Comparative Medicine
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Vol 57, No 1
February 2007
Pages 33-43

Animal Models for HIV AIDS: A Comparative Review

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Human immunodeficiency virus (HIV), the causative agent for acquired immune deficiency syndrome, was described over 25 y ago. Since that time, much progress has been made in characterizing the pathogenesis, etiology, transmission, and disease syndromes resulting from this devastating pathogen. However, despite decades of study by many investigators, basic questions about HIV biology still remain, and an effective prophylactic vaccine has not been developed. This review provides an overview of the viruses related to HIV that have been used in experimental animal models to improve our knowledge of lentiviral disease. Viruses discussed are grouped as causing (1) nonlentiviral immunodeficiency-inducing diseases, (2) naturally occurring pathogenic infections, (3) experimentally induced lentiviral infections, and (4) nonpathogenic lentiviral infections. Each of these model types has provided unique contributions to our understanding of HIV disease; further, a comparative overview of these models both reinforces the unique attributes of each agent and provides a basis for describing elements of lentiviral disease that are similar across mammalian species.

Abbreviations: AIDS, acquired immune deficiency syndrome; BIV, bovine immunodeficiency virus; CAEV, caprine arthritis-encephalitis virus; CRPRC, California Regional Primate Research Center; EIAV, equine infectious anemia virus; FeLV, feline leukemia virus; FIV, feline immunodeficiency virus; HIV, human immunodeficiency virus; JDV, Jembrana disease virus; MuLV, murine leukemia virus; MVV, maedi-visna virus; NERPRC, New England Regional Primate Research Center; SIV, simian immunodeficiency virus; SRV type D, simian retrovirus type D

The emergence of human immunodeficiency virus (HIV)-induced acquired immune deficiency syndrome (AIDS) has illustrated that humankind remains alarmingly vulnerable to new pathogens. When HIV was discovered to be a lentivirus, virologists had already defined properties of several related agents that infected horses, cattle, sheep, and goats. The intensive scientific investigation that has followed HIV's discovery has revealed much about not only the human virus and disease but also a closely related group of viruses discovered since recognition of HIV, which infect nonhuman primates and domestic and nondomestic felids. This review will describe, compare, and contrast characteristics of these naturally occurring or experimentally induced lentiviral infections as well as nonlentiviral retroviral infections that share some characteristics of HIV and AIDS. The utility of each model, its contribution to our current state of knowledge about HIV disease, and the practicalities of managing these experimental models in the laboratory also are described.

Lentiviral Classification

Retroviruses were originally classified according to the morphology and position of the nucleocapsid core as determined by electron microscopy. Core characteristics together with location of virion assembly and budding were used to group viruses as A-, B-, C-, or D-type. The International Committee on Taxonomy of Viruses has replaced this classification system and now assigns viruses of the retroviridae family to the following genera: alpharetrovirus, betaretrovirus, gammaretrovirus, deltaretrovirus, epsilonretrovirus, lentivirus, and spumavirus. Members of the alpharetrovirus, betaretrovirus, and gammaretrovirus genera are considered simple retroviruses and encode only *gag*, *pro*, *pol*, and *env* genes. Members of the deltaretrovirus, epsilonretrovirus, lentivirus, and spumavirus genera are considered complex retroviruses and encode small regulatory proteins in addition to the genes of the simple retroviral groups. Organization of reading frames and type of tRNA necessary to prime the genome also are used to assign viral groupings.[47]

Retroviruses are unique in encoding reverse transcriptase as part of the polymerase (*pol*) gene. This enzyme directs the synthesis of double stranded DNA from an RNA template, resulting in a DNA copy of the retroviral genome (referred to as 'proviral DNA').[100] Proviral DNA is spliced into the host genome and serves as a template for further viral replication. Rous sarcoma virus was the first retrovirus identified and was shown to fulfill Koch's postulates in 1910;[112] retroviruses capable of infecting humans were not known until the early 1980s, when HTLV1 was described.[8,103,145]

The designation 'lentivirus' is used to distinguish viruses in the retroviridae family that cause cytopathic effects in vitro and are clinically characterized by slowly progressing disease. Lentiviruses, like other complex retroviruses, encode small open reading frames that are transcribed as accessory proteins, with essential but poorly defined function during part of the viral lifecycle.[18] *Tat*, *rev*, and *vif* are examples of such proteins.[6,42] The genus lentiviridae includes HIV (HIV1 and HIV2), simian immunodeficiency viruses (SIVs), feline immunodeficiency viruses (FIVs), equine infectious anemia virus (EIAV), the small ruminant lentiviruses (maedi-visna virus [MVV] and caprine arthritis-encephalitis virus [CAEV]), bovine immunodeficiency Virus ([BIV] and the closely

Received: 15 Jun 2006. Revision requested: 18 Sep 2006. Accepted: 18 Sep 2006.
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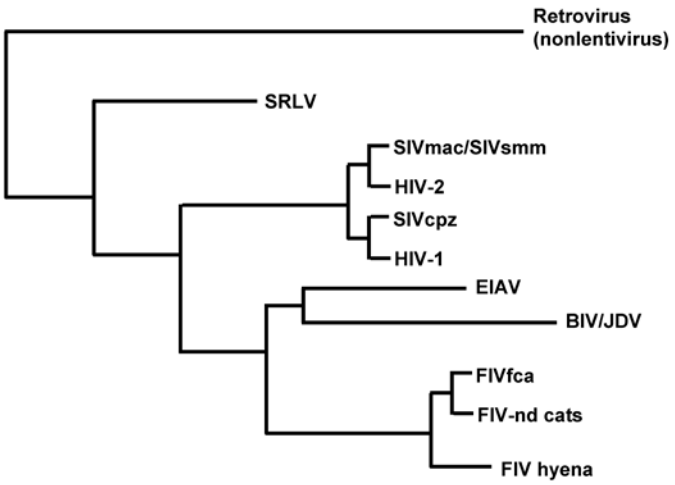

Figure 1. Reported relationships among lentivirus species follows host genotype. Approximate phylogenetic relationships among groups of lentiviruses discussed in this article, from reference Troyer and colleagues.[133] Groupings are based on analyses of partial or complete genomic sequences from multiple viruses in each group. SRLV, small-ruminant lentivirus (includes maedi-visna virus and caprine arthritis encephalitis virus); SIVmac, SIVsmm, and SIVcpz, simian immunodeficiency virus isolates from macaque (mac), sooty mangebey (smm), or chimpanzee (cpz); HIV-1 and HIV-2, human immunodeficiency virus types 1 and 2; EIAV, equine infectious anemia virus; BIV/JDV, bovine immunodeficiency virus/Jambrana disease virus; FIVfca, FIV-nd cats, and FIV hyena, feline immunodeficiency virus isolates from domestic cat (fca), nondomestic felids (nd cats), or hyena. Branch length not to scale.

related virus Jembrana disease virus [JDV]). Each of these virus types infects a particular species and is genetically and serologically divergent from other species' lentiviral strains. Figure 1 demonstrates relationship among lentiviral families according to genetic structure, and Table 1 lists the retrovirus family genera with representative viruses.

HIV Clinical Disease

HIV disease results from the loss of CD4+ T cells, leading to susceptibility to opportunistic pathogens that ultimately cannot be controlled by the patient.[78] Recent studies have shown that early and dramatic CD4+ T cell loss occurs at mucosal sites, and failure of these cell populations to recover may play a key role in setting the stage for later disease progression.[51] The mechanism of CD4+ cell death after HIV infection remains unknown, with both direct viral-induced cell death and immune cell death based on cell signaling (bystander effect) implicated as potential mechanisms. Viral load, total CD4+ T cell numbers, and decreasing CD4+/CD8+ T cell ratio are predictive of disease course. In addition to opportunistic infections resulting from immunodeficiency, many organ systems are affected adversely by HIV infection.[83,108,111,128,143]

Antiretroviral drug therapies have extended the lives and reduced the suffering of patients with HIV. These advances have been made possible by the judicious use of animals to understand the lentiviral lifecycle, leading to the development of drugs that target viral binding, fusion, reverse transcription, protease function, integration, virion formation, and budding.

HIV vaccine development has been challenging due to many unique viral factors.[46] The high rate of viral replication, high error rate of reverse transcriptase, and host immune pressure contribute to rapid viral evolution and mutation, leading to alteration of key viral proteins important for targeting by the host immune system. Thus, lentiviruses are capable of rapidly changing their 'identity,' leading to effective evasion of neutralizing antibodies and viral-specific cytotoxic T cells of the adaptive immune response, which would be generated by vaccination. The HIV envelope protein (Env), the main target of neutralizing antibody, is highly glycosylated, further restricting effective neutralizing antibody binding.[56] Rhesus macaques infected with SIV or the SIV–HIV hybrid virus SHIV have been used most widely for development of vaccines currently in clinical trials.

Despite years of extensive study, some basic observations about HIV disease—that is, the pathogenesis of CD4+ T cell depletion—remain unexplained and possibly can best be studied in animals with naturally occurring or experimentally induced lentiviral disease. In addition, naturally occurring lentiviral infections that

Table 1. Viruses of the family Retroviridae[47,93]

Family	Virus
Alpharetrovirus	Avian carcinoma virus
	Avian leucosis virus
	Avian myelocytomatosis virus
	Fujinami sarcoma virus
	Rous sarcoma virus
Episilonretrovirus	Snakehead retrovirus
	Walleye dermal sarcoma virus
	Abelson murine leukemia virus
	Friend murine leukemia virus
	Murine osteosarcoma virus
	Murine sarcoma virus
	Murine type C retrovirus
	Porcine endogenous retrovirus
	Spleen focus-forming virus
Spumavirus	Bovine foamy virus
	Equine foamy virus
	Human spumaretrovirus
	Simian foamy virus
	Feline foamy virus
Betaretrovirus	Mason-Pfizer monkey virus
	Ovine pulmonary adenocarcinoma virus
	Mouse mammary tumor virus
	Simian type D virus 1
Deltaretrovirus	Bovine leukemia virus
	Human T-lymphotropic virus 1
	Simian T-lymphotropic virus 1
	Human T-lymphotropic virus 2
	Simian T-lymphotropic virus 2
	Simian T-lymphotropic virus 3
Gammaretrovirus	Feline leukemia virus
	Moloney murine sarcoma virus
	Murine leukemia virus
	Wooly monkey sarcoma virus
Lentivirus	Bovine immunodeficiency virus
	Jembrana disease virus
	Caprine arthritis encephalitis virus
	Ovine lentivirus
	Visna virus
	Equine infectious anemia virus
	Feline immunodeficiency virus
	Human immunodeficiency virus 1
	Human immunodeficiency virus 2
	Simian immunodeficiency virus
	Simian immunodeficiency virus 2
	Simian-human immunodeficiency virus (SHIV)

Table 2. Characterization of animal models for HIV/AIDS

	Host	Cell tropism	Clinical disease
Pathogenic animal models of HIV/AIDS			
Gammaretrovirus			
Feline leukemia virus-Feline acquired immune deficiency syndrome (FeLV-FAIDS)	Domestic cat	White blood cells, other	Immune deficiency, cancer
Murine leukemia virus (MuLV)	C57Bl mouse	White blood cells, other	Immune deficiency, cancer
Simian type D retrovirus (SRV type D)	Macaque	White blood cells, other	Immune deficiency, cancer
Lentivirus			
Feline immunodeficiency virus (FIV)	Domestic cat	T cell, monocyte/macrophage	Immune deficiency, lymphoma
Equine infectious anemia virus (EIAV)	Horse	monocyte/macrophage	Anemia, hemorrhage
Maedi-visna virus/caprine arthritis-encephalitis virus (MVV/CAE)	Sheep, goat	monocyte/macrophage	Pneumonia, encephalitis, arthritis, mastitis
Bovine immunodeficiency virus/ Jembrana disease virus (BIV/JDV)	Cattle	monocyte/macrophage	Acute disease in Balinese cattle
Simian immunodeficiency virus sooty mangeby SIVsm (cross-species)	Asian Macaque	T cell, monocyte/macrophage	Immune deficiency, lymphoma
Human immunodeficiency virus type 1 (HIV1)	Severe combined immunodeficiency-human (SCID-hu) chimera, Mouse	T cell, monocyte/macrophage	Localized viral replication
Simian-human immunodeficiency virus (SHIV)	Asian macaque	T cell, monocyte/ macrophage	Immune deficiency
HIV type 2 (HIV2)	Baboon Pig-tail macaque	T cell monocyte/macrophage	Immune deficiency
Apathogenic lentiviral infections			
FIV	Nondomestic cats	T cell, monocyte/macrophage	Typically none, rare immunodeficiency disease
FIV from nondomestic cats	Domestic cats	T cell, monocyte/macrophage	None
SIV	African nonhuman primates	T cell, monocyte/macrophage	Typically none, rare immunodeficiency disease
HIV1	Chimpanzee Pig-tail macaque	T cell Monocyte/macrophage	Typically none

are minimally pathogenic in their native hosts recently have been used to study how prolonged lentiviral–host adaptation contributes to host control of viral infection or disease. Specific agents described in this article are listed in Table 2.

Pathogenic Nonlentiviral Models

Murine AIDS. Murine AIDS is an important small animal model of retrovirally induced immune deficiency, malignancy, and organ pathology. The virus was discovered after cell-free extracts from irradiation-induced murine thymomas were inoculated into C57BL/6 mice and unexpectedly resulted in lymphadenopathy and splenomegaly. Murine leukemia (MuLV) virus, a gammaretrovirus, was identified as the causal agent.[67] Further characterization revealed that inoculation of adult C57BL/10 or C57BL/6 mice with MuLV strains ts1 or LP-BM5 resulted in lymphoproliferative disease and profound immunosuppression; this syndrome was referred to as 'murine AIDS' (MAIDS).[7,24,67] The disease has many clinical similarities to human AIDS, including splenomegaly, lymphadenopathy, hypergammaglobulinemia, late-onset aggressive B cell lymphomas, and susceptibility to opportunistic infection.[35,81] Cardiovascular disease can be a complication of HIV infection; comparable cardiac pathology is seen in mice with murine AIDS.[7,9,20,21] This model has been used to study viral pathogenesis, host immunopathogenesis, altered immune function and associated lymphokine levels, disturbance of hematopoietic cell populations, and AIDS-related human cytomegalovirus retinitis.[24,33,34,124]

Although C57BL/6 and C57BL/10 are highly susceptible to the before mentioned MuLV viral strains, other mouse strains range from moderately susceptible to highly resistant.[24,60] Most MuLV strains do not induce AIDS-like disease in mice; resistance has been mapped to a gene in the H2 complex.[53] Further, murine AIDS results in nonselective decreases in CD4+ T-helper cells and super-antigen-driven polyclonal activation of both T and B cells, leading to secondary immune dysregulation—pathology not described in AIDS. Therefore, although this mouse model affords the opportunity to study the contribution of both viral and host genetics to retrovirally induced immunodeficiency disease pathogenesis and provides various practical advantages of a small animal model, marked differences in viral structure and pathogenesis limit its overall utility as an animal model of AIDS.

FeLV and feline AIDS. Naturally occurring feline leukemia virus (FeLV) infection is an important disease of domestic cats. This gammaretrovirus is transmitted by salivary and nasal secretions.[28,58,88,129] Infection has 1 of 3 outcomes: 1) persistent viremia with progression to disease (progressive infection); 2) transient viremia followed by viral clearance (regressive infection); or 3) containment of initial infection without viremia and development of immunity to further infection (abortive infection).[58,130] Persistently viremic cats die within 3 to 4 y, whereas regressive

and abortive infections are asymptomatic. One manifestation of FeLV is a neurologic syndrome consisting of lower motor neuron disease, behavioral and locomotor disorders, and polyneuropathy, similar to HIV neuropathy.[58,130] Successful vaccines have been developed against FeLV and have been studied as model correlates of successful retroviral prophylactic vaccines. Studies of successful vaccine outcomes and cats with persistent or controlled infection have determined that early viral control predicts disease outcome.[130]

Experimental FeLV AIDS (FAIDS) results from infection by a group of cytopathic, T cell tropic variants. The subsequent disease is characterized by rapid CD4+ T cell depletion in cats, leading to rapid progression to immunodeficiency, opportunistic infection, variable outcomes, and parallels to the clinical course of HIV infection.[36,90,99,105] FeLV is an important model for studying mechanisms of latent versus progressive infection. Limitations of this model include lack of feline-specific reagents, an outbred species as host, and, as for murine AIDS, variation in viral genotype with respect to lentiviruses.

SRV type D. After the recognition of human AIDS, an unusual set of disease outbreaks in primates that had occurred years earlier at the California Regional Primate Research Center (CRPRC) and the New England Regional Primate Research Center (NERPRC) were investigated for evidence of underlying lentiviral infection. A retrovirus designated simian retrovirus D (SRV type D) was isolated from tissues of some of the animals that died from a fatal immunosuppressive disease.[43] This virus was later classified as a betaretrovirus.

SRV type D has been identified in wild-caught Asian macaque species and is endemic in captive populations at primate centers in the United States that are not specific pathogen-free. Genetic and serologic studies have established 5 serogroups, all related to the prototype Mason-Pfizer monkey virus originally isolated in 1970 from tumor tissue.[23] SRV type D causes immune deficiency of varying severity depending on the viral strain and macaque species. Clinical disease in juvenile rhesus macaques that are experimentally infected with molecularly cloned SRV1 is marked by wasting, chronic diarrhea, disseminated cytomegalovirus infection, bacterial pneumonia, decreased response to mitogens, anemia, and lymphopenia.[57] Coinfection of SRV and an activated latent herpesvirus closely related to Kaposi sarcoma herpesvirus is associated with outbreaks of retroperitoneal fibromatosis in several macaque species.[44] This presentation is very similar to AIDS-related Kaposi sarcoma, which also relies on coinfection with a herpesvirus agent. Although this disease model is useful for elucidating retroviral determinants of immune suppression and certain cancers, it is also a pathogen of nonhuman primates that has negatively affected primate research in other realms of science and a zoonotic concern for those working closely with primates.[74] Subsequent identification of simian immunodeficiency virus (SIV) decreased the importance of SRV type D as a primate model of AIDS. Therefore, attempts have been made to eliminate SRV type D infection from primate colonies, and it is no longer studied as an animal model for AIDS.

Pathogenic Naturally Occurring Lentiviral Infections

Common characteristics of pathogenic lentiviral infection are a long incubation period, immunopathology due to chronic immune activation, viral replication despite a robust virus-specific humoral and cell-mediated immune response, and inability of the host to eliminate free virus or virally infected cells, leading to lifelong persistent infection. Viral clearance is retarded due to the unique ability of retroviruses to stably integrate into the host cell genome and achieve replication competence. High rates of viral replication coupled with an error-prone reverse transcriptase enzyme and host immune pressure result in the phenomenon of intrahost quasispecies and antigenic variation, contributing to immune evasion.

Although all lentiviruses infect monocytes and macrophages, HIV, SIV, and FIV also infect T cells. Receptor usage directs this cell tropism and is a primary basis for differences in disease presentation. The primarily monocyte–macrophage-tropic lentiviruses—EIAV, MVV, CAEV, BIV, and JDV—are associated with diseases resulting from chronic inflammation. In contrast, T-cell-tropic viruses—HIV, SIV, and FIV—cause disease characterized by immune deficiency with secondary infections and tumors.

EIAV. EIAV has been extensively studied in relation to its impact on the health and productivity of symptomatic horses. The clinical disease caused by EIAV was first described by Linée in 1843, and in 1859 Anginiard recognized the infectious nature of the disease.[61] Charman and colleagues[19] recommended that EIAV be included in the retrovirus family in 1976, and in 1985, genomic, morphologic, and serologic characterization placed EIAV in the lentiviral genus with HIV and MVV.[22, 75,114]

EIAV replication is dependent on the maturation of infected monocytes into macrophages.[18] Like JDV, some strains of FIV, and some strains of SIV and SHIV in rhesus macaques, EIAV causes acute disease that differs from the slowly progressive diseases caused by FIV, MVV, and HIV. The acute clinical phase of EIAV is marked by fever, splenomegaly, lymphadenopathy, anemia, thrombocytopenia, widespread hemorrhages, edema, emaciation, lymphoid necrosis, perivascular infiltration of lymphocytes into many organs, and glomerulitis 1 to 4 wk postinfection. Viral titers are highest during febrile stages. Death may occur within 4 wk of infection, or the acute phase may be followed by a clinically quiescent persistent infection. EIAV infection is marked by recurrent phases of clinical disease that are unique among lentiviruses. These episodes occur at intervals that vary from weeks to months and last for 3 to 5 d.[18,89,115] Virus isolated from animals during recurrent phases is antigenically distinct from initial viral inoculum and represents viral variants capable of immune escape.[75] Most horses are able to achieve control of viral replication and become clinically inapparent, persistently infected carriers.[18,64] Virus-specific immune responses are necessary for viral control and maintenance of an asymptomatic state. Tabanid flies transmit EIAV over short distances, and disease transmission is much higher in horses located in swampy areas.[18,61] EIAV is the only known vector-borne lentivirus.

Studies of EIAV have focused on characterization of rapid disease progression and virologic and immunologic components during clearly defined cycles of disease. The unique features of viral recrudescence and arthropod-borne transmission also provide opportunities for comparative lentiviral pathogenesis studies. However, equine-specific immunologic reagents are not widely available, and animal and per diem costs restrict the use of this model. Ponies are susceptible to disease and are less expensive to purchase and maintain than horses and thus have been used for most experimental studies.

MVV and CAEV. MVV and CAEV have been studied primarily for their veterinary importance and as causes of substantial

financial loss to the sheep and goat industries worldwide. Because these viruses were the most well-studied lentiviral infections when AIDS was first recognized, many of the preliminary investigations of HIV were based upon knowledge of lentivirus biology obtained through MVV virologic and pathogenesis studies.[39,92]

The small-ruminant lentiviruses, MVV and CAEV, form 4 sequence groups based on phylogenetic analysis of *gag* and *pol* genes and have worldwide distribution. Of these groups, some subtypes have been isolated only from sheep, some only from goats, and some from both sheep and goats.[102] Heteroduplex assays of 38 amplified envelope sequences suggest a history of multiple interspecies transmissions.[45] Because the disease syndromes were recognized long before viral isolation and genetic characterization, the syndrome descriptors have remained the basis for the naming of the viruses, implying inappropriate species specificity. Clinical disease is chronic and progressive and characterized by mononuclear infiltration of target organs including lungs, joints, mammary gland, and central nervous system. Progressive pneumonia (maedi) and paralysis (visna) were first described during an epidemic in Icelandic sheep between 1939 and 1952; MVV was subsequently isolated from the lungs of a symptomatic sheep.[52]

Early lymph node pathology is similar to that of HIV infection. Lymph node cannulation has allowed direct study of efferent lymph and early stages in the development of both virologic and immunologic events.[86]

CAEV was first isolated from synovial membrane of an arthritic adult goat from an affected herd in the United States in 1974. Goat herds with established CAEV infection experience sporadic cases of leukoencephalomyelitis and subclinical interstitial pneumonia in kids and arthritis in adult goats.[27]

Severe lymphocytic infiltration of the mammary gland is unique to MVV and CAEV. Transmission is inefficient in the open environment and increases dramatically when animals are housed indoors in the winter, indicating possible airborne transmission. Virus has also been shown to be transmitted to kids and lambs by virus-contaminated milk.[18,127]

The MVV and CAEV models of lentiviral disease provide the opportunity to study genetic susceptibility and host adaptation, because clear breed susceptibility has been established. Flock-related resistance has been reported in Iceland, and the Karakul sheep of German origin implicated in the initial viral introduction show no signs of maedi-visna in German flocks.[127] Studies in the Netherlands, Germany, and the United States show distinct breed-associated susceptibility to disease but not to infection.[127]

Three of the accessory genes found in MVV and CAEV correspond to open reading frames in HIV. The products Rev and Vif from the small-ruminant lentiviruses have similar function to their counterparts from HIV, whereas MVV and CAEV Tat functions not in transactivation (as for HIV) but has a function analogous to the Vpr protein of HIV.[139,140]

The MVV and CAEV models provide interesting avenues for studying lentiviral biology, such as milk transmission, genetic susceptibility, and macrophage infection and tropism requirements. However, in recent years, study of these viruses has been supplanted primarily by nonhuman primate and feline models, because SIV and FIV are T-cell-tropic and result in an immunodeficiency disease that more resembles the clinical course of HIV.

BIV and JDV. BIV was first isolated from tissues taken from an 8-y-old dairy cow with a chronic wasting disease, and classification as a lentivirus followed subsequent molecular and immunologic studies.[49] A closely related virus, JDV, was isolated from Balinese cattle (*Bos javanicus*) with an unusual acute disease.[122] BIV has since been shown to have a worldwide distribution, whereas JDV is found only in Indonesia. Similar to EIAV and the small-ruminant lentiviruses, BIV replicates in monocytes and macrophages.[41,96,113]

Colostrum-deprived calves experimentally infected with BIV develop lymphadenopathy and transient leucopenia but no clinically apparent disease.[63] Although lymphoid changes and neutrophil dysfunction have been documented to occur in experimentally infected cattle,[41,121] BIV is considered to cause a mildly pathogenic, persistent infection. Because of the lack of overt disease, naturally occurring viral prevalence is not well known.

In contrast to BIV, JDV causes an acute pathogenic disease with a 20% case fatality rate after a 5- to 12-d incubation period. JDV disease is characterized by fever, lymphadenopathy, lymphopenia followed by rapid lymphoproliferation, multiorgan lymphoid infiltration, weakness, emaciation, and high viral titers.[122,141] Interestingly, kidney mesangial cell proliferation leading to uremia and death of infected cattle has been described and may offer clues to HIV-induced renal pathology.[18] In nonfatal infections, lesions regress by about 5 wk, and recovered animals are resistant to further clinical signs.

BIV has been the least studied lentivirus and, despite some inherent practical limitations to use of cattle in biomedical research, offers opportunities for study of apathogenic or acutely pathogenic lentiviral disease.

FIV. Other than HIV, FIV is the only T cell-tropic pathogenic naturally occurring lentivirus. FIV was first isolated in 1986 from animals showing clinical signs of fever, leukopenia, gingivitis, conjunctivitis diarrhea, and cachexia in a California cattery.[101] Shortly thereafter, a T-lymphotrophic virus with lentiviral characteristics was isolated from cats at a different California location. Subsequent studies have demonstrated FIV-specific antibody in serum collected in 1968.[116]

Since the early 1990s, more than 24 nondomestic feline species have been determined to be seropositive for antibodies that cross-react with FIV antigens. Each feline species appears to harbor its own FIV strain, and with few exceptions, clinical disease has been associated only with FIV infection in domestic cats. Thus, the epidemiologic and clinical history of domestic cat FIV parallels that of HIV, whereas the biology of nondomestic feline FIV is more similar to African monkey SIV (see next section).

FIV uses CXCR4 as an entry receptor and CD134/OX40L as a binding receptor.[30,142] As these molecules are on CD4+ T cells, FIV—like HIV—primarily targets CD4 cells. The virus binding and entry mechanisms of FIV also are similar to those of HIV.[31] Transmission occurs via direct contact, fighting and transfusions, and dam-to-kitten transmission cocurs during pregnancy and after parturition.[2,17,68] Acute-phase viremia peaks 8 to 12 wk after infection and is accompanied by clinical signs, which may include anorexia, pyrexia, lethargy, and generalized lymphadenopathy. A measurable cytotoxic T cell response is generated within a week of infection, and an antibody response develops after several weeks. The CD4+:CD8+ ratio declines immediately after infection, followed by a CD8+ rebound while CD4+ numbers remain low; mucosal T cell populations are depleted also.[32,72] Terminal lymphocyte counts are typically less than 300 cells per microliter. Plasma viremia is an indicator of progression to disease.[50] Naturally occurring opportunistic infections occur, with progression to AIDS.[55,144] These clinical symptoms are all highly reminiscent of HIV disease. In 2002 an FIV vaccine was licensed for clinical use

in domestic cats. This product marks the first commercially available lentiviral vaccine and provides some optimism that an HIV vaccine may someday be attainable.[37]

Because of the many similarities between FIV and HIV, the FIV experimental model has been used extensively for studies of pathogenesis, immunopathology, prophylaxis, and vaccine development. In addition, FIV has been examined for use as a retroviral gene delivery system.[82] A PubMed search using keywords 'FIV or feline immunodeficiency virus' retrieved more than 1900 citations of articles published between 1986 and 2006. The shortage of nonhuman primate resources and recently completed sequencing of the feline genome makes FIV an increasingly attractive animal model for many facets of HIV research.

African monkey SIV. Macaques with a syndrome similar to SRV type D infection were noted during the SRV outbreaks at CRPRC and NERPRC. Sera from the affected macaques at NERPRC cross-reacted with HIV1 antigens, leading to the first report of SIV.[29] Further investigation revealed that simian AIDS had affected macaques at the CRPRC since the 1960s.[44] This viral infection eventually was found to result from cross-species transmission of the SIV strain associated with the naturally occurring SIV infection of healthy sooty mangebey monkeys (designated SIVsmm); this transmission most likely occurring during serial transfer of brain tissue during kuru experiments.[4,5] Because the initial SIV infection at CRPRC was unrecognized, some of the surviving macaques were moved to NERPRC, establishing the infection at this facility. SIVsmm therefore was an emergent pathogen in rhesus macaques; the isolate passaged through and ultimately recovered from macaques was designated SIVmac.[4] Genomic sequencing of SIVsmm and SIVmac revealed their close relationship to HIV2, establishing SIVsmm as the origin of HIV2 in humans.[6] Similar investigations have established the naturally occurring SIV of chimpanzees, SIVcpz, as the cross-species origin of the HIV1 virus in humans (Figure 1).[6,70,110]

Our understanding of the divergent nature of SIV infection has expanded rapidly since the initial description in the 1980s. Eight different SIV lineages have been described in naturally occurring infections in African monkeys. With few exceptions, these natural infections do not appear to result in immunodeficiency disease, despite high levels of viral replication. In contrast, SIV arising via accidental or experimental transmission in Asian macaques has resulted in several SIV strains that are highly pathogenic for these species. SIVs predominantly use a CD4/CCR5 receptor entry mechanism, and SIV contains several open reading frames that are unique to primate lentiviruses, including the genes *nef*, *vpu*, and *vpr*.[40,131]

SIVmac infection of rhesus macaques is generally considered the most important primate model of HIV disease, as it results in clinical and immunologic manifestations closely mirroring human AIDS. High viral loads peak between 10 and 14 d as CD4+ T cell counts drop in the periphery; massive depletion of intestinal mucosal CD4+ cells also occurs during acute infection.[80] Virus-specific cytotoxic T cells and antibody responses develop as plasma viral loads decrease, but immune responses are not directly correlated with viral control. CD4+ T cells initially plateau but decrease as disease progresses. The CD4+:CD8+ lymphocyte ratio is often decreased, as is lymphocyte response to mitogens. Clinical signs occur during the acute and chronic phases and include chronic diarrhea, emaciation, and peripheral lymphadenopathy. Progression to AIDS is dependent on both SIV strain and macaque species, but occurs on average 1 y postinfection.[119] All of these SIV disease characteristics are seen with HIV1 infection, although progression to AIDS in the absence of therapeutic intervention is generally 10 y or longer.[77]

The SIV model of pathogenic primate lentiviral infection has been used extensively to evaluate vaccine strategies.[59] SIV infection of rhesus macaques also has contributed greatly to understanding lentiviral-induced central nervous system disease, maternal transmission, and transmission through breastfeeding.[3,25,83] Further, key studies of cell population dynamics and immune activation during the acute, chronic asymptomatic, and clinical disease stages have used this model.[6,69] The observation that early and extensive depletion of gut mucosal CD4+ CCR5+ T cells during pathogenic SIV infection prompted subsequent studies of HIV-infected patients, revealing an important role for gastrointestinal mucosal pathogenesis and leading to a growing area of study in AIDS research.[80] Many other important aspects of HIV infection, including molecular, immunologic, and mechanistic characteristics of infection have been explored in the SIV animal model. For these reasons, SIV infection of macaques has been considered the most relevant animal model for AIDS; more than 4700 articles published between 1980 and 2006 are retrieved from MedLine by using the keywords 'SIV or simian immunodeficiency virus.' Recently, naturally occurring SIV in African monkeys has been studied intensively for clues to host–virus adaptation mechanisms.

Despite the virologic and clinical similarities between SIV and HIV, the SIV model has both practical and experimental limitations. As outlined earlier, virulent SIV arose during accidental cross-species transmission studies, and thus its emergence does not closely mimic that of HIV1, which is thought to have arisen during human exposure to chimpanzees.[70] The rapid course of SIV and high viral loads obtained after experimental inoculation do not mimic the more measured course of HIV AIDS and may have hampered vaccine trials by providing a more virulent challenge than would occur naturally.[59,135] Undoubtedly the most difficult limitation to the use of the SIV model has been the lack of primate resources, particularly animals that do not have other pathogenic diseases and that are genetically defined.[13,26,134] However, the nonhuman primate model of AIDS is likely to remain the most highly used animal model of HIV due to the close genetic relationship of both viruses and primate hosts.

HIV1 infection of nonhuman primates. Efforts to establish HIV1 infection in primates have proven largely unsuccessful. Early studies inoculating chimpanzees with plasma from HIV1-infected patients did not result in measurable pathogenic changes or AIDS induction.[59] Pigtail macaques inoculated with HIV1 were infected only transiently and sporadically.[59] Although HIV2 types have been adapted in baboons and pigtail macaques and lead to declining CD4+ T cell counts, persistent viremia, and AIDS, these models have not been widely used due to research focus on HIV1.[59]

SHIV. One of the major disadvantages of the SIV–macaque model for HIV1 vaccine research is the high divergence of the SIV envelope glycoprotein from that of HIV1, resulting in limited cross-reactivity of virus-neutralizing sera. To circumvent this difficulty, SIV–HIV chimeras have been developed that express the HIV1 envelope glycoprotein and accessory genes within the backbone of SIV. Although some chimeras resulted in limited infection and no pathologic consequences in infected animals,[62,76,79,84] others such as SHIV89.6, SHIVKU-1, and SHIV162P3—produced from multiple passage in macaques—led to persistent infection, CD4+ lymphopenia, and AIDS-like disease.[54,65,106,107] These char-

acteristics make SHIVs most important for use in vaccine development. Variation among strains in viral tropism, setpoint, and rate of CD4+ T cell decline, however, demand careful interpretation of vaccine efficacy data, and further refinement and study of this model is ongoing.[59]

Infection of SCID-hu chimeric mice with HIV. Immunodeficient C.B17 *scid/scid* mice will accept subcapsular kidney grafts of human fetal thymus and liver tissue.[87] Although this model is limited due its lack of functional peripheral human lymphoid tissue, low levels of human immunocytes in peripheral circulation, and lack of any primary immune response,[87] no other model offers the opportunity to experimentally infect human tissues with HIV. This mouse-human chimeric model has been especially useful for evaluation of HIV pathogenesis in thymic tissue and effects on thymopoiesis.[1,14,71,124] Further, this model has been used to evaluate differences in CCR5-tropic and CXCR4-tropic HIV strains[10] that originate at different times during infection and has been valuable for testing the efficacy and toxicity of antiretroviral drugs.[1]

Apathogenic (Naturally Occurring) Lentiviral Infections

Although lentiviral infections of nondomestic cat species and African monkeys are difficult to study in experimental settings, these often highly prevalent viruses may offer important clues to mechanisms of host control that transcend our current concepts of therapeutic intervention for chronic lentiviral disease.

FIV in nondomestic cats. Serologic cross-reactivity to FIV antigens has been identified in 27 feline species from the Americas and Africa and a few species in Europe and Asia.[132,133,135] Although antibody prevalence has been found to approach 100% in sampled adult populations of puma and lion,[11,16,132] infection does not appear to cause widespread disease.[12,135] High genetic divergence among circulating virus strains suggests that virus–host adaptation has occurred on an evolutionary time scale, although relationships between viruses of different feline species appears to be more related to recent habitat geography than species relatedness.[135] Intrahost viral variation is comparatively low in the puma, suggesting little immunologic pressure and a highly adapted virus–host relationship.[11] In contrast, highly divergent quasispecies and, in fact, multiple clades of virus have been identified in individual lions.[132] The fact that seroprevalence increases with age suggests that virus transmission occurs during mating or fighting, although rare mother-to-offspring transmissions have been confirmed via virus sequence analysis.[11,16]

Apathogenic infection of domestic cats with FIVs from nondomestic cats. Cats experimentally infected either parenterally or mucosally with puma or lion lentivirus become productively infected but do not develop clinical signs or hematologic abnormalities.[126,137,138] In several cases, animals have been able to completely eliminate virus. Conventional indicators of adaptive immunity (that is, humoral and cellular immune responses) do not correlate with viral clearance in these animals. However, hypermutation of the virus indicates that nonspecific host restriction factors may be partially responsible for aborted viral replication.[104,126] Further, cats with pre-existing puma or lion lentiviral infection are partially protected against clinical disease after challenge with virulent FIV.[136] This model offers an opportunity to study host restriction factors that limit cross-species transmission as well as lentivirus–host adaptation mechanisms resulting in absence of lentiviral disease in chronically infected hosts.

SIV in African monkeys. As discussed earlier, SIVmac infection of Asian macaque species represents an established animal model of HIV AIDS that emerged after accidental laboratory exposure of macaques to tissues from SIV-positive African (sooty mangabey) monkeys. However, intensive study of naturally or experimental infection of African species with SIV of host origin has not revealed evidence of disease, despite persistently high viral replication.[15,48,95,97,109,118] As in nondomestic FIV infections, a few recorded cases of African monkey AIDS have been reported, but these are rare and involve animals that have lived in captivity beyond their normal lifespan in the wild.[98]

Striking parallels characterize the epidemiologic and virologic properties of nondomestic cat FIV and African monkey SIV. More than 40 different African species have been found to harbor anti-SIV antibodies, and partial genetic characterization has revealed strain variation by species.[135] The relationship of viral genotype to host genotype is unclear; the most striking division in genetic structure of the African SIVs is that the profile of accessory gene open reading frames in arboreal species tends to differ from that of terrestrial animals.[135] Although it is well-established that HIV1 arose after human exposure to a chimpanzee isolate of SIV and although HIV2 has great genetic similarity to SIV from sooty mangabey monkeys, cross-species transmission appears to be the exception rather than the rule, in light of the close association of virus genotype with host species.

Recent studies have focused on identifying the mechanisms that underlie the lack of disease in African monkeys infected with SIV. Infected animals that undergo CD8+ cell depletion show increased viral load, suggesting cell-mediated immune control, but a growing body of evidence suggests that host adaptation results in a muted immunologic response, with slower turnover of immunocytes and concomitant decreased rate of destruction of infected cells.[38,73,98,117] In addition, the role of innate immune parameters and mucosal immunity are under intense study in apathogenic models of SIV infection.

Apathogenic infection of Asian macaques with African SIVs. Although Asian macaques generally are viewed as susceptible to virulent SIV disease,[85,91,94] recent description of the evolution of SIV emergence suggests that SIV may not be universally intrinsically pathogenic to Asian macaques.[135] Emerging lines of evidence suggest that cross-species transmission of SIV typically is apathogenic, as described for cross-species transmission models in the cat. For example, strains of SIV other than SIVsmm replicate transiently and at relatively low viral loads after inoculation of rhesus macaques.[66,120,125] Further, experimental cross-species transmission of SIV originating from African green monkeys, SIVagm, to different species of Asian macaques demonstrates variable pathogenic outcomes. SIVagm is cleared by rhesus macaque hosts after replicating to high levels during the primary infection,[6,66] and ongoing experiments suggest that field isolates of SIVsmm may also be apathogenic in rhesus macaques.[135]

Future Directions

Work in animal models must parallel or precede the movement of HIV vaccines into clinical trials by identifying immune responses that may be either effective or ineffective in humans. HIV vaccines vary widely according to antigen composition and mode of delivery, prime-boost schedule, and adjuvant. Comparative models will offer invaluable information in the development of an HIV vaccine that offers protection from infection and improved clinical outcome for those already infected.

Despite the strides made in therapeutic treatment, patients experience many side effects, drug-resistant viral variants continue to emerge, and no current treatment protocol completely eliminates replication-competent virus. The understanding of the lentiviral lifecycle that has been achieved through the various comparative studies of the diverse lentiviral models has led to the development of antiretroviral compounds specifically targeting every viral stage. Novel targets are being developed and promise to markedly improve the capacity to treat HIV-infected patients. Both large and small animal models will continue to play vital roles in evaluating the efficacy and toxicity of new therapeutics.

In addition to practical translational research, animal models of naturally occurring and experimentally induced lentiviral disease can provide important information about pathogenesis of chronic diseases, mucosal immunity, innate immunity, and cross-species transmission events leading to emergent disease. The body of scientific knowledge generated by studies of animal models of HIV therefore is not limited to direct application to AIDS and will provide novel approaches to disease diagnosis and control for many other conditions that affect man and animals.

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