

IMPLICATIONS OF SIMIAN RETROVIRUSES FOR CAPTIVE PRIMATE POPULATION MANAGEMENT AND THE OCCUPATIONAL SAFETY OF PRIMATE HANDLERS

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Abstract: Nonhuman primates can be naturally infected with a plethora of viruses with zoonotic potential, including retroviruses. These simian viruses present risks to both captive nonhuman primate populations and persons exposed to nonhuman primates. Simian retroviruses, including simian immunodeficiency virus, simian type D retrovirus, simian T-lymphotropic virus, and gibbon ape leukemia virus, have been shown to cause clinical disease in nonhuman primates. In contrast, simian foamy virus, a retrovirus that is highly prevalent in most nonhuman primates, has not been associated with clinical disease in naturally infected primates. Although it has been shown that human retrovirus infections with human T-lymphotropic virus and human immunodeficiency virus originated through multiple independent introductions of simian retroviruses into human populations that then spread globally, little is known about the frequency of such zoonotic events. In this article, exogenous simian retroviruses are reviewed as a concern for zoo and wildlife veterinarians, primate handlers, other persons in direct contact with nonhuman primates, and other nonhuman primates in a collection. The health implications for individual animals as well as managed populations in zoos and research institutions are discussed, the cross-species transmission and zoonotic disease potential of simian retroviruses are described, and suggestions for working safely with nonhuman primates are provided.

Key words: Nonhuman primates, occupational safety, simian retroviruses, zoonoses.

INTRODUCTION

Retroviruses are a large and diverse group of enveloped RNA viruses in the family *Retroviridae* that replicate in a unique way, using a viral reverse transcriptase (RT) enzyme to transcribe the RNA genome into linear double-stranded DNA. Retroviruses can be either exogenous in nature, replicating independently of the host genome and transmitted as infectious virions, or endogenous in nature, appearing as proviral DNA integrated into the germ line of the host and transmitted vertically. All retrovirus genomes are composed of three major genes flanked by long terminal repeats (LTRs). The

three major genes include the Gag or group-specific antigen that codes for the viral structural proteins, the polymerase (Pol) gene that codes for the RT and integrase enzymes, and the envelope (Env) gene that contains information for the transmembrane and surface proteins of the viral envelope. A smaller genomic region, Pro, is also present in all retroviruses and codes for the protease enzyme used in posttranslational processing of viral proteins. Complex retroviruses also contain additional genes coding for regulatory proteins that control viral replication.

Taxonomically, retroviruses are divided into two subfamilies: the *Orthoretroviridae* subfamily, composed of six genera (*Alpha*, *Beta*, *Gamma*, *Delta*, and *Epsilonretroviruses* and the *Lentiviruses*), and the *Spumaretrovirinae* subfamily, composed of only the *Spumavirus* (foamy virus) genus.³⁸ Exogenous retroviruses of simian origin and of veterinary and public health significance are found in five genera in both retrovirus subfamilies, including the type D simian retrovirus (SRV; *Betaretrovirus*), gibbon ape leukemia virus and simian sarcoma virus (GaLV and SSV, respectively; *Gammaretroviruses*), simian and human T-lymphotropic viruses (STLV and HTLV, respectively; *Deltaretroviruses*); simian and human immunodeficiency viruses (SIV and HIV, respectively; *Lentiviruses*); and simian foamy virus (SFV, *Spumavirus*).³⁸ Retroviruses typically cause life-long, persistent infections with ex-

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tended periods of clinical latency prior to disease development.

Simian retroviruses have received renewed public health interest since it was discovered that HIV types 1 and 2 (HIV-1 and HIV-2, respectively) originated zoonotically from cross-species transmission of SIV from infected chimpanzees (*Pan troglodytes*) and sooty mangabeys (*Cercocebus atys*) in central and west Africa, respectively.^{23,33,34,56,57} Similarly, HTLV type 1 (HTLV-1) has been shown to have originated from cross-species infection with STLV-1 from many primate species, and SFV and SRV infections have been recently observed in persons occupationally exposed to nonhuman primates (NHPs).^{21,25,37,61,62,64,67} Together these results have heightened awareness regarding the public health significance of these cross-species infections and have raised animal and occupational health concerns over the retrovirus status of captive and wild NHPs. The focus of this review article is a brief summary of exogenous retroviruses identified in NHPs, with discussion of the health implications for individual animals and managed populations in zoos and research institutions, description of the cross-species transmission and zoonotic disease potential of SRVs, and highlighting of suggested procedures for working safely with NHPs.

DISCUSSION

SIV

A complex retrovirus that is endemic in many species of African primates, SIV has been found in over 30 species of both wild and captive primates (Table 1).^{3,5,23,42,56} Seroprevalences as high as 76% have been seen in some naturally infected primates, with higher prevalence found in adults.^{3,42} Strains of SIV from different NHP species can be highly genetically diverse, with 10 distinct phylogenetic lineages that share about 60% genetic identity being reported.^{3,5,23,56} Most SIVs can grow in human peripheral blood mononuclear cells (PBMCs) in vitro, thus providing concern regarding the zoonotic potential of this virus.³

SIV usually produces lifelong and clinically unapparent infections in the naturally infected host species. However, when SIV infection jumps from its "natural" host species to a naïve species, as was the case with viral transmission between African NHPs (sooty mangabeys) and Asian macaques (genus *Macaca*) in primate vivaria in the 1960s, immunosuppression and disease was demonstrated.⁴⁰ Clinical signs of immunosuppression and disease due to naturally occurring SIV are rare in African species, but they have been recognized in some pri-

mates after long-term infections.^{3,54,55} Asian primates, especially macaques, are not natural hosts of SIV but are very susceptible to potentially devastating acquired immunodeficiency syndrome (AIDS)-like disease when SIV is accidentally or experimentally introduced into a population.⁴¹ Clinical signs in susceptible populations range from acute epizootic infections to chronic, latently infected animals that may act as disease reservoirs and that may not show clinical signs for years. Lesions may include nonsuppurative histiocytic meningoencephalitis with syncytial giant cell formation, giant cell interstitial pneumonia, and disseminated giant cell disease. Persistent SIV infection may also result in lymphoproliferative diseases.⁴⁰ Similar to HIV infection in humans, SIV infection of macaques has also been reported to cause severe lymphocyte depletion, resulting in immunosuppression and the acquisition of a spectrum of opportunistic infections, such as cytomegalovirus, *Candida*, and *Cryptosporidium*, and the onset of clinical pathology associated with these agents.^{40,41} Natural transmission of SIV is thought to occur predominantly horizontally through sexual contact or via bite wounds, and less frequently by vertical transmission. Cross-species transmission of SIV to primates both in the wild and in captivity has been reported.⁵ Although New World primates and prosimians are not natural hosts to SIV, and although in vitro studies demonstrate resistance of New World monkey cells to SIV infection, the in vivo susceptibility of New World monkeys and prosimians to SIV is unknown.⁶⁵

Diagnosis of SIV infection in NHPs and exposed humans is typically made using a combination of serologic and molecular assays. Screening of plasma and sera with enzyme-linked immunosorbent assay (ELISA) tests using HIV-1 and HIV-2 as antigens, and assays using SIV-specific synthetic peptides have been shown to be useful in detecting cross-reacting antibodies to a variety of SIVs in each of the major phylogenetic lineages.⁵³ Serologic confirmation of virus infection may be done using Western blot (WB) testing utilizing SIV and HIV-1 or HIV-2 antigens, either alone or in combination. Specimens showing WB reactivity to both Env and Gag proteins are considered seropositive. Samples showing reactivity to either Env or Gag alone or in combination with other viral proteins are considered indeterminate and may require additional testing for final resolution. However, caution must be used in interpreting the results if screening for distantly related viral strains that may only show limited SIV cross-reactivity in these assays, appearing as seroindeterminate or seronegative samples. Be-

cause seroconversion may not be immediate after exposure and infection, new animals or animals with indeterminate serologic results may require testing upon arrival and again in 3–6 mo. During this quarantine period, polymerase chain reaction (PCR) testing for viral sequences with or without virus isolation using PBMCs or other tissues containing lymphocytes may also be needed to certify that an animal is SIV negative. Specific PCR primers for the suspected SIV strain may be used for diagnosis and to confirm the serologic results. Generic PCR primers from conserved regions in different SIV genomes may be necessary to confirm infection in cases in which a divergent virus or cross-species infection is suspected. Screening of free-ranging NHPs for SIV can be done noninvasively using feces or urine specimens.⁶³

Detection of genetically modified SIV/HIV (SHIV) recombinants, commonly used as viral inocula in research studies using primates as models of HIV infection, may be complicated by the specific HIV or SIV genes contained in the genetic hybrid. For example, testing for SIV in this case should be restricted to primers located in the SIV portion of the SHIV hybrid. In addition, some SHIVs destroy CD4+ T cells so rapidly that an antibody response is not initiated, resulting in false-negative serologic results.⁷⁴ Thus, molecular testing is needed to confirm infection in some SHIV-infected animals and in persons potentially exposed to these viruses.

Type D SRV

A simple retrovirus and an oncovirus, SRV may be prevalent in up to 90% of some populations of wild and captive macaques (Table 1), and SRV includes five different serotypes (types 1–5).³⁵ Serotypes 1 and 3 are found mainly in rhesus macaques (*Macaca mulatta*), serotype 2 is found in pig-tailed (*Macaca nemestrina*) and cynomolgus macaques (*Macaca fascicularis*), serotype 4 has only been isolated from a cynomolgus macaque, and serotype 5 was found in rhesus macaques imported from China.³⁵ Serotype 3 is also known as the Mason-Pfizer monkey virus.^{35,39} In addition to macaques, SRV has been isolated from squirrel monkeys (*Saimiri sciureus*), spectacled langurs (*Trachypithecus obscurus*), and yellow baboons (*Papio cynocephalus*).²⁸ All three isolates were determined to be endogenous retroviruses that are found in the germline and are thus present in every host cell and are recognized as ‘self’; hence, endogenous retroviruses usually do not trigger an immune response and present a seronegative status. Endogenous retroviruses are typically not highly transmissible horizon-

tally. A new SRV, designated type 6, has been reported recently in the PBMCs of an Indian langur (*Semnopithecus entellus*), but SRV antibodies and multiple tissues were not tested in this animal to confirm if this was also an endogenous retrovirus.⁵¹ Antibodies for SRV have been reported in wild captured talapoin monkeys (*Miopithecus talapoin*), indicating that this virus may be endemic in primates from West Africa.²⁸

As the etiologic agent of simian AIDS (SAIDS), SRV was associated with outbreaks occurring in the 1980s in many U.S. primate centers. This syndrome has been associated with opportunistic infections, cutaneous and retroperitoneal fibromatosis, necrotizing stomatitis with osteomyelitis, acute death, fever, anemia, neutropenia, lymphopenia, thrombocytopenia, hypoproteinemia, persistent diarrhea, lymphadenopathy, splenomegaly, weight loss, thymic atrophy, and fibroproliferative disorders.³⁵ Disease has only been associated with macaques and may be sporadic in individually housed chronic carrier animals, enzootic in large breeding groups with positive animals, or epizootic with high mortality rates following virus introduction to a group of naïve animals.^{35,42}

The virus has been isolated from blood, saliva, urine, and other body fluids, and, thus, SRV is transmitted readily through sexual contact, bite wounds, and from dam to infant, both transplacentally and postnatally.³⁵ Latent infections may occur, and apparently healthy carrier animals have been recognized, particularly in cynomolgus macaques. These animals remain clinically asymptomatic but may shed the virus either continuously or intermittently for long periods before SAIDS eventually develops. Asymptomatic virus-positive animals may be antibody negative, making their identification by serology alone difficult. Because of these unapparent carrier states and the extremely high mortality rates in some naïve macaque populations, adequate testing of both long-term collection animals as well as newly acquired animals is essential to prevent spread of the virus. Both serologic screening as well as virologic screening by culture, PCR testing of PBMCs, or both are needed to detect potentially healthy, virus-positive, seronegative animals.³⁵ Seropositive animals that have recovered from clinical disease but that are latently infected, and so are negative by viral isolation, may undergo recrudescence and may shed virus later.⁴⁰ Criteria for WB positivity included reactivity to at least one Gag protein (p24, p27) and at least one Env protein (gp20, gp70). Sera showing no reactivity to these antigens are considered negative, whereas sera showing reactivity to a single viral protein are con-

Table 1. Simian retrovirus infection documented in various nonhuman primate species^{a,b}

| Genus | Primate species | Common name | Retroviruses ^c |
|-----------------------|--------------------------|-----------------------------|----------------------------------|
| Old World prosimians | | | |
| <i>Otolemur</i> | <i>O. crassicaudatus</i> | brown greater galago | SFV |
| Old World monkeys | | | |
| <i>Allenopithecus</i> | <i>A. nigroviridis</i> | Allen's swamp monkey | SFV, STLV, SIV |
| <i>Chlorocebus</i> | <i>C. pygerythrus</i> | Vervet | SFV, STLV, SIV |
| | <i>C. sabaues</i> | African green monkey | SFV, STLV, SIV |
| | <i>C. aethiops</i> | Grivet | SFV, STLV, SIV |
| | <i>C. tantalus</i> | tantalus | STLV, SIV |
| <i>Erythrocebus</i> | <i>E. patas</i> | patas monkey | SFV, STLV, SIV ^d |
| <i>Lophocebus</i> | <i>L. albigena</i> | grey-cheeked mangabey | SFV, SIV |
| <i>Miopithecus</i> | <i>M. talapoin</i> | Angolan talapoin | SFV, SIV, SRV |
| | <i>M. ougouensis</i> | Gabon talapoin | STLV, SIV |
| <i>Cercopithecus</i> | <i>C. albogularis</i> | Sykes's monkey | SFV, STLV, SIV |
| | <i>C. mitis</i> | blue monkey | STLV, SIV |
| | <i>C. lhoesti</i> | L'Hoest's monkey | SFV, SIV |
| | <i>C. solatus</i> | sun-tailed monkey | SIV |
| | <i>C. cephus</i> | mustached guenon | SFV, STLV, SIV |
| | <i>C. erythrotis</i> | red-eared guenon | SIV |
| | <i>C. ascanius</i> | red-tailed monkey | SIV |
| | <i>C. neglectus</i> | De Brazza's monkey | SFV, SIV |
| | <i>C. mona</i> | mona monkey | SFV, STLV, SIV |
| | <i>C. lowei</i> | Lowe's monkey | SIV |
| | <i>C. campbelli</i> | Campbell's mona | SFV, SIV |
| | <i>C. denti</i> | Dent's mona | SIV |
| | <i>C. pogonias</i> | crested mona | SFV, STLV, SIV |
| | <i>C. diana</i> | Diana monkey | SFV, SIV |
| | <i>C. nictitans</i> | greater spot-nosed monkey | SFV, STLV, SIV |
| | <i>C. hamlyni</i> | Hamlyn's monkey | SIV |
| <i>Macaca</i> | <i>M. mulatta</i> | rhesus macaque | SFV, STLV, SRV |
| | <i>M. nemestrina</i> | pig-tailed macaque | SFV, STLV, SRV |
| | <i>M. fascicularis</i> | cynomolgus macaque | SFV, STLV, SRV |
| | <i>M. arctoides</i> | stump-tailed macaque | SFV, STLV |
| | <i>M. radiata</i> | bonnet macaque | SFV, STLV, SRV |
| | <i>M. fuscata</i> | Japanese macaque | SFV, STLV, SRV |
| | <i>M. silenus</i> | lion-tailed macaque | SFV |
| | <i>M. sylvanus</i> | Barbary macaque | SFV, STLV |
| | <i>M. tonkeana</i> | tonkean macaque | STLV, SRV |
| | <i>M. cyclopsis</i> | Formosan rock macaque | STLV, SRV |
| | <i>M. nigra</i> | Celebes crested macaque | SFV, STLV |
| | <i>M. maura</i> | moor monkey | STLV |
| | <i>M. nigrescens</i> | Gorontalo macaque | STLV |
| | <i>M. ochreata</i> | booted macaque | STLV |
| <i>Mandrillus</i> | <i>M. sphinx</i> | mandrill | SFV, STLV, SIV |
| | <i>M. leucophaeus</i> | drill | SFV, STLV, SIV |
| <i>Papio</i> | <i>P. anubis</i> | olive baboon | SFV, STLV |
| | <i>P. cynocephalus</i> | yellow baboon | SFV, STLV, SIV, ^d SRV |
| | <i>P. papio</i> | Guinea baboon | SFV, STLV |
| | <i>P. hamadryas</i> | hamadryas baboon | SFV, STLV |
| | <i>P. ursinus</i> | chacma baboon | SFV, STLV, SIV ^d |
| <i>Theropithecus</i> | <i>T. gelada</i> | gelada baboon | SFV, STLV |
| <i>Colobus</i> | <i>C. guereza</i> | mantled guereza | SFV, SIV |
| <i>Piliocolobus</i> | <i>P. badius</i> | western red colobus | STLV, SIV |
| <i>Procolobus</i> | <i>P. verus</i> | olive colobus | SIV |
| <i>Pygathrix</i> | <i>P. nemaues</i> | red-shanked douc | SFV |
| <i>Trachypithecus</i> | <i>T. francoisi</i> | Francois' langur | SFV |
| | <i>T. obscurus</i> | Spectacled langur | SRV |
| <i>Semnopithecus</i> | <i>S. entellus</i> | northern plains gray langur | SRV |

Table 1. Continued

| Genus | Primate species | Common name | Retroviruses ^a |
|--------------------|---------------------------|-------------------------------|---------------------------|
| Old World apes | | | |
| <i>Hylobates</i> | <i>H. pileatus</i> | pileated gibbon | SFV |
| | <i>H. leucogenys</i> | northern white-cheeked gibbon | SFV |
| | <i>H. lar</i> | white-handed gibbon | GALV |
| | <i>H. syndactylus</i> | Siamang | STLV |
| <i>Gorilla</i> | <i>G. gorilla gorilla</i> | western gorilla | SFV, STLV |
| <i>Pan</i> | <i>P. paniscus</i> | bonobo or pygmy chimpanzee | SFV, STLV |
| | <i>P. troglodytes</i> | chimpanzee | SFV, STLV, SIV |
| <i>Pongo</i> | <i>P. pygmaeus</i> | Bornean orangutan | SFV, STLV |
| | <i>P. abelii</i> | Sumatran orangutan | SFV, STLV |
| New World primates | | | |
| <i>Ateles</i> | <i>A. species</i> | spider monkey | SFV |
| <i>Cebus</i> | <i>C. species</i> | Capuchin | SFV |
| <i>Saimiri</i> | <i>S. sciureus</i> | squirrel monkey | SFV, SRV |
| <i>Callithrix</i> | <i>C. jacchus</i> | common marmoset | SFV |
| <i>Cacajao</i> | <i>C. species</i> | Uakari | SFV |
| <i>Lagothrix</i> | <i>L. lagothrica</i> | wooly monkey | SSV |

^a Primate nomenclature is as described by Groves.²²

^b Infection determined by presence of cross-reacting antibodies, virus isolation, and/or retroviral sequences.

^c SFV, simian foamy virus; SIV, simian immunodeficiency virus; STLV, simian T-lymphotropic virus; SRV, type D retrovirus; GALV, gibbon ape leukemia virus; SSV, simian sarcoma virus.

^d Monkey-to-monkey cross-species infection.

sidered seroindeterminate. All nonnegative (i.e., positive and indeterminate) sera are further tested in an indirect immunofluorescence assay (IFA) to provide serologic resolution. It has been suggested that PBMCs may not be the optimal tissue to analyze for detection of latent SRV infections and that SRV proviral DNA may be more readily detected in bone marrow and other tissues from infected seropositive macaques whose PBMCs are repeatedly virus negative.⁴⁹

STLV

STLVs are complex retroviruses and are composed of three major groups termed types 1, 2, and 3. STLV-1 and STLV-2 are antigenically and genetically closely related to HTLV types 1 and 2 (HTLV-1, -2), respectively.^{14,17,21,72} STLV has been found in more than 33 species of Old World primates, both in captivity and the wild (Table 1).^{14,17,21,72} The seroprevalence of STLV has been shown to range from 0% to 95% in captive and wild NHPs and increases with age.¹⁷ STLV-1 is found in a variety of Asian and African primates and STLV-2 has only been observed in captive bonobos (*Pan paniscus*), whereas STLV-3 (previously referred to as STLV-L) has only been observed in African NHPs such as red-capped and agile mangabeys (*Cercocebus torquatus* and *Cercocebus agilis*, respectively), greater spot-nosed monkeys

(*Cercopithecus nictitans*), and baboons (*Papio hamadryas*, *Papio papio*, and *Theropithecus gelada*).^{12,14,45,46,69,73} Dual infections with different groups of STLV occur, with STLV-1 and STLV-3 co-infections found in agile mangabeys and baboons.^{12,69} STLV has not been found in New World monkeys in the wild, although experimental infection of squirrel monkeys and common marmosets (*Callithrix jacchus*) has been described.^{17,30} A single report of an STLV-2-infected spider monkey (*Ateles* sp.) has not been confirmed and is believed to represent a laboratory contaminant.¹¹ Collectively, STLVs and HTLVs are referred to as primate T-lymphotropic viruses (PTLVs).

The close genetic relationship between STLV-1 and HTLV-1 strongly indicates that STLV-1 has crossed over into humans from NHPs.⁷² Likewise, the finding of similar STLV-1 genotypes in sympatric primates or captive animals indicates that cross-species transmissions between different primate species can also occur, possibly as a result of fighting and mixed-species exhibits.⁷³ Transmission of STLV is hypothesized to occur via sexual routes since prevalence increases with age. Vertical transmission from dam to offspring may occur, possibly via infected cells in milk.¹⁷

STLV-1 has been implicated in the development of persistent lymphocytosis and abnormal T cells, T-cell lymphomas and leukemia, lymphadenopathy,

generalized skin lesions, and splenomegaly in infected individuals.¹⁷ In three captive lowland gorillas (*Gorilla gorilla gorilla*), STLV was also implicated in a chronic wasting syndrome.⁴⁰ Interspecies transmission of STLV-1 from macaques to baboons in a primate center resulted in an outbreak of malignant lymphoma in a large number of animals.⁷⁵ Clinical presentations included lethargy, low body weights, anemia, pneumonia, skin lesions, and non-Hodgkin's lymphoma.²⁶ In contrast, to date STLV-2 and STLV-3 have not been documented as being pathogenic in NHPs, but these findings are limited to the identification of only a small number of infected NHPs, with no clinical follow-up.

Screening for STLV infection is performed by using serologic assays, such as ELISA or particle agglutination containing HTLV-1 and or HTLV-2 viral lysates, and with IFA by using HTLV-infected cells. Confirmation of infection is done using HTLV-1 WB assays spiked with recombinant Env proteins (GD21) common to both HTLV-1 and HTLV-2 and with peptides specific for HTLV-1 (MTA-1) and HTLV-2 (K55), thus allowing for serologic differentiation of HTLV-1 and HTLV-2, respectively. Animals with reactivity to Gag (p24) and Env (GD21) proteins are considered seropositive, whereas samples showing reactivity to either Env or Gag alone or in combination with other viral proteins are considered indeterminate and may require follow-up testing for resolution.⁷³ The enzyme immunoassays and WB assays have been shown to be capable of detecting antibodies to a broad range of PTLVs.⁷³ Interestingly, STLV-3-infected animals have demonstrated a broad pattern of WB cross-reactivity including indeterminate, HTLV-1-like, and HTLV-2-like cross-reactivities.⁷³ PCR testing of PBMC DNA can also be used to determine infection with this virus, and sequence analysis is required for genotyping into the STLV-1, -2, or -3 groups.

SFV

Spumaviruses, also known as foamy viruses, have been isolated from many species of mammals, including cats (*Felis catus*), cattle (*Bos taurus*), horses (*Equus caballus*), hamsters (*Cricetinae* sp.), sheep (*Ovis* sp.), and sea lions (*Otariidae* sp.).⁴⁷ Unlike SIV, STLV, and SRV, which tend to be more geographically restrictive and host restrictive, SFVs tend to be widespread across species and have been identified with a high degree of prevalence in many Old and New World monkeys, apes, and prosimians (Table 1).^{27,47} In captivity, more than 70% of adult NHPs are infected with SFV.^{27,47} Less is known about the prevalence of SFV in wild-living pri-

mates, but rates as high as 62% have been observed in some species.²⁷ The wide distribution of SFV among a variety of NHPs has been shown recently to be the result of co-speciation of SFV with the primate host, indicating a long history of viral evolution and infection in NHPs estimated to have begun over 30 million years ago.⁶⁸

SFV has a broad host range and can infect many types of cells from a variety of animal species, including humans, in vitro, resulting in cytopathology and cell death. Persistent infection of cell lines with SFV has also been reported.⁴⁷ Although SFV infection was reported in one orangutan (*Pongo pygmaeus*) with encephalopathy, no other clinical diseases have been reported with SFV infection in other species of NHP.⁴⁴ The pathogenicity of SFV in many species appears unclear, and no direct association between infection and disease has been proven. The persistent and subclinical nature of SFV infection may be related to the ancient co-speciation of NHPs with this virus.⁶⁸ Although cross-species transfer of SFV has been reported between NHP species, it is unclear whether or not these infections will lead to disease formation in the new host, as occurs with SIV and STLV.⁶⁸

Latent SFV proviral DNA has been found in most cells and tissues of persistently infected animals, with infectious isolates obtained mainly from the oral mucosa and blood.^{9,27,47} Contact with these two body fluids has been implicated in horizontal transmission of SFV, such as occurs with biting, licking, and transfusions, although sexual transmission is also suspected to occur.^{9,10,47} More recently, viral RNA was found in the feces of 75% of wild-living chimpanzees, indicating that contact with feces, especially mucocutaneously, may also increase the risk of SFV infection.³⁹ Evidence of vertical transmission has been reported in a chimpanzee, although additional data is needed to confirm this route of transmission.⁶⁷ Newborn and infant primates often test negative upon losing passive maternal antibodies, but may acquire positive serologic status from infection when they become juveniles, presumably through contact with infected adults.^{6,10}

The SFV genome is organized like other complex simian retroviruses and consists of Gag, Pol, and Env genes flanked by LTRs. In WB analysis, seroreactivity in SFV-infected primates is consistently detected to either the p68/71 or p71/74 Gag precursor proteins and is thus considered to be a diagnostic marker of infection in monkeys or apes, respectively. However, the Gag proteins from SFV-infected apes and monkeys share only about 60% amino acid identity and only weakly cross-react in

WB assays using a single SFV antigen from either an infected ape or monkey. Therefore, serologic WB testing for SFV antibodies in monkeys and apes, or in humans exposed to these primates, requires the use of two tests—one that contains antigen from a monkey and the other containing antigen from an ape, which will allow detection of antibodies to the Old World monkey or ape SFV variants, respectively. Recently, an assay has been designed that combines both ape and monkey SFV antigens into a single WB assay, thus eliminating the need for two WB tests on each sample.²⁷ Other serologic methods, such as ELISA, IFA, and radio-immunoprecipitation assays (RIPA), have also been used for the detection of SFV antibody.^{6,10,64,67,78} In addition to serologic testing, PCR testing for SFV sequences in PBMCs using generic integrase, Pol, and LTR primers and virus isolation have been used to detect the presence of SFV infection.^{6,10,25,67,78} Screening of free-ranging NHPs for SFV using noninvasive collection of urine and feces has also been reported.³⁹

GaLV/SSV

GaLV is an exogenous, oncogenic type C retrovirus that has been isolated from the white handed gibbon (*Hylobates lar*) (Table 1).¹⁸ The presence of the virus in zoo collections has been associated with lymphoid and myelogenous malignancies as well as osteo-proliferative lesions with marrow infiltration.⁴⁰ Chronically infected, apparently healthy, antibody-negative but virus-positive gibbons have been reported, making diagnostic screening of captive populations difficult. The virus is shed in urine and feces and may be transmitted horizontally by contact with these biomaterials and is also suspected to be transmitted sexually. SSV has been found in a single isolate from a fibrosarcoma in a woolly monkey (*Lagothrix lagotherica*) that was housed with a gibbon. SSV has a defective genome that requires the helper virus simian sarcoma associated virus (SSAV) for replication. Genetic analysis shows that the SSV/SSAV complex is very similar to GaLV, indicating that SSV/SSAV is a strain of GaLV acquired via cross-species infection by the woolly monkey.¹³ SSV/SSAV inoculation of marmosets has produced astrocytomas, fibrosarcomas, and fibromas, although its clinical significance is unknown in captive populations at this time. Serologic assays for GaLV and SSV/SSAV are not readily available and have only limited validation. Thus, molecular screening using PCR assays is the preferred method for detection of infection with this group of retroviruses.

Epidemiology of zoonotic SRV infections of humans

NHPs are commonly used in biomedical research and are typical members of zoo collections and sanctuaries around the world. Given the ubiquity and high seroprevalence of these retroviruses in their natural hosts, it is expected that viral exposures to blood and bodily fluids of NHPs will occur in persons working directly with captive NHPs. To evaluate this possibility, a serologic survey for SRVs in persons exposed to NHPs was conducted by the Centers for Disease Control and Prevention (CDC) at North American primate centers, research institutions, and zoos. This voluntary study screened consenting participants for antibodies to SIV, STLV, SRV, and SFV.^{25,67} In addition, specific exposure information and histories of NHP work were obtained through questionnaires completed by the participants.

Analysis of questionnaire data obtained during the first year of this study found frequent exposures to NHP blood, bodily fluids, and tissues in occupationally exposed workers.⁶⁶ The risk for exposure was highest for animal care workers and persons performing invasive procedures and increased with duration of occupational risk.⁶⁶ Needle-stick or mucocutaneous exposures were reported by 35% of workers with a median of 7.5 years of occupational risk.⁶⁶ The laboratory workers and animal care handlers have occupational risk for exposure to SRVs from naturally or experimentally infected NHPs. Occupational exposure to these retroviruses is not only of concern with regard to the potential adverse health effects for individual workers who are occasionally infected but also because transmission in the occupational setting represents a potential route of secondary transmission from infected workers into the general human population.

Human infection with SIV

As described earlier, cross-species transmission of SIVs from chimpanzees and sooty mangabeys has been linked to the origin of the HIV-1 and HIV-2 epidemics, respectively.^{3,23} Approximately 40 million people worldwide are infected with HIV-1 and HIV-2, with over half of them residing in sub-Saharan Africa.^{3,23} While SIV asymptotically infects many NHPs present in zoo collections, such as mandrills (*Mandrillus sphinx*), drills (*Mandrillus leucophaeus*), De Brazza's monkeys (*Cercopithecus neglectus*), mangabeys, and talapoin monkeys (Table 1), experimental infection of macaques with SIV or the genetically engineered SHIV recombinants can result in a clinical immu-

nodeficiency disease indistinguishable from human AIDS. Therefore, persons working with SIV- or SHIV-infected primates have increased risk of exposure to these lentiviruses, with unknown health consequences.

To investigate the possible exposure of workers to SIV, a study was conducted by the CDC, which tested over 3,000 samples from humans with occupational exposure to NHPs using HIV-2 serologic assays.^{25,67} Two samples (0.06%) were positive for antibodies cross-reactive to SIV, although the sample pool included an unknown number of repeated tests for some participants, and, therefore, the actual prevalence may be slightly higher. One sample was associated with a laboratory worker previously identified to be infected with SIV who reported handling SIV-infected primate samples and SIV-infected culture material without wearing gloves and while having severe dermatitis of the hands and forearms.³¹ The worker has remained seropositive to SIV shortly after the exposure occurred without increases in antibody titer. SIV sequences were detected in this person at two time points surrounding the isolation of SIV from this individual's PBMCs 2 yr after the exposure.³¹ The second worker, also identified previously, had remained persistently seropositive for antibodies to HIV-2/SIV for approximately 11 yr after a needle-stick exposure with SIV-infected macaque blood.⁶⁶ A third person with antibodies to SIV had seroreactivity to SIV disappear shortly after a needle-stick accident involving an SIV-infected macaque.³² Evidence of SIV infection in zoo workers has not been reported.⁶⁷

Viral sequences or isolates have not been detected in either the second or third SIV-exposed persons. The viral load in both persons with persistent anti-SIV antibodies is probably very low, as evidenced indirectly by the low anti-SIV antibody titers and the difficulty in detecting SIV in their PBMCs. Since high viral loads are associated with disease and transmission in HIV-infected persons, the possible low viral load in both persistently SIV-infected persons may help explain why they remain free of AIDS-like symptoms. Combined, these results indicate that primary cross-species transmission of lentiviruses may not always result in associated pathology, although additional clinical follow-up of these persons may be necessary to evaluate diseases with periods of long clinical latency. Similarly, "end-point" infections have been suggested for HIV-2 subtypes D and E, which are believed to be the result of cross-species transmissions of SIV from sooty mangabeys.¹⁹

Human infection with SRV

Screening of humans for SRV indicates that these infections are very rare or nonexistent in the general population. Serosurveys have described partial serologic reactivity against SRV in human sera, but additional evidence of infection has been lacking.^{24,36} Antibodies to type D retrovirus have been reported in 2 of 418 persons (0.48%) who were occupationally exposed to macaques at research centers.^{37,67} One of these workers had persistent, long-standing seropositivity with neutralizing antibody specific to SRV-2, while the second person had waning antibody with eventual seroreversion. The inability to isolate virus and the absence of detectable SRV sequences in the PBMCs of these persons indicate low-level viremias. No disease was reported in either individual.

The finding of SRV seroreversion in the absence of detectable virus in one initially seropositive individual is similar to the report described above of an accidental needle-stick exposure to SIV, in which a transient humoral immune response was documented.³² Taken together, these data indicate a possible abortive infection in this person and indicate that cross-species transmission of SRVs may not always result in the establishment of a persistent infection. Various recently discovered host restriction factors may be at least partially responsible for preventing these infections.⁶⁵

Evidence of SRV infection was reported in one patient with AIDS and lymphoma who had no known contact with NHPs.⁷ SRV was isolated from patient lymphoma tissue, bone marrow was positive for integrated proviral DNA for two viral regions by PCR, and antibodies to both Gag and Env SRV viral gene products were detected in the patient's serum by WB analysis and RIPA.⁷ Genetic characterization of the isolate revealed a close relationship to SRV-3 and SRV-1.¹⁶ This individual had no known history of contact with NHPs or their blood or tissues, and the source of infection remains unknown.

Interestingly, one of the SRV-seropositive participants in the CDC study is also infected with SFV originating from an African green monkey.³⁷ These results show that working with NHPs can lead to infection with more than one primate retrovirus, providing a biological environment that could alter the transmissibility and pathogenicity of these viruses.

Human infection with STLV

Like HIV, evidence indicates that HTLV originated via cross-species infection from STLV-in-

fecting NHPs. Since crossing to humans, HTLV has spread globally to at least 22 million persons through sexual contact, from mother-to-child via infected cells present in breast milk, and by exposure to contaminated blood through transfusions and injectable drug use.^{4,21,79} HTLV-1 causes adult T-cell leukemia and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and other inflammatory diseases in about 2–5% of those infected.^{21,79} HTLV-2 is less pathogenic than HTLV-1 and has been associated with a neurologic disease similar to HAM/TSP.⁴

STLV-1-like infections continue to be reported in persons in central Africa exposed to the blood and bodily fluids of wild NHP populations through hunting, butchering, or keeping of primate pets.^{43,61,77} The viruses found in these individuals include strains genetically similar to STLV-1 from mandrills, gorillas, common chimpanzee, colobus (*Ptilocolobus badius*), and crested mona monkeys (*Cercopithecus pogonias*).^{43,61,77} In addition to STLV-1-like viruses, a novel HTLV, named HTLV-3 as a result of its genetic similarity to STLV-3, was recently identified in African hunters.⁷⁷ A fourth HTLV, designated HTLV-4, was found in the same population and is most likely of primate origin, although an STLV-4-infected NHP has yet to be identified.⁷⁷

Despite evidence that STLV can enter into humans zoonotically, screenings of sera from 418 persons working with NHPs in zoos and research institutions were all found to be negative for antibodies to HTLV/STLV.^{67,77} These results indicate that the risk for infection with STLV in the work place may be low. The absence of STLV-1 infection in primate workers may be explained by a lower prevalence of this virus in captive animals as a result of the inclusion of STLV-1 in pathogen-free breeding programs at many research institutions.

Human infection with SFV

Early studies described a relatively high rate of seroreactivity to SFV among human populations, but these studies lacked definitive evidence of human infection and were not subsequently confirmed by other investigators using more sensitive tests.⁴⁷ Improved diagnostic assays have not documented evidence of foamy virus infection in large numbers of persons in the general population.⁴⁷ In contrast, screening of primate handlers and researchers exposed to NHP-origin retroviruses revealed that SFV can cross into people with NHP exposure.^{25,67} A voluntary study conducted by the CDC screened sera from 418 persons working at North American zoos and primate centers. Fourteen workers

(3.35%) were identified as seroreactive to SFV, and workers comprised both men and women in both facilities in various occupations, including veterinarians, animal handlers, and scientists.^{25,67} Genetic analysis and serotyping of the SFV found in these persons showed that the infection originated from African green monkeys (AGM) ($n = 1$), baboons ($n = 4$), and chimpanzees ($n = 9$). In a separate study, 4 of 133 persons (3%) who worked with mammals, including NHPs, were found recently to be seroreactive to SFV in an anonymous serosurvey of 322 zoo workers.⁶² Antigen-specific WB assays indicated that the SFV infections of these four persons may have originated from apes. Additional studies have identified SFV infection of two additional workers who are infected with either an AGM-like SFV or chimpanzee-like SFV.⁴⁷ SFV screening of 46 exposed Canadian workers identified two seropositive workers (4.3%), including one with a macaque-type SFV infection.⁹

The identification of infection originating from chimpanzees and baboons in five workers, none of whom reported any specific injuries from either chimpanzees or baboons, although they all worked directly with these NHP species, is important. These results indicate that transmission of SFV to humans from exposure to NHP bodily fluids may occur more casually than previously thought. These findings reinforce the importance of adhering to appropriate biosafety precautions while working with NHPs, including using personal protective equipment.⁵²

The high prevalence of SFV infection in these workers raises the question of transmission of SFV to persons exposed to NHPs in natural settings, such as hunters and persons with primate pets. Recently, SFV infection in persons exposed to NHPs in a natural setting in Africa and Asia has been reported, thereby demonstrating that this virus can be transmitted by hunting, butchering, keeping of NHP pets, or visiting religious temples in which free-ranging monkeys live.^{29,78} SFV infection in these studies was determined by genetic analysis to have originated from mandrills, De Brazzas's monkeys, gorillas, and cynomolgus macaques. These results indicate that SRVs are actively crossing into human populations exposed to NHPs and that humans are susceptible to infection with at least seven different SFV strains.

To help understand the transmissibility of this potentially emerging infectious disease, the spouses of six men identified in the CDC study were tested for SFV infection. Analysis of fresh blood specimens by serologic and molecular assays indicated the absence of SFV infection. Published findings

from different studies of SFV-infected humans also indicated that these infections are asymptomatic infections; however, the limited number of cases, short duration of follow-up, and selection biases inherent in the enrollment of healthy workers all limit the ability to identify either potential disease associations or secondary transmission.^{25,47,67} Both the absence of transmission of SFV to spouses and the absence of disease in all six workers after 9–19 yr of infection indicate that cross-species transmission of SFV to humans is not associated with an abrupt change in pathogenicity.⁶⁷

The lack of disease association in the SFV-infected persons is consistent with natural SFV infection of NHP. However, these data cannot exclude the possibility of disease occurrence following long latency periods or by transmission via other routes, such as blood donation. A recent retrospective study of recipients from a blood donor infected with chimpanzee-like SFV failed to identify evidence of SFV infection in two recipients of red cells, one recipient of filtered red cells, and one recipient of platelets.⁸ Nonetheless, more data are needed to better define the risks for SFV transmission through donated blood. Data are also not available to comparatively assess different SFV variants for their relative infectivity, transmissibility, or pathogenic potential in humans. Additional studies are needed to better understand the natural history of SFV infections in humans and to assess the public health implications of these infections.

Human infection with GaLV

Following the discovery of GaLV in the 1970s, serologic evidence of human infection with GaLV was described in persons with different leukemia hematologic disorders and in sera from healthy humans.^{1,2,70,71} Additional studies could not confirm the previous findings, demonstrating that the observed seroreactivity to GaLV antigens was most likely nonspecific reactivity to cellular antigens contaminating the viral preparations or related antigens present in the fetal calf serum used for cell line maintenance.⁵⁹ In addition, testing using more sensitive PCR-based assays has not supported the serologic evidence of GaLV infection. GaLV has been shown to infect many human cell lines *in vitro*, indicating that GaLV may also be able to infect humans *in vivo*.¹⁵ Since GaLV infection is restricted to essentially one or two primate species, diagnostic tools for NHP and human surveillance are limited. However, given the pathogenicity of this virus in gibbons and woolly monkeys, public health surveillance for GaLV, using improved diagnostic

assays, may be needed in persons exposed to these primates at work or in the wild.

Suggestions for prevention of occupational NHP zoonoses

In response to the growing evidence that SRVs may be of important zoonotic potential, and given that the viral status of many captive NHP species in zoos is unknown, a retrospective retroviral survey was distributed by the American Association of Zoo Veterinarians Infectious Disease Committee Retroviral Working Group (AAZV IDC RWG) to all American Zoo and Aquarium Association (AZA) institutions housing Old World NHPs. This survey revealed that a number of NHPs in AZA institutions tested positive for retroviruses via a variety of laboratory methods.⁵⁰ The AAZV IDC RWG then developed guidelines (<http://www.aazv.org/PRIMATESAFETYGUIDELINES.htm>) to provide a framework for specific institutional policies to minimize the risks of disease transmission in zoo collections. The guidelines were designed to minimize human exposure to SRVs as well as other zoonoses while working with NHPs while maintaining the animals' quality of life. The guidelines included sections on personnel responsibilities, personal protective equipment used to prevent exposures, definitions of primate areas, various husbandry and veterinary procedures, staff training, policy development and enforcement, public protection, special procedures, veterinary consulting sources, and necropsy guidelines.⁴⁸ Although these guidelines were developed for working safely with NHPs housed at zoos, they may also be applicable to other settings or institutions in which humans have direct contact with NHPs.

Specific guidelines for the prevention of occupational exposures to SIV have been described in detail elsewhere.⁵⁸ These same recommendations also apply to other SRVs.⁵⁸ These recommendations include the use of "universal precautions" and personal protective equipment (such as gloves, gowns, face shields or masks, and barrier clothing) when handling primates and primate bodily fluids, aerosol control, proper decontamination techniques, personnel training, and institution-specific medical surveillance programs that may include archiving and testing of baseline and postexposure serum samples of workers exposed to NHPs. Consultation with an occupational health physician and institutional safety officers are also suggested for the development and implementation of institution-specific medical surveillance and biosafety programs.

Postexposure prophylaxis (PEP) with antiretroviral drugs may be indicated for some NHP expo-

tures, especially mucocutaneous exposures to bodily fluids from SIV-infected animals.⁷⁶ Similar chemoprophylaxis for SRV and STLV may also be warranted, although the activity of current antiretroviral drugs on these viruses is not fully known.^{20,60} Since SFV is currently not known to cause disease in either NHPs or accidentally infected humans, PEP with antiretrovirals may not be justified for this virus. Ideally, a PEP strategy should be developed prior to an exposure by a team of infectious disease and occupational health physicians and epidemiologists who are all familiar the biology and epidemiology of retroviral zoonoses and the efficacy of available PEP treatments. As described above for SRV, STLV, and SFV, PEP can be complicated and requires knowledge of both the risk of infection following a viral exposure and the efficacy of PEP with different viruses. Educating persons who work with NHPs and NHP biomaterials about exposure risks, personal protection equipment, the availability of antiretrovirals, and the possible side effects and risks of PEP is important for prevention of zoonotic retroviral infection and for decisions regarding PEP treatment.

For reasons of both animal health and occupational safety, determination of the retroviral status of NHP collections, as well as newly acquired animals, should be considered.^{9,23,25,26,29,31,32,35,37,41,42,55,61,62,64,66,67,75,77,78} This may be accomplished by initial serial serologic screening of all animals for antibodies to the SRVs discussed in this review, followed by additional testing 1 yr later to help identify recently exposed animals that may have seroconverted. Serologic testing alone may be sufficient for detection of SIV, STLV, and SFV infection in adult NHPs that are not directly housed with other NHPs with seropositive or unknown infection status.^{10,17,21,25,27,53,73,77} For SRV, initial testing by both serology and virus detection methods, such as tissue culture or PCR, are required to identify all infected animals.^{35,37} Testing for GaLV is currently not routinely available.

It should be recognized that different laboratories may use different assays and reagents to optimize laboratory tests to detect individual viral variants. Thus, several factors should be considered when choosing a particular laboratory for any test used to determine viral infection, including availability, cost, use of quality assurance measures, and verification of assay validation to document the sensitivity and specificity of the test to particular viral strains of interest. Unusual or unexpected results, particularly in highly endangered species or when breeding groups are being established, may require

confirmation in two different laboratories or by different assays. Once an individual NHP has been confirmed to be positive for any retrovirus, it should be considered to be infected for life, and retesting for that virus is not necessary. If an animal is test negative but is housed with test-positive animals, retesting on an annual basis may be necessary to monitor for seroconversion. If all animals in the collection are negative after repeated testing, and no new animals are introduced, alternate or every-third-year testing, with serum banking in between, is justifiable in some cases, depending on the species involved, the risk of anesthesia, the social housing, and the breeding conditions. It must be noted, however, that even in animals with documented negative retroviral status, the potential for spontaneous seroconversion of a previously negative animal is such that annual testing may be recommended, particularly since seroconversion of one animal can result in subsequent conversion of all cohorts over time. If possible, negative animals may be isolated from contact with positive animals and screened periodically until a specific agent has been effectively removed from the cohort and institution. The retroviral status of new acquisitions should be determined prior to their introduction into existing populations. As captive collection size and management allows, positive animals should only be introduced into groups with other positive animals. Introduction of positive animals into known all-negative groups may result in transmission of retrovirus infection and related diseases in the naïve animals. The documented differential pathogenicity of some retroviruses between Asian and African species should reinforce the standard practice of preventing direct contact between members of these two groups of NHPs.^{3,55,75} The pathogenic potential of variants of these viruses among different species of African primates and their ability to infect New World primates and prosimians is largely unknown.

Currently, insufficient information is available to make recommendations for individual risk assessment for movement of NHPs infected with retroviruses to other zoos. The Old World primate Taxonomic Advisory Group and Species Survival Plan veterinary advisors should be consulted for specific advice (www.AAZV.org).

CONCLUSIONS

In recent years, concern for the prevalence and zoonotic risk potential of retroviruses in captive NHP collections at zoos has grown. In addition, concern has also grown with regard to the potential impact these viruses may have on captive NHP

populations, animal breeding, and transfer of specimens to new zoo collections. A growing body of ongoing research has documented retroviral disease risks to captive and wild NHP populations, as well as risks of retrovirus transmission to zookeepers, research workers, and other human populations exposed to NHPs by hunting or keeping of primate pets or following direct contact during visits to Old World countries where NHPs are endemic. Numerous analyses of morbidity, mortality, viral prevalence, and zoonoses risks should be used to develop sound recommendations for good preventative health programs and captive management of NHPs as well as comprehensive occupational health programs for people exposed to NHPs. Institutions housing NHPs will need to continuously review and update their occupational health programs with the latest biosafety and health information associated with retroviral zoonoses to help prevent zoonotic transmission and disease.

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