples from Kinshasa, Democratic Republic of Congo (DRC) (formerly known as Zaire), were available from 180 persons, including CSWs who had samples collected in 1985 (n = 97) and HIV-1–positive CSWs (n = 42) and patients with tuberculosis (TB) or STDs (n = 41) who had samples collected in 1999–2000 [8, 9]. Discarded blood units that were collected in 2002 were also available from 179 blood donors from Yaoundé and Douala in Cameroon. HIV-1 infection was detected using commercial EIAs and Western blot (WB) assays, as described elsewhere [8, 9]. HIV-1 subtypes were determined using phylogenetic analysis of gag and envelope (env) sequences that were amplified from plasma RNA by means of polymerase chain reaction (PCR) analysis [8–10].

Plasma samples underwent screening for SFV antibodies by use of EIA and WB assays, as described elsewhere [2, 5, 6]. These assays can detect seroreactivity to both monkey- and ape-type SFV. The criteria for WB positivity included reactivity to the Gag doublet (p68 and p71 or p71 and p74 proteins characteristic of infection with either monkey- or ape-type SFV, respectively) and absence of a similar reactivity in a WB assay performed using uninfected control antigen [2, 5, 6].

When available, DNA was prepared from matching peripheral blood lymphocytes (PBLs), and DNA integrity was confirmed by means of β-actin PCR analysis, as described elsewhere [5, 6]. PBL DNA was tested using 2 generic, nested PCR assays that can detect 465-bp polymerase (pol) and 330-bp long terminal repeat (LTR) proviral sequences from highly divergent SFVs [4–6]. Positive controls for both the pol and LTR PCRs included dilutions of DNA lysates prepared from cells infected with an Asian macaque SFV (SFVmac) isolate. SFVmac is specific to Asian macaques and is not expected to be found among African primates or humans; therefore, it controls against cross-contamination from positive controls [6].

Sequences from PCR-amplified products were phylogenetically analyzed, as previously reported, by use of the neighbor-joining and maximum likelihood methods and 1000 bootstrap replicates or 10,000 puzzling steps, respectively [4–6], to test the reliability of the final tree topologies. The New World SFV-8 sequence obtained from a spider monkey, Asp(SFVspm8) (GenBank accession no. EU010385), was used as an outgroup for phylogenetic analysis of the pol and LTR sequences. The percentage of identity between the human and selected primate SFV sequences was determined using the GAP software program in the Wisconsin sequence analysis package (version 1.03; Genetics Computer Group).

The primate taxonomic nomenclature and geographic range used in the present study are the same as those described elsewhere [2, 4–6]. NHPs were assigned codes based on the first letter of the genus name and the first 2 letters of the species or subspecies name, with the house name or code appearing within parentheses. When known, an abbreviation of the name of the country of origin was included at the end of the house names for wild-caught, wild-born animals (e.g., “CAM” denotes Cameroon and “GAB” denotes Gabon).

**Results.** The HIV-1 seroprevalence among discarded blood units from Yaoundé was 53.6% (96 of 179 units). A total of
28.7% of samples obtained from CSWs in Kinshasa, DRC, in 1985 were HIV-1 seropositive [8], whereas all CSWs and patients with STDs or TB in Kinshasa from 1999 to 2000 were HIV-1 positive, as reported elsewhere [9].

One (0.72%) of 139 CSWs was found to be SFV positive by means of a WB assay (figure 1, lane 13). This specimen was obtained in 1985 from an HIV-1–infected person. One (0.56%) of 179 blood donors from Cameroon was also found to be SFV positive by WB assay, as well as HIV-1 positive (figure 1, lane 9).

A few samples (figure 1, lanes 6, 7, and 15) demonstrated atypical WB profiles and had WB reactivity similar to that of the uninfected control antigen; therefore, they were considered to be SFV negative (data not shown). All 41 samples obtained from patients with TB or STDs were found to be SFV negative by means of EIA. Sequence and phylogenetic analysis of gag and env sequences revealed that both SFV-seropositive persons were found to be infected with HIV-1 subtype A, which is prevalent in Central Africa [8–10].

SFV pol and LTR sequences were PCR amplified from PBL DNA available from the SFV-positive blood donor (CAMBB9). PBL DNA was not available from the CSW. Both the CAMBB9 pol and LTR sequences shared the highest percentage of identity to other SFVmd sequences (97.41%–98.35% and 98.16%–98.52%, respectively), compared with other SFVs. This genetic relationship was confirmed by phylogenetic analysis of pol and LTR sequences from person...
CAMBB9, which inferred that the SFV infection in this person originated from a mandrill (figure 2).

Discussion. Our identification of what are, to our knowledge, the first reported cases of coinfection with SFV and HIV highlights the importance of defining the clinical and public health consequences of zoonotic SFV infection, especially in the context of AIDS. Although HIV-induced immunosuppression can cause a significant increase in the number of opportunistic infections seen in infected persons, it is not clear whether SFV will be an opportunistic pathogen in immunocompromised hosts. The cellular tropism of SFV was recently shown to expand to the small intestinal jejunum of SIV-immunosuppressed macaques, a site for significant CD4+ T cell depletion and inflammation in these animals. This finding suggests that SFV may play a role in the gut-associated pathologic findings observed during progression to simian AIDS in experimental SIV infection [3]. In addition, in vitro data show that SFV-infected cells have increased permissiveness to HIV-1, compared with SFV-uninfected cells [3]. Infection with >1 retrovirus may also provide a biological setting that could alter the pathogenicity and transmissibility of these viruses via such mechanisms as genetic recombination, especially because both HIV and SFV infect CD4+ lymphocytes [3]. Therefore, more research is needed to assess the influence of SFV on the natural history of HIV-1 and to determine whether HIV-induced immunosuppression will increase the likelihood of development of any disease due to SFV. NHPs infected with both SFV and SIV may provide a model in which to investigate further the consequences of these dual infections.

The identification of SFV in a blood donor and a female CSW suggests opportunities for bloodborne and sexual transmission of this virus. However, it is currently unknown whether SFV can be transmitted by sexual contact with an infected person. Although limited testing of a few spouses of SFV-infected men has not shown any evidence of male-to-female transmission, more data are needed to assess sexual transmission of SFV. Currently, there is no available information on the ability of SFV to be transmitted from infected women, including female CSWs [5]. Female-to-male sexual transmission of HIV occurs, but it is less efficient than male-to-female sexual transmission, except in developing countries, where women transmit HIV more easily to men with genital ulcerative lesions [11].

In 2 recent studies, bloodborne transmission of SFV has been documented in macaques by experimental transfusion of whole blood from SFV-infected macaques [12, 13]. Because blood banks do not screen for SFV, secondary transmission via contaminated blood donations may be possible and could contribute to the spread of SFV in the general population. Person-to-person spread could also allow SFV to adapt and evolve to become more transmissible to humans, as has been suggested for other retroviruses after cross-species transmission [1]. In the present study, SFV infection was identified in a blood unit that was discarded because it was positive for HIV-1. However, to date, SFV infections have been identified predominantly in HIV-negative persons, with the majority of infected US primate handlers having donated blood while SFV seropositive [3, 5], thus potentially permitting occult secondary spread of SFV in the general population via blood transfusion. These findings raise questions as to whether strategies are needed to prevent the introduction of SFV into the blood supply. In Canada, deferral of blood donors who report exposure to NHPs has recently been implemented to prevent the introduction of SFV and other primate microbes into the blood supply [14].

In the present study, we document what is, to our knowledge, the first case of SFV infection reported outside of Cameroon in Africa; the case was identified by analysis of plasma samples collected in 1985 from a CSW from DRC. Our findings indicate that SFV infection in humans, as well as coinfection with HIV, may have existed in Central Africa for decades. Although primate contact is common in those areas of West Central Africa where humans and NHPs coexist, and although such contact could be the source of SFV infection in this person, information about primate exposures was not available to evaluate the origin of this infection. Thus, it is not known whether this is a primary zoonotic infection or whether an SFV-infected person was the source of the virus.

In this study, we also reported the second case of human infection with a mandrill SFV, which may be associated with increased exposure to this primate species in Central Africa via hunting and butchering mandrills or keeping them as pets [6]. Interestingly, mandrills are also naturally infected with SIV (SIVmnd), and serologic evidence of infection with SIVmnd has been reported in an asymptomatic man from Cameroon [15]. Similarly, human T cell lymphotropic virus type 1 (HTLV-1) infection in West Central Africa is believed to have originated from simian T lymphotropic virus type 1–infected monkeys, including mandrills [2, 16]. Combined, these results suggest that frequent contact with mandrills in this region may explain the widespread zoonotic transmission of mandrill retroviruses. Effective strategies to reduce the hunting of mandrills and other NHPs are needed to help preserve these endangered species and to prevent their viruses from being transmitted to humans.

References


