Isolation of a T-lymphotropic retrovirus from naturally infected sooty mangabey monkeys (Cercocebus atys)

(cross-neutralization/serologic relationship/acquired immunodeficiency syndrome)

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ABSTRACT   Healthy mangabey monkeys in a colony at the Yerkes Regional Primate Research Center were found to be infected with a retrovirus related to human immunodeficiency virus (HIV). Virus was isolated from peripheral blood cells of 14 of 15 randomly selected mangabeys. All virus-positive animals had antibodies to the mangabey virus at the time of virus isolation and, in a retrospective study, 82% of mangabey serum samples obtained in 1981 had antibodies to the virus. The newly isolated retrovirus is (i) morphologically identical to HIV by electron microscopy; (ii) serologically related to the human virus by enzyme immunoassay, immunoblotting experiments, radioimmunoprecipitation, and neutralization; and (iii) cytopathic for human OKT4$^+$ cells. The mangabey virus also shares these properties with the simian T-lymphotropic virus type III (STLV-III) recently isolated from diseased macaques and from healthy African green monkeys (STLV-III$_{AGM}$). However, the mangabey virus, like STLV-III$_{AGM}$, differs from both HIV and STLV-III in that it apparently does not cause clinical immunodeficiency or disease following natural infection of the host from which it was isolated. Comparison of the virus–host interactions of these isolates may be valuable in defining determinants of pathogenicity for cytopathic retroviruses.

Acquired immunodeficiency syndrome (AIDS) is caused by a retrovirus, human T-lymphotropic virus type III/lymphadenopathy-associated virus/AIDS-associated retrovirus (HTLV-III/LAV/ARV) or human immunodeficiency virus (HIV), (1–4), that replicates in and is cytopathic for helper T lymphocytes (OKT4$^+$ cells) (5). Recently, a related virus was isolated by Daniel et al. (6) from rhesus macaques (Macaca mulatta) that had either immunodeficiency disease or a transmissible lymphoma. The simian isolate, termed simian T-lymphotropic virus type III (STLV-III), has many of the characteristics of human HIV. These common characteristics include (i) a tropism for OKT4$^+$ cells with concomitant cytopathology, (ii) a virion morphology typical of retroviruses but unusual in nucleoid morphology, (iii) a Mg^{2+}-dependent reverse transcriptase enzyme, and (iv) a distinct virion protein profile. Also, serologic cross-reactivity was demonstrated (7, 8) when it was shown that antiserum specific for either HIV or STLV-III precipitated proteins of the other.

Although STLV-III was isolated from an Asian primate species, antibodies to STLV-III have also been found in serum samples obtained from a species of monkey commonly found in Africa. Serum samples from 42% of wild-caught African green monkeys (Cercopithecus aethiops) had antibodies to STLV-III proteins (8). Subsequent to these find-

ings, a virus resembling both STLV-III and HIV was isolated from African green monkeys and was designated STLV-III$_{AGM}$ (9).

We have isolated a virus related to STLV-III and HIV from healthy sooty mangabey monkeys (Cercocebus atys) which, like African green monkeys, are indigenous to central and western Africa. Because the mangabey isolate appears to be similar to the prototype simian virus, STLV-III, and in accordance with proposed nomenclature (21), we will refer to the mangabey isolate as SIV/SMM (simian immunodeficiency virus/sooty mangabey monkey).

MATERIALS AND METHODS

Animals. The Yerkes Regional Primate Research Center maintains a colony of approximately 88 colony-born or wild-caught mangabey monkeys that are used primarily for reproductive and behavioral studies. Mangabeys also are used for experimental leprosy infection because of their unique susceptibility to Mycobacterium leprae (10, 11). The 15 animals used in this study were selected at random from among mangabey monkeys that are housed together in an indoor/outdoor facility. The mangabeys selected from the colony were between 4 and 22 years old, and all were colony-born except for nos. 2 and 8 (see Table 1). Blood was collected to obtain peripheral blood mononuclear cells (PBMC) and serum. None of the animals was neutropenic or lymphopenic, and all were clinically normal at the time of blood collection.

Virus Strains. LAV was the gift of L. Montagnier, J. C. Chermann, and F. Barre-Sinoussi, and ARV-2 was obtained from Jay Levy.

Isolation of Virus. Virus was isolated from PBMC of mangabeys by coculturing PBMC with phytohemagglutinin P-stimulated adult human leukocytes (PHA-AWBC). Cell-free supernatants from cocultures were monitored for Mg^{2+}-dependent reverse transcriptase activity as described previously (4). Culture supernatants with positive reverse transcriptase were tested for their ability to transfer infectivity to fresh PHA-AWBC or to established cell lines; some of the initial cocultures were tested by electron microscopy for the presence of virus.

Cellular Tropism. The cellular tropism of SIV/SMM was determined in two ways. First, PHA-AWBC were infected with an isolate of SIV/SMM and, periodically, the number of

Abbreviations: HIV, human immunodeficiency virus; SIV, simian immunodeficiency virus; HTLV-III, human T-lymphotropic virus type III; LAV, lymphadenopathy-associated virus; ARV, AIDS-associated retrovirus; STLV-III, simian T-lymphotropic virus type III; SMM, sooty mangabey monkey; AGM, African green monkey; PBMC, peripheral blood mononuclear cells; PHA-AWBC, phytohemagglutinin-stimulated adult human white blood cells; IFA, indirect immunofluorescence assay; EIA, enzyme immunoassay; RIP, radioimmunoprecipitation.

T-helper (T4) and T-cytotoxic/suppressor cells (T8) in the infected culture and in an uninfected control culture were determined by indirect immunofluorescence assay (IFA) using a T-helper/suppressor ratio test kit (Becton Dickinson). At least 500 cells were counted for each determination. Reverse transcriptase activity in both cultures was also assayed and, in the infected culture, peaked at $>10^6$ cpm per reaction, while that in the control culture never exceeded 1400 cpm. Second, the ability of isolates of SIV/SMM to replicate in established cell lines of different lineages was tested. Approximately 10^5 cpm of SIV/SMM reverse transcriptase activity was used to infect 10^7 cells. Culture supernatants were monitored for reverse transcriptase activity. The cell line HT was provided by R. C. Gallo (National Institutes of Health); HUT78 and 6D5, a subclone of HUT78, by J. Getchell (Centers for Disease Control); and K562, by S. McDougal (Centers for Disease Control).

Serologic Assays. Mangabey serum samples were tested at a 1:50 dilution by enzyme immunoassay (EIA) using Abbott Laboratories HTLV-III EIA kit, at a 1:100 dilution by immunoblot using H9/HTLV-III antigen, and at a 1:20 dilution for SIV/SMM-specific antibodies by indirect IFA using acetone-fixed, virus-infected PHA-AWBC. The second antibody was a fluorescein-labeled goat anti-monkey IgG (Cooper Biomedical, Malvern, PA). Metabolic labeling, immunoprecipitation, NaDodSO$_4$/polyacrylamide gel electrophoresis, and fluorography have been described (12). Briefly, virus-infected cells were labeled with [^{35}S]methionine and [^{35}S]cysteine (200 μCi/ml; 1 Ci = 37 GBq) for 1 hr and then lysed. Viral proteins were immunoprecipitated with rabbit antiserum to HIV (CDC isolate 451), and the proteins were separated on a 10% acrylamide resolving gel. Easy detection of the p18 of HIV required radiolabeling the infected PHA-AWBC for 5 hr (as opposed to the 1-hr labeling period used for the radioimmunoprecipitation (RIP) assay in Fig. 1) and/or longer exposure times.

Neutralization Assay. Serum samples from the 15 mangabeys were screened at a 1:10 dilution for neutralizing activity against SIV/SMM; some of the sera were tested against the LAV strain of HIV. In addition, serum with LAV-neutralizing activity that had been obtained from a chimpanzee infected with LAV (13) was tested for its ability to neutralize SIV/SMM. Approximately 4×10^3 cpm of viral reverse transcriptase activity (LAV or SIV/SMM) was incubated with serum in RPMI 1640 medium for 60 min at room temperature (total volume, 0.5 ml). The virus/antibody mixture was then used to infect 10^7 PHA-AWBC in 2.5 ml of medium B (RPMI containing 10% fetal bovine serum, interleukin 2, and DEAE-dextran). After overnight adsorption, the cells were washed and resuspended in 15 ml of medium

B. Culture supernatants were monitored for extracellular reverse transcriptase activity on days 6, 9, 12, and 16. Neutralizing antibody activity was considered to be present if there was at least 80% inhibition of reverse transcriptase activity compared to reverse transcriptase activity in control cultures.

Nucleic Acid Hybridization. Concentrated virus, prepared from SIV/SMM-infected cell culture supernatants, was lysed, spotted onto nitrocellulose filters, and hybridized to genomic ($\approx$9-kilobase) HIV (clone Zr6; A.S., R.A., P. Luciw, unpublished work) as described (14). High molecular weight DNA was isolated from SIV/SMM-infected cells and digested with several restriction enzymes before it was used with the Zr6 cDNA clone of HIV in Southern hybridization assays (15).

RESULTS

Incidence of Disease in the Mangabey Colony. Since the mangabey colony was established at the Yerkes Primate Center, there has been no apparent difference in the incidence of disease in this species when compared with the incidence of disease in other species of monkeys at the Yerkes field station. During the past 16 years, 55% (42 animals) of the deaths in the mangabey colony resulted from spontaneous disease problems in animals older than 1 month. Neoplastic diseases were not found in any of these animals, and lymphadenopathy of one or more lymph node groups was seen in only six animals. Thus, it appears that SIV/SMM infection of mangabeys does not cause a significant degree of immunodeficiency with opportunistic infections and lymphomas as occurs in rhesus macaques infected with STLV-III (6, 16).

Isolation of Virus. Virus was detected in cocultures of PHA-AWBC and PBMC from 14 of 15 randomly selected mangabeys (Table 1). Reverse transcriptase activity was detected in initial cultures as early as 6 days and as late as 23 days after establishing the cocultures, and peak reverse transcriptase activity reached $>3 \times 10^6$ cpm/ml. Cell-free supernatants of positive cultures transferred infectivity to fresh PHA-AWBC. Examination of cultures by thin-section electron microscopy showed retrovirus particles with eccentric nucleoids that were morphologically indistinguishable from HIV, STLV-III, and STLV-III$_{AGM}$ (data not shown).

Retrospective Analysis of Serum from Mangabeys at the Yerkes Primate Center. Serum obtained in 1981 and 1983 from mangabeys at Yerkes was analyzed to determine how long SIV/SMM had been present in the colony. As shown by indirect IFA, SIV/SMM-specific antibodies were present in serum samples obtained from 9 of 11 (82%) and 7 of 11 (64%)

Table 1. Relationship between serology of and retrovirus isolation from individual mangabeys

Test	Mangabey														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
HIV antibodies*	−	−	−	−	−	−	+	−	+	−	−	−	−	−	−
HIV p24[†]	−	+	−	+	+	+	+	−	+	+	+	+	−	+	+
SIV/SMM[‡]	3+	1+	2+	2+	3+	3+	3+	3+	2+	2+	3+	2+	−	3+	2+
SIV/SMM isolation	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Neutralizing antibodies[¶]	+	−	+/−	+/−	+	+/−	−	+	+/−	+/−	+/−	+/−	−	+/−	−

*Mangabey serum samples were tested at a 1:50 dilution against HTLV-III antigens with the Abbott EIA kit.
[†]Mangabey serum samples were tested at a 1:100 dilution by immunoblot, using H9/HTLV-III antigen.
[‡]Mangabey serum samples were tested at a 1:20 dilution by IFA on SIV/SMM-infected PHA-AWBC. −, No detectable fluorescence; 1+, 2+, 3+, degree of fluorescence, with 1+ < 2+ < 3+.
[¶]Mangabey serum samples were tested at a 1:10 dilution with SIV/SMM isolate 3. Neutralizing activity was determined from reverse transcriptase activity (measured in cpm) in cultures relative to that in a control culture 9 and 12 days after infection. −, reverse transcriptase ≥ 50% of control; +/−, 20% ≤ reverse transcriptase ≤ 50% of control; +, reverse transcriptase < 20% of control.

mangabeys in 1981 and 1983, respectively. Therefore, SIV/SMM infection was probably widespread in the mangabey colony before 1981. Four of the stored serum samples tested retrospectively were from animals in this study. Serum that was obtained from mangabey 1 (Table 1) in 1983 did not have detectable antibodies to SIV/SMM, indicating that seroconversion in this animal occurred between 1983 and June 1985, when the current study began. However, sera obtained in 1981 from mangabeys 3, 5, and 14 (Table 1) were positive for antibodies to SIV/SMM. All four of these animals were colony-born between 1970 and 1976, and none of the animals has had any significant clinical problems.

Antibody Cross-Reactivity to SIV/SMM and HIV. At a serum dilution of 1:50, 2 of the 15 mangabey serum samples were positive by EIA for antibodies to HIV. In contrast, 11 of the 15 mangabey serum samples had antibodies that bound HIV p24 by immunoblot assay (using a minigel system that identifies antibodies to the viral proteins p18, p24, and gp41) (Table 1). That the human and mangabey retroviruses had antigenic determinants that were related was supported by data from RIP assays that were done with various types of serum and PHA-AWBC infected with SIV/SMM or HIV. Precipitation of viral proteins in lysates of SIV/SMM-infected cells with a hyperimmune rabbit antiserum against HIV strain CDC451 identified SIV/SMM-related proteins that were analogous to HIV proteins p18, p24, gp41, p55, gp120, and gp160 (Fig. 1). None of these protein bands were immunoprecipitated when normal rabbit serum was used (data not shown). Although the protein profiles of the two viruses were similar, two of the SIV/SMM proteins had apparent molecular weights that differed from the molecular weights of the corresponding proteins of HIV. The SIV/SMM protein analogous to gp41 was smaller than its HIV counterpart (Fig. 1), and the smallest detectable virion protein immunoprecipitated from SIV/SMM-infected cells was slightly larger than the p18 of HIV (not visible in Fig. 1). A serum sample from mangabey 11 or pooled sera from several mangabeys immunoprecipitated p18 from both SIV/SMM- or HIV-infected cells (data not shown) but did not precipitate a protein of similar molecular weight from uninfected cells.

When serum from the 15 mangabeys was tested by indirect IFA, all 14 virus-positive animals had antibodies that bound to SIV/SMM-infected cells but not to uninfected cells. Serum from the single virus-negative animal was negative for antibodies to SIV/SMM and showed no reactivity to HIV by EIA and immunoblot (Table 1). Serum samples from three LAV-infected chimpanzees reacted with LAV- and SIV/SMM-infected cells by IFA, while serum samples from uninfected chimpanzees were negative in the same assays. When SIV/SMM-specific antisera were tested against LAV-infected cells, little or no reactivity was observed.

Neutralization of SIV/SMM. Serum samples from all 15 mangabeys were tested for neutralizing activity against the SIV/SMM isolate from mangabey 3 (Table 1). Very little, if any, neutralizing activity was detected in any of the sera at the dilution used (1:10). At this dilution, none of the serum samples from the persistently infected mangabeys completely neutralized SIV/SMM. Because HIV-specific antiserum immunoprecipitated most or all of the SIV/SMM proteins, we investigated whether serum that neutralized HIV also neutralized SIV/SMM. A chimpanzee (C-560, ref. 13) serum sample that had a neutralizing titer of approximately 300 against LAV (P.N.F., unpublished work) was used. In a representative experiment, a 1:10 dilution of the anti-LAV serum from chimpanzee C-560 completely neutralized LAV and showed some neutralizing activity against SIV/SMM (Fig. 2). After 11 days in culture, reverse transcriptase activity in the culture (determined as cpm) established after incubation of SIV/SMM with LAV-specific antiserum was decreased by 98% compared to that in the culture established after incubation of SIV/SMM with mangabey serum. Serum from mangabey 14 had a slight effect on the replication of SIV/SMM but no effect on the replication of LAV. Serum obtained from C-560 prior to LAV infection did not neutralize either LAV or SIV/SMM and resulted in virus growth curves
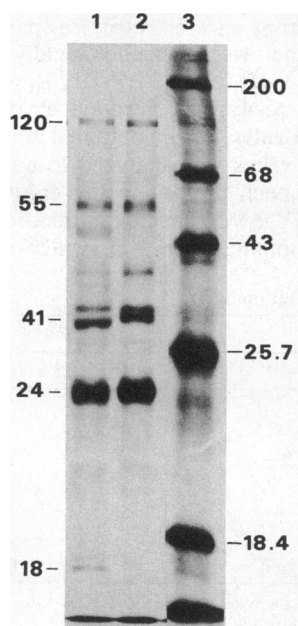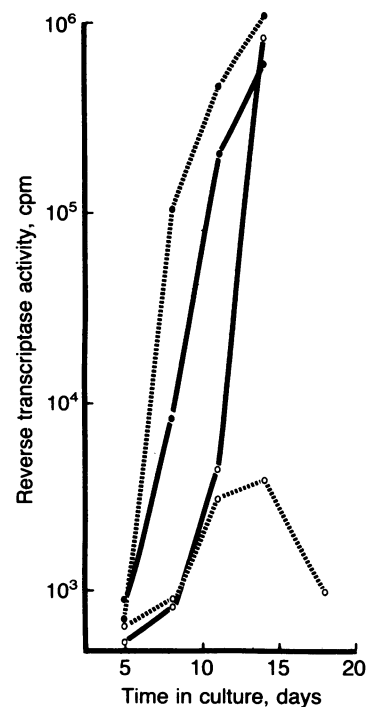

FIG. 1. Comparison of SIV/SMM and HIV gene products by RIP assay. Proteins from PHA-AWBC infected with SIV/SMM (lane 1) or HIV (lane 2) were immunoprecipitated with rabbit antiserum to HIV (CDC isolate 451). Lane 3: ^{14}C-labeled molecular weight markers.

FIG. 2. Neutralization of SIV/SMM and LAV by antiserum elicited by LAV. SIV/SMM (—) and LAV (- - -) were incubated with serum from a LAV-infected chimpanzee (○) or with serum from mangabey 14 (●) prior to infection of PHA-AWBC.

(data not shown) similar to those obtained with serum from mangabey 14 (Fig. 2).

Nucleic Acid Homology Between SIV/SMM and HIV. We were unable to detect homology at the nucleic acid level between two mangabey virus isolates and HIV using two different techniques at high- and low-stringency conditions. Dot-blot hybridization of SIV/SMM viral RNA and a 9-kilobase clone of HIV showed no detectable RNA·DNA sequence homology between SIV/SMM, and HIV. In addition, Southern hybridization of cloned HIV and high molecular weight DNA, isolated from SIV/SMM-infected cells and digested with a battery of restriction enzymes, confirmed that there was no detectable homology between SIV/SMM and HIV at the DNA·DNA level.

Cellular Tropism of SIV/SMM. PHA-AWBC were infected with SIV/SMM; periodically, the number of helper (T4) and cytotoxic/suppressor (T8) cells and particulate reverse transcriptase activity were determined. Although the T4/T8 ratio in a control culture remained essentially constant, the number of T4 cells and, thus, the T4/T8 ratio in infected cultures decreased as the reverse transcriptase activity increased (Fig. 3). During the 18 days of assay, the total number of T4 and T8 cells decreased in both cultures, but the greatest decrease was in the number of T4 cells in the SIV/SMM-infected culture. Although infection of T4 cells was not demonstrated directly, the data indicate that SIV/SMM infection of human PBMC results in a loss of T4 cells. In addition, some isolates of SIV/SMM replicated to high titers in the T-cell lines HUT78, HT, and 6D5, but no isolates infected the K562 myeloid cell line or the Raji B-cell line (data not shown). Although all SIV/SMM isolates replicated in PHA-AWBC, some isolates did not grow in all T-cell lines. In order to reach maximum reverse transcriptase values, SIV/SMM cultures were maintained for a longer time than was required for a similar inoculum of HIV.

Replication of SIV/SMM in PBMC from Rhesus Macaques. SIV/SMM replicated to high titer *in vitro* in PBMC from rhesus macaques, but we have not been able to detect replication of LAV or ARV-2 *in vitro* (or *in vivo*, P.N.F., unpublished data) in cells from rhesus macaques (Table 2).

Infection of Rhesus Macaques with SIV/SMM. Replication of SIV/SMM in PBMC from rhesus macaques suggested that the virus would establish infection *in vivo*. SIV/SMM ob-
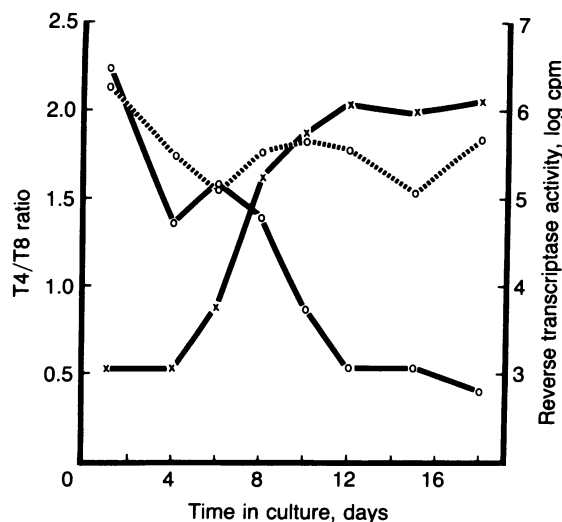

FIG. 3. Cytopathic effect of SIV/SMM on helper T lymphocytes. Samples of PHA-AWBC that were either uninfected (○- - -○) or infected (○—○) with SIV/SMM from mangabey 7 were taken at 2- to 3-day intervals and assayed for numbers of helper (T4) and suppressor (T8) T cells and for reverse transcriptase activity (x) present in the culture.

Table 2. Growth of SIV/SMM, LAV, and ARV-2 in PBMC from rhesus macaques

Virus	Rhesus	Reverse transcriptase activity at days in culture, cpm × 10⁻³				
		6	14	20	28	36
SIV/SMM	12	2.7	6.4	1063.0	—	—
	W289	2.4	175.0	2694.0	—	—
LAV*	12	2.3	1.5	1.7	2.1	0.6
	W289	1.8	1.2	1.0	0.5	1.6
ARV-2	12	1.4	2.3	1.2	3.5	0.7
	W289	2.8	1.6	1.7	0.5	0.8

PBMC from normal rhesus macaques were stimulated with PHA for 3 days prior to infection with various strains of virus.
*Chimpanzee PBMC infected with LAV reached a maximum of 338,700 cpm on day 10 of culture. LAV and ARV-2 stocks routinely infect PHA-AWBC.

tained from two mangabeys (nos. 7 and 9) was injected intravenously into three 12- to 14-month-old macaques each. At various times after infection, attempts were made to isolate virus from PBMC by cocultivation with PHA-AWBC and to detect antibodies to SIV/SMM in serum by IFA. Virus was isolated from PBMC from five of the six macaques, and the five infected animals seroconverted by 6 weeks after inoculation (Table 3). Virus was no longer detected in PBMC from macaques 128 and 134 at 13 weeks and 19 weeks, respectively, suggesting that they had eliminated the virus or were latently infected. (Macaques 128 and 134 received different isolates of SIV/SMM.) Macaque 129 showed no evidence of infection at any time. None of the macaques showed clinical signs of disease at any time, although macaque 131 had a 4% weight loss as of 19 weeks after infection compared to increases in weight in the other five experimental and in three control, uninfected macaques.

DISCUSSION

Approximately 95% of healthy mangabey monkeys from a colony with no unusual incidence of disease were found to be infected with a T-lymphotropic retrovirus, designated SIV/SMM, that is similar to the human virus HIV and the simian viruses STLV-III and STLV-III$_{AGM}$. All of the animals from which virus was isolated had serum antibodies that reacted with SIV/SMM-infected cells in IFAs, but the antibodies had little, if any, neutralizing activity. Persons infected with HIV also have been reported (17–19) to have low serum neutralizing-antibody titers. Antibodies from some mangabeys were cross-reactive with HIV p24 by immunoblot experiments and immunoprecipitated HIV p18 in RIP assays. Both p24 and p18 are encoded in the *gag* region of the viral genome. In contrast, rabbit antiserum to HIV

Table 3. Detection of virus and virus-specific antibodies after infection of rhesus macaques with SIV/SMM

Time, wk*	Parameter	Rhesus macaque					
		128	129	130	131	132	134
3	Virus	+	−	+	+	+	+
	Antibody	−	−	−	+	+	+
6	Virus	+	−	+	+	+	+
	Antibody	+	−	+	+	+	+
13	Virus	−	−	+	+	+	+
	Antibody	+	−	+	+	+	+
19	Virus	−	−	+	+	+	−
	Antibody	+	−	+	+	+	+

All macaques were negative for antibodies to SIV/SMM and HIV prior to inoculation.
*After inoculation with SIV/SMM.

immunoprecipitated at least five SIV/SMM-specific proteins, with molecular weights from 18,000 to 160,000. These data suggest that the cross-reactivity of antibodies to the human and mangabey viruses is, to a large extent, unidirectional. That is, antibodies to HIV, bound to SIV/SMM *gag*- and *env*-encoded proteins, but antibodies to SIV/SMM bound only to HIV *gag*-encoded proteins. This one-way cross-preference for *env* gene products was also observed when antibodies generated to HIV and STLV-III or STLV-III$_{AGM}$ were tested reciprocally (7, 9). It is also of interest that the cross-reactivity of antibodies to HIV for SIV/SMM included neutralizing antibodies. Because no high-titer neutralizing antiserum to SIV/SMM has been identified, we cannot determine whether the one-way cross-preference will extend to this functional class of antibodies.

Even though extensive cross-reactivity of antibodies was observed, no nucleic acid hybridization between SIV/SMM and HIV was detected using two different techniques. R. C. Desrosiers and colleagues (personal communication) also have been unable to detect nucleic acid hybridization, even with low-stringency conditions, by Southern blot analysis of prototype STLV-III and a cloned isolate of HTLV-III. These data suggest that, if the various STLV-III and HIV viruses had a common progenitor, their divergence could not have occurred recently unless one or both have an extremely high rate of mutation. Some sequence homology must exist between the STLV-III isolates and HIV; however, it appears that the extent of homology cannot be determined until STLV-III is cloned and sequenced.

Because serum samples from the mangabeys were not available earlier than 1981, we do not know when SIV/SMM was introduced into the Yerkes colony. The virus might have been present either in one or more of the original wild-caught mangabey monkeys from which the colony was established or in an animal brought in at a later time; however, no wild-caught mangabeys have been added to the colony since 1968. It is of interest that beginning in May 1976, the Yerkes breeding group of 40 sooty mangabeys was housed for approximately 1 year with 11 African green monkeys. During this period, a variety of social interactions, including limited sexual activity, occurred between the mangabeys and the African green monkeys (20). Unfortunately, the Yerkes Primate Center no longer maintains African green monkeys, and no stored serum samples from these monkeys are available.

Although it is not yet known whether SIV/SMM, STLV-III from macaques, and STLV-III$_{AGM}$ are identical, we assume that they may differ. Even though serum from an SIV/SMM-infected mangabey reacted strongly (OD greater than 1.5) in an ELISA using the prototype STLV-III as antigen (R. C. Desrosiers, personal communication), the fact that not all SIV/SMM isolates grew in all T-cell lines suggests that variation may exist even among SIV/SMM isolates. Prototype STLV-III readily infects rhesus macaques and causes immunodeficiency disease (6, 16). No signs of disease had been observed as of 19 weeks after infection of five rhesus monkeys with SIV/SMM; therefore, we cannot yet determine whether the disease potentials of SIV/SMM and STLV-III are similar. Because SIV/SMM apparently does not cause severe immunodeficiency disease in mangabey monkeys, the host from which it was isolated, this property of the virus may prove useful in defining viral determinants of pathogenesis for cytopathic retroviruses. In addition, if different STLV-III strains show the same degree of genomic heterogeneity that is seen with HIV isolates, vaccination and challenge of rhesus macaques with STLV-III isolates may

prove valuable as a model system for developing a vaccine for HIV.

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