

# Animal Model Systems of HIV-Diseases

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## 1. INTRODUCTION

Human immunodeficiency virus (HIV) infection is arguably the most significant global health problem of the modern era. Infection has all but devastated third-world countries and continues to threaten public health in developed nations. With the numbers of deaths approaching tens of millions each year, the greatest imperative for world health is the realization of an effective preventative vaccine. The major obstacles prohibiting this goal include a better understanding of protective immunity in the natural host of the virus. In working toward this objective, animal model systems were developed to recapitulate disease processes and viral diversity as it occurs in natural infections of man. Nonetheless, HIV is species specific and is difficult to study in animal systems. Transgenic animals have been developed expressing human receptors in order to overcome some of these limitations; but an animal model that can be progressively infected by HIV remains elusive. Thus, a number of animal models have been established that utilize “other” lentiviruses that mimic HIV infection in specific ways and provide the means to mirror natural infection in its human host. Alternatively, relevant animal models replicate aspects of human disease through the engraftment of infected human cells. Ultimately, these animal model systems of HIV disease provide insight into specific disease processes and serve to elucidate underlying mechanisms of infection and subsequent disease.

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Arguably, the most significant epidemic of the modern age is that of HIV infection. In endemic regions such as sub-Saharan Africa, HIV is the leading cause of death in adults.<sup>36</sup> Case numbers in North America have exceeded 1 million as of 2004.<sup>126</sup> HIV infection leads over time to progressive immunosuppression heralded by a specific loss of CD4+ T lymphocytes, a wasting syndrome and a wide range of opportunistic infections. Disease course is debilitating and inevitably fatal. Although highly active anti-retroviral therapy (HAART) can attenuate disease by lowering viral load, increasing CD4+ T lymphocyte numbers and limiting secondary infection, these drugs are rarely available in the developing world. Global economic and political events have further accelerated the rates of HIV infection worldwide. The paucity of preventative measures in affected regions has further affected any measures to control the epidemic. In December 2003, 40 million people in the world were currently living with AIDS,<sup>126</sup> rendering the need for eradication of this infection clear and immediate. Efforts are under way to reverse the trends, but they remain planned rather than realized.

Although intensive biomedical research efforts have been under way for more than two decades, a safe and effective vaccine has not yet been realized. Studies have pinpointed the diversity of viral strains and antigen recognition by induced humoral and cellular immune responses and the ability of the host to control viral growth is being unraveled. HIV is separated into two distinct types: HIV-1 and 2 that are clinically and biologically distinct.<sup>25,49,125</sup> The majority of HIV research focuses on Type 1, as Type 2 is primarily seen in remote world regions and is more attenuated in disease outcome.<sup>34,58,73,81</sup> HIV-1 can be divided into three groups: major (M), outlier (O), and new (N). The majority of HIV-1 isolates to date are derivatives of M. Both groups O and N are geographically restricted.<sup>21,47,115</sup> The HIV-1 M group is further fragmented into 10 distinct clades (A through J) based upon viral sequence variation.<sup>91</sup> Clade variations affect the molecular structure of important viral molecules including the envelope glycoproteins (Env), which are commonly targeted in vaccine strategies. Clades A, B, and C account for approximately 90% of all HIV-1 infections worldwide with clade C being responsible for 48% of infections.<sup>82</sup> Thus, preventative vaccine research is primarily aimed at clades and designed to take advantage of ways to affect antigen expression and recognition and viral diversity.<sup>119</sup> Unique aspects of disease pathogenesis, spread, and dissemination also remain critical avenues of current research pursuits.

Clearly, the need for animal models of human disease is mandatory if effective preventative measures are to be realized. One major factor hampering research progress is the fact that HIV only infects human cells and produces significant disease only in humans. Simian immunodeficiency virus (SIV) can infect rhesus macaques among other nonhuman primates,

but pathogenic, molecular, biochemical, and structural dissimilarities between this virus and its human counterpart are operative. Feline and bovine immunodeficiency viruses (FIV and BIV, respectively) target animals that are readily available and easily maintained but are even more diverse than SIV in affecting disease. Simian-human immunodeficiency virus (SHIV) infections provide HIV/SIV chimeras, but differences in disease course and pathogenesis abound. Visna-Maedi, caprine arthritis encephalitis virus (CAEV) and equine infectious anemia virus (EIA) are the prototypic lentiviruses but produce only modest immunosuppression and nearly exclusively infect cells of monocyte-macrophage lineage. Mouse-human chimeras have been produced utilizing nonobese diabetic severe combined immunodeficient mice and can mimic a number of primary and secondary aspects of human disease. However, human cells reconstituted into mice still can affect graft versus host disease, leading to a hyperactivation of the reconstituted human cells. Moreover, differences between mouse and human innate and adaptive immune responses are frequently observed. Transgenic or knockout animals either expressing viral proteins or receptors have aided much in HIV studies but remain developmental especially in regard to disease mechanisms and drug or vaccine testing. This certainly also includes studies of mouse leukemia virus and other oncogenic retroviruses. The intent of this chapter is to provide the reader with a broad review of animal model systems of HIV disease. It is only intended as an introduction to the field for future reference in other chapters of the current book, not as a comprehensive review.

## **2. HIV-1 PATHOGENESIS**

To best evaluate the potential relevance of an animal model for human disease, events in disease pathogenesis need to be best understood. As analogous events are observed in species-specific disease processes, animal model with full potential to mirror human disease may be fully realized. Through recapitulation of human pathobiology in animal systems, scientists will have a readily available tool with which to study potential therapeutic and drug treatments.

### **HIV-1 Transmission**

HIV infection occurs through an exchange of body fluids. Such transmission can occur by direct inoculation of infected materials into the bloodstream as with a needle stick,<sup>54</sup> transplanted infected tissue,<sup>93,100,108,116</sup> or blood transfusions.<sup>31,93</sup> Additionally, HIV may enter into a host through open wounds or sores, mucous membranes, through receptive anal and

vaginal intercourse,<sup>2,52,134</sup> or perinatal transmission.<sup>41,74</sup> The virus infects cells primarily through the CD4 receptor but also uses the coreceptors CXCR4 and CCR5. This principally involves CD4+ T lymphocytes and mononuclear phagocytes (MP; monocytes, tissue macrophages, dendritic cells, and microglia). These infected cells transport the virus through the bloodstream and lymph nodes where it can further spread to tissue.

### **The Acute Seroconversion Reaction**

Often presenting as a transient symptomatic or asymptomatic illness, acute HIV-1 infection heralds a seroconversion reaction. In many cases illness manifests as an infectious mononucleosis<sup>27</sup> syndrome accompanied by a plethora of clinical signs and symptoms such as fever, fatigue, weakness, and rash. This reaction follows extensive viral replication without adaptive humoral and cellular immune responses. Importantly, at this time, several steps in the disease transpire. First, as CD4+ T lymphocytes decline, virus preferentially infects virus-specific CD4+ T-cells.<sup>5,37,38,104</sup> This allows for the development of concurrent infections.<sup>46,129</sup> CD4+ T lymphocyte counts typically rebound following resolution of the primary infection but rarely rise to baseline numbers without effective antiretroviral drugs. Second, it is during the initial infection that seeding of the virus into tissues occurs, including the establishment of persistent HIV-1 infection in lymphoid organs. An expansive viremia eventually declines coincident with the appearance of antiviral-specific CD8+ T lymphocytes.<sup>11,17,63</sup> These CD8+ T-cells typically remove infected cells directly by MHC I-mediated cytolysis, or indirectly through secreted factors, effectively culling the blood of progeny virus.<sup>128,136</sup>

### **Humoral and Cellular Immune Responses**

Humoral and cellular immune responses serve to control viral infection. Following acute HIV-1 infection, cytotoxic T lymphocytes (CTL) mount an HIV-1-specific adaptive immune response against infected cells. These cells will leave a pool of HIV-1 specific CD8 memory cells. The gradual decline of the CD8+ T lymphocyte cellular immune response during progressive HIV-1 infection is inevitable due to viral mutation.<sup>137</sup>

An HIV-infected individual shows continuous HIV RNA, antigens, and progeny virus in blood and other body tissues throughout the course of disease. Within days to weeks, the host immune system will produce antibodies to the genetic structure of virus particles. The majority of antibodies target free-floating virions, although some may ultimately assist in the destruction of infected cells. As with the CD8 responses to HIV-1 infection, the effectiveness of the humoral response also gradually declines, due, in large measure, to viral mutation.

### **Subclinical Period of Viral Infection**

In the plasma, the levels of HIV-1 antigen typically drop after the acute seroconversion reaction by immune system clearance, or the establishment of a steady-state between progressive viral infection and the production of available CD4+ T lymphocyte host cells.<sup>97</sup> HIV titers drop significantly after primary infection and remain relatively stable for months or even years. This period is typically and on average 10 years.<sup>9,69,78</sup> An average drop of 100 CD4+ T lymphocytes/mm<sup>3</sup>/year occurs starting from an average of 1000 cell/mm<sup>3</sup>. The human host is commonly asymptomatic until the CD4+ T lymphocytes drop to less than 200 cells/mm<sup>3</sup>, when the incidence of opportunistic infections increases substantially.

### **Clinical Disease**

Advanced HIV disease is typically marked by a reduction in CD4+ T-cells to below 200 cells/mm<sup>3</sup>, an increase in levels of plasma HIV RNA, and coincident opportunistic infections and disease manifestations. Common symptoms include wasting and anemia accompanied by episodes of secondary infections. Clinical manifestations that typically occur in advanced HIV disease include, but are not limited to, HIV-1-associated dementia (HAD), peripheral neuropathy, Kaposi's sarcoma, renal disease, diarrhea, weight loss, interstitial pulmonary disease, cardiac injury, and bacterial, fungal, parasitic, and opportunistic viral infections. Opportunistic infections and malignancies are common as the host immune system is severely weakened. When the CD4+ T lymphocyte counts drop to below 50 cells/mm<sup>3</sup>, mycobacterial and opportunistic viral infections typically occur, and damage to the central nervous system (CNS) is common. Ultimately, death results, likely due to electrolyte abnormalities, circulatory failure, and nervous system damage.

## **3. ANIMAL MODELS FOR HIV-1 INFECTION: OVERVIEW**

The central challenge toward controlling or inevitably eradicating HIV-1 is to find ways to appropriately treat or prevent infection. The greatest test is to prevent primary infection through effective vaccination. Viral mutation and escape from immune surveillance and the emergence of reservoirs for persistent viral infection make a vaccination success difficult to realize. Furthermore, HIV and its clinical manifestations cannot be easily studied because of the dynamics between the virus, the host cell, and the immune system. In answer to this conundrum, a number of animal models have been developed in which human disease pathogenesis is paralleled.

None are optimal but each has inherent strengths and weaknesses. These are cited below.

Ideally, studies of HIV infection and disease pathogenesis would be conducted in an animal system that would manifest all aspects of human disease. However, since no one animal model has been able to exactly replicate human illness, several model systems were developed in different species utilizing a broad range of viral strains. In order for the model to be relevant, it must present HIV-associated pathological and clinical manifestations and be used successfully to test vaccine and therapeutic regimens.

In efforts to drive HIV research the World Health Organization (WHO) outlined what would be considered an ideal animal model.<sup>133</sup> Characteristics were defined that include availability, expense, and utility for HIV research. The first consideration was whether the animal model should make use of HIV. This has not easily been realized. Although several easily available animal models can utilize immunodeficiency or leukemia viruses and provide some insight into human disease, limitations abound, and WHO suggested that the animal model be easily acquired and maintained and that the genetics, immunology, and metabolism be well known and appreciated. Optimally, the target cells affected by the virus should also be the ones affected in human disease, namely CD4<sup>+</sup> T lymphocytes and MP. Similarly, the target organs affected would include blood, lymphoid, lung, and brain tissues. The transmission of the virus would also mimic that of HIV including perinatal transmission. Infection of the animal should be possible with both virus-infected cells and free virus. The induced disease should have a short incubation and resemble human AIDS. Table I presents a summary.

Despite the lack of a single animal model that fills all of these criteria several recapitulate specific and critical aspects of human disease. The two primary paradigms employed include infection by HIV in a relevant animal model or alternatively infection with other viruses that induce an AIDS-like

**TABLE I**  
**Ideal Animal Model Recommendations by the World Health Organization**

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Makes use of HIV
Is a small animal model
Established knowledge of the genetics, immunology, and metabolism
Target cells are CD4 <sup>+</sup> T lymphocytes and mononuclear phagocytes
Target organs include blood, lymphoid, lung, and brain
Transmission mimics that of HIV, including perinatal transmission
Infection is possible with both virus-infected cells and free virus
Induced disease has a short incubation period
Induced disease resembles AIDS

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illness. Both of these have been used to great effect in understanding viral pathogenesis and for vaccine testing. Several animal model systems derived from these paradigms are summarized below.

#### **4. MOUSE MODELS**

Rodents are a common and assessable option in the pursuit of any model of human disease. Mice and rats are easily obtainable, relatively inexpensive to maintain, and their immunology, genetics, and metabolism are well known and appreciated. As mice and rats are not naturally susceptible to HIV infection, and there is no known naturally occurring murine lentivirus, the effects of HIV and AIDS had to be studied through immune chimeras, heterologous viruses or genetic approaches.

##### **Murine Leukemia Virus (MuLV)**

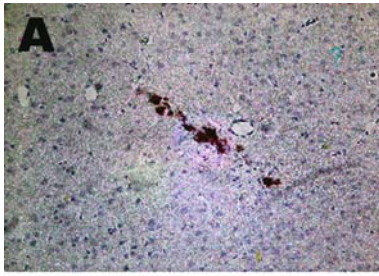
A limited number of murine AIDS models utilize well-recognized retroviruses. These models have primarily made use of oncoviruses. Select laboratory strains of MuLV can induce AIDS-like effects including suppression of humoral and cellular immunity. The MuLVs are closely related and include the Friend, Moloney, and Raucher strains.<sup>13</sup> The Friend and Raucher viral strains affect immunosuppression by infecting precursor B, T, and macrophage-lineage cells. The Moloney strain, on the other hand, is not immunosuppressive but is transferred from the mother to its offspring, thereby providing a model for transplacental viral passage. While primarily utilized in studying drug treatments, there are mutant strains of the Moloney MuLV that are immunosuppressive, such as the ts-mutant.<sup>135</sup> Due to the specific immunosuppressive nature of the ts-mutant, it can model human disease including virus-induced neurodegeneration.<sup>24,72</sup>

Murine AIDS (MAIDS) was described in C57/Bl6 mice that had been infected with a radiation-induced strain of MuLV.<sup>77</sup> Commonly referred to as the LP-BM5 model, this form of MuLV is ecotropic, recombinant mink cell focus-forming, and expresses an aberrant gag-encoded polyprotein.<sup>22</sup> The strain induces polyclonal B-cell proliferation, lymphadenopathy, splenomegaly, and hypergammaglobulinemia. Such processes result in significant immunosuppression and death.<sup>24,92,132</sup>

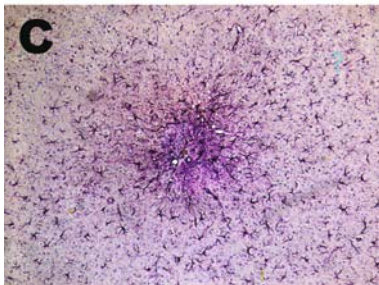
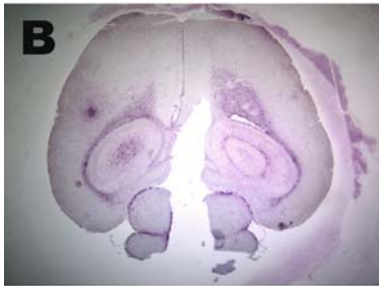
##### **Transgenic (CCR5/CD4, gp120, tat, rev, nef, and Full-Length Proviral DNA)**

The widespread use of genetic manipulation has produced transgenic rodent models for modeling HIV disease. Of these transgenic mouse models, the most popular are mice that have incorporated viral transgenes,





**FIGURE 1.** Pathobiology of HIV encephalitis in SCID mice. Seven days following injection of HIV-1 infected MDM into the basal ganglia of SCID mice, pathological features of human HIVE are observed readily. Panel A illustrates the presence of human vimentin antigen positive MDM in the subcortex of recipient mice. Panel B shows widespread astrogliosis by GFAP immunopositive cells present around the site of cell implantation (Panels A and C, 100 $\times$ , B, 10 $\times$ ).



those that are genetically modified through the incorporation of specific cellular receptors and coreceptors for viral entry into the cell, and the genetically modified mice that allow for the engraftment of infected cells or tissue (Figure 1).<sup>92</sup> Other transgenic rodent models use autoimmunity to study AIDS.

The transgenic models that have incorporated the virus into its genome have been useful in modeling select pathogenic manifestations of chronic HIV-1 diseases, for example, the HIV-1 transgenic rat that contains full-length proviral DNA with expression in virus target organs.<sup>56,65</sup> These



affected tissues, including the lymph nodes, thymus, liver, kidney, and spleen, showed significant pathology consistent with clinical manifestations of disease.<sup>61,101</sup> Likewise, transgenic murine models of HIV also express the HIV-1 transgene in immune cells, resulting in an AIDS-like disease.<sup>33a,62</sup>

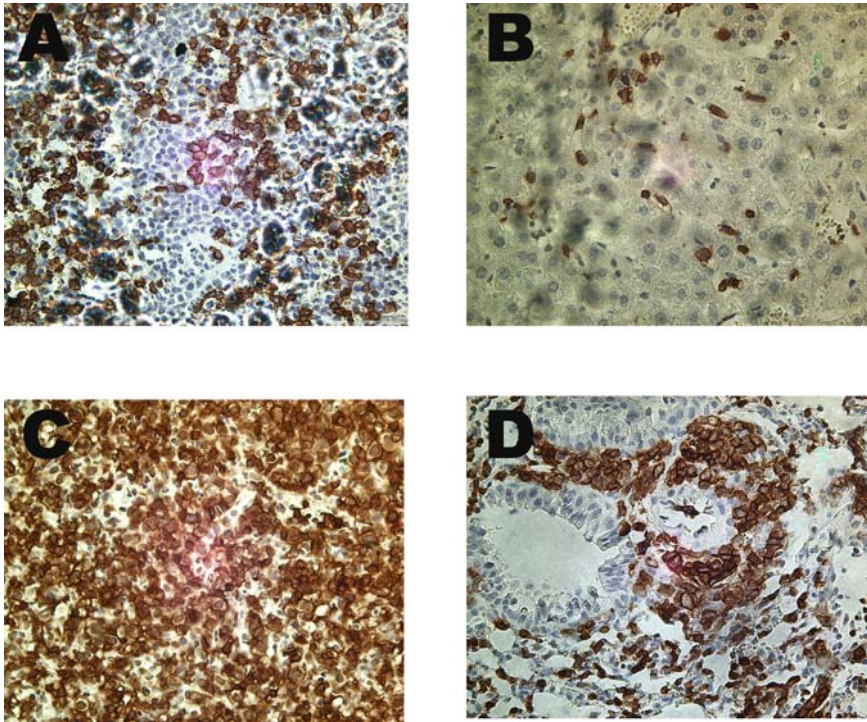
### **Human-Mouse Chimeras**

Finally, transgenic rodent models have allowed for the engraftment of infected tissues or cells. The transgenic mouse that serves as the core for this area of animal research is the severe combined immunodeficient (SCID) mouse. These models are typically engrafted with human immune cells or target organs that are associated with immune function. Such organs include the fetal liver, thymus, lymph nodes, peripheral blood, and bone marrow.<sup>1,16,20</sup> These immune-competent human tissues implanted into SCID mice allow for the immune cells derived from the implanted tissue to reconstitute the immune system of the mice. With the advent of these models, human disease may be simulated in part, and resultant disease pathology can be examined (Figure 2).

Rodent models that have been genetically altered in such a way that human receptors and coreceptors are incorporated brought the reality of a small animal model of HIV-1 closer. Furthermore, by understanding the interplay between the virus and the cell, viral transmission and pathology can now be studied. The addition of the human CD4 and CCR5 to rats,<sup>59,60</sup> mice,<sup>18</sup> and rabbits<sup>118</sup> permits the development of transgenic animals that are susceptible to HIV-1 infection.<sup>121</sup> Later, with the addition of the human protein cyclin T1, the infected cells produce viral gene products.<sup>60</sup> However, while these animal cells are able to produce CD4, CCR5, and cyclin T1, they do not elicit persistent infection, indicating that there still remain missing pieces to the puzzle of viral entry and replication. Nonetheless, with continuous research, the hope of creating a small animal model that can be productively infected with HIV can be realized.

## **5. UNGULATES**

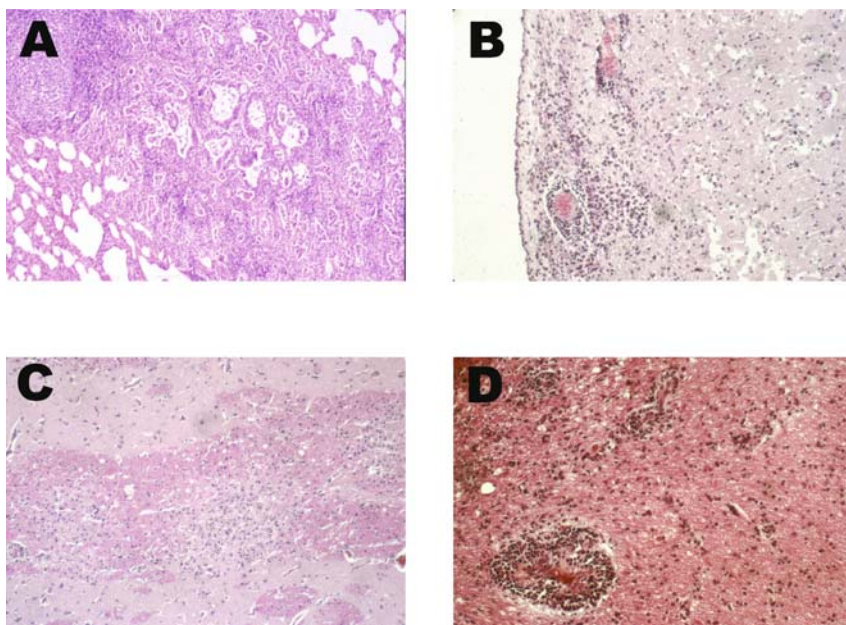
Lentiviral infection of sheep, goats, cattle, and horses are models for persistent infection. While ungulate lentiviral infections are not generally immunosuppressive, they share similarities with HIV. These include persistent infection, a prolonged incubation period, integration of proviral DNA and its restricted expression, macrophage tropism, and viral mutation or antigenic drift. Moreover, because these lentiviruses pose no threat for human infection and disease, they are quite safe and economical to utilize for studies of disease pathogenesis and to evaluate antiviral therapies or vaccine candidates.



**FIGURE 2.** Human lymphocyte reconstitution of SCID mice. Human blood lymphocytes are injected intraperitoneally then observed in a variety of issues in the reconstituted SCID mice. Mice were sacrificed after 21 days and tissue sections immunostained with antibodies for human CD45. Panels show human cells in spleen (A), liver (B), lymph node (C), and lung (D) of the reconstituted animals. Magnification  $\times 100$ .

### Caprine Arthritis Encephalitis Virus (CAEV)

CAEV is a nosologic disease that was first described in 1974.<sup>30</sup> CAEV is a retrovirus that is antigenically related to lentiviruses of sheep. This disease was found to be long-established and widespread in dairies, transmitted primarily through colostrum and milk, and also passed perinatally.<sup>105</sup> Persistent viral infection is intimately associated with the macrophage<sup>80</sup> and microglia.<sup>12</sup> Disease follows a lengthy incubation period and causes joint degeneration and encephalitis. The latter is common in children less than six months of age, which may progress to paralysis within a few months.<sup>29,96</sup> Although the joints are the most notably affected tissue, viral transcripts have been identified in inflamed areas of the brain, spinal cord, lung, and mammary gland.<sup>139</sup> The encephalitis and resultant brain inflammation induced by CAEV, combined with its tropism for macrophages and microglia, make it suitable for studies of human HAD.



**FIGURE 3.** Pathobiology of interstitial pneumonitis and encephalitis of visna infected sheep. All panels depict tissue samples taken from sheep infected with visna virus. Panel A shows productive viral replication occurs in the macrophages inciting an adaptive immune response and significant T cell lung infiltration. Panel B shows subependymal encephalitis as a product of progressive viral infection in brain macrophages. Panel C and D depict an advanced form of leukoencephalitis. All slides are at 20X magnification and counterstained with hematoxylin. Contributed by Dr. Opendra Narayan.

### Visna Maedi

Visna Maedi is a retrovirus of sheep inducing an interstitial pulmonary disease as well as a wasting degenerative process that includes lameness and neurodegeneration. Commonly, a progressive pneumonia precedes and often accompanies other aspects of disease (Figure 3).<sup>45,83,84</sup> Like other lentiviruses, it replicates principally in cells of monocyte/macrophage lineage.<sup>33</sup> Lymphocytes are not infected, indicating that the mechanism of viral tropism, while unknown, is not through the CD4 receptor.<sup>32</sup> Visna Maedi is primarily transmitted through aerosolized nasal discharge, leading to primary infection of free and sessile macrophages in the respiratory tract.<sup>28,44</sup> It is thought that trafficking monocytes and monocyte-derived macrophages provide the vehicle from which to disseminate the virus throughout the body. Postmortem findings typically identify massive amounts of lymphocytes in the lungs infected with Visna Maedi.<sup>19</sup> Study of this retrovirus has allowed for parallels in viral structure and functions to

be drawn to HIV, including genomic organization, regulatory and structural proteins, and viral mutation.<sup>51,130</sup> These analogies have resulted in a sheep model system for the testing of antiretroviral drugs that may be used in humans.<sup>107</sup>

### **Equine Infectious Anemia Virus (EIAV)**

EIAV is a naturally occurring lentivirus that can infect horses, mules, and donkeys worldwide. EIAV primarily resides in the tissue macrophages of its host, rather than the peripheral circulating monocytes.<sup>111</sup> Nevertheless, the transmission of the disease is through blood by insects, needles, and surgical instruments.<sup>53</sup> Vertical transmission is also known to occur.<sup>124</sup> The disease typically presents in its host in acute, chronic, or unapparent infection.<sup>110</sup> Hosts with acute EIAV typically suffer from high fever, anemia, and thrombocytopenia.<sup>26</sup> A chronic EIAV infection is manifest by recurrent fever, weight loss, severe anemia, and edema. Those who have an unapparent infection seem healthy but may lapse into acute or chronic stages at any time.<sup>23</sup> EIAV was the first virus shown to be related to HIV through antigenic and molecular tests.<sup>75</sup> Indeed, the two viruses share many structural and biochemical similarities. EIAV is believed to be a useful model for studies of HIV control and persistence.<sup>76</sup>

## **6. IMMUNODEFICIENCY LENTIVIRUSES**

Lentiviral infections are species-specific and can induce an AIDS-like illness reminiscent of what occurs in man. The majority of these viruses show similarities in molecular structure and in causing disease. Through the study of these immunodeficiency causing lentiviruses much has been learned regarding underlying mechanisms of viral infection, tissue reservoirs, and therapeutics and vaccines.

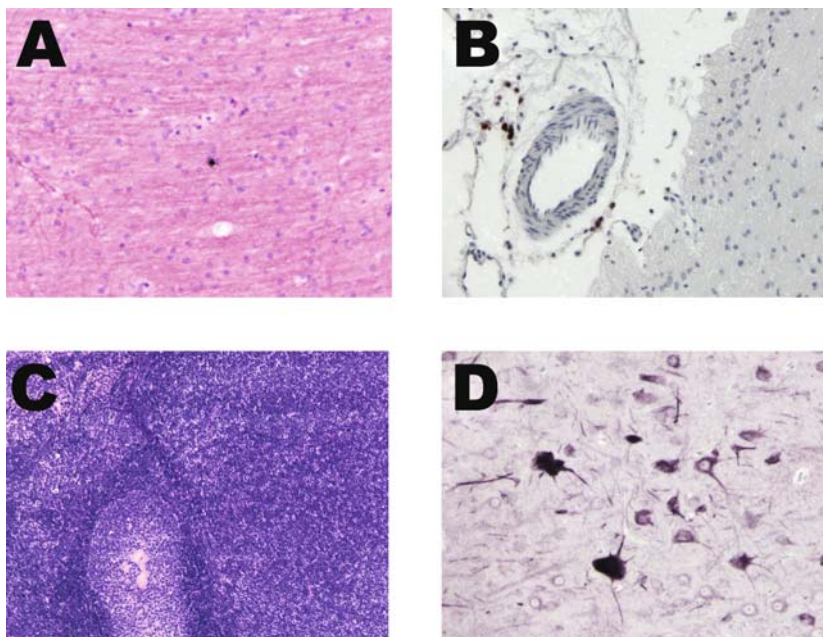
### **Feline Immunodeficiency Virus (FIV)**

FIV was first discovered in 1987 and was found to be quite common in pet and feral cats worldwide.<sup>89</sup> FIV is a lentivirus that closely resembles HIV and SIV in its tropism, protein composition, and morphology.<sup>90</sup> FIV has been cloned and sequenced in its entirety that confirmed its lentiviral structure and organization. It is distinguished from other lentiviruses, implying that it did not arise from a common origin.<sup>85,86,123</sup> FIV has been found to be transmitted between cats primarily through saliva and blood during fights and by vertical<sup>3,4</sup> and horizontal transmission.<sup>57</sup> Pathological manifestations of disease include infections of the oral cavity, upper respiratory track, intestine, conjunctiva, and nervous system.<sup>14</sup> Histological



studies have localized the presence of virally infected cells in the bone marrow, lymph node, thymus, mucosal-associated lymphoid tissue, and spleen, but few cells in the liver and none in the kidney or brain.<sup>103</sup> Although cats seroconvert following infection, they do not succumb to the immunodeficiency disease until after several years of viral incubation.

This animal model has been utilized primarily as a vehicle with which to test antiviral drugs but also as a model of human disease. Specifically, the FIV model has been utilized to examine virus-induced neurodegeneration. Similarities between HIV-1 associated cognitive deficits and FIV induced neurological deficits have supported the use of FIV for the study of human HAD (Figure 4).<sup>39,88,114,138</sup> Furthermore, the FIV model can examine the range of disease affected by drugs of abuse.<sup>10,42</sup> Because FIV represents a lentivirus model that progressively infects its host then induces immunodeficiency, it serves as a very useful system to study AIDS in man.



**FIGURE 4.** Pathobiology of FIV. Cats infected with FIV show rare brain pathology. Panel A shows rare brain cells immunostained for FIV antigens. Panel B demonstrates inflammatory macrophages in the meninges. Panel C illustrates a hypertrophic lymph node with a large germinal center that has lost some of its architecture. Panel D is an immunochemical stain for nonphosphorylated neurofilaments showing increases in cortical neurons in FIV infected cats. All slides are at 20X magnification and were counterstained with hemotoxylin and eosin. Contributed by Dr. Howard Fox.

### **Bovine Immunodeficiency Virus (BIV)**

BIV is a lentivirus that shares antigenic and genetic homology with HIV-1. Although the disease is not generally immunosuppressive,<sup>7,40,120</sup> BIV host cells and tissue tropisms correspond to affected human organs, in particular the spleen.<sup>122</sup> BIV is also distinct from HIV in regards to tat transcriptional activities and, unlike other lentiviruses, BIV does not require specific cellular cofactors to complete its life cycle.<sup>15</sup> This variation in tat has provoked further study in the cellular mechanics involved in BIV with the hope to better understand the viral mechanics in human disease.

### **Simian Immunodeficiency Virus (SIV)**

As far as animal models are concerned, the system that bears the most resemblance to that of human biology is the nonhuman primates. Non-human primates have been used extensively in animal research and their utility has been quite beneficial to HIV research. Chimpanzees and gibbon apes in particular are the only nonhuman primates that are susceptible to infection with HIV-1. Scientists have achieved infection with HIV-1 producing both measurable viral loads and significant amounts of antibodies to viral coat proteins.<sup>8,71,79</sup> Regrettably, HIV-1 infections in these primate models have led generally to asymptomatic infections.<sup>81a,87</sup>

Although HIV-2 is specifically relevant to a focused region in Africa, this strain is used in AIDS studies through its abilities to infect nonhuman primates. HIV-2 is not as debilitating as HIV-1, but is utilized in animal model systems because the study permits insights into viral processes or mechanics. HIV-2 is similar to SIV and has been speculated to represent a rare crossover from nonhuman primates to humans. HIV-2 has been shown to progressively infect and seroconvert macaques<sup>35,99</sup> and baboons.<sup>68</sup> Although HIV-2 infection of simians has not been studied as extensively as HIV-1 or SIV, there have been instances of AIDS-like disorders occurring in these animals,<sup>67</sup> supporting their utility as an animal model for studying the pathogenesis of HIV-2 and for their potential for testing vaccine strategies or treatment regimens.

SIV is a nonhuman primate strain that has been found in certain populations of primates. It has several derivatives, which include SIVagm, SIVmac, and SIVsm among others. Different isolates of SIV have been acquired from several different regions of the world.<sup>6</sup> The SIVs are the closest relatives to HIV and can infect nonhuman primates. SIV infection of nonhuman primates is arguably the most widely accepted animal model for HIV.

Importantly, SIV has been shown to be genetically similar to HIV and utilizes the typical pathway of infection in nonhuman primates as does in humans.<sup>127</sup> Similarly, researchers isolated specific viral proteins that operate

in a similar manner to HIV proteins.<sup>70</sup> SIV relies on specific chemokine receptors in order to infect different cell types. The receptor type that remains constant in the HIV and SIV strains is CCR5.<sup>127</sup> HIV-2 bears remarkable genetic similarity to SIV and shares the same route of infectivity through receptors such as Bonzo and BOB that are not utilized by HIV-1.<sup>98,131</sup> HIV-2 is speculated to represent an intermediary virus that stemmed from nonhuman primates and crossed over to the human population.<sup>112</sup> However, due to the distinct sequence dissimilarity between HIV-1 and any of the SIVs, the origins of HIV-1 remain uncertain.

Interestingly, while the pathogenesis of SIV does parallel that of the human virus, the detrimental manifestations observed in HIV-1 infection in humans do not typically occur in nonhuman primates infected with SIV. However, the resultant symptoms observed following the injection of specific strains (SIVmac) into macaques parallel human clinical disease and pathology. Such efforts have yielded macaque models for AIDS associated neurodegeneration,<sup>64,95</sup> AIDS-associated non-Hodgkin's lymphoma,<sup>48</sup> AIDS-related gastrointestinal complications,<sup>50,117</sup> and AIDS pathogenesis (Figure 5).<sup>92,102,109</sup>

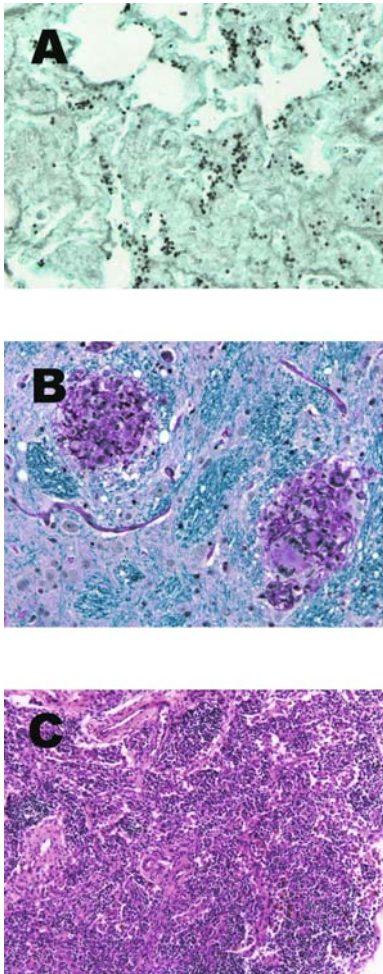
### **Simian-Human (SHIV)**

While SIV and its various strains may provide some insight into mechanisms commonly shared by lentiviruses that may be attributable to HIV-1, specific treatments generated to combat the human disease must be established utilizing HIV-1 or its viral components. In order to address this idea, a transgenic virus was used in simians to replicate some aspects of HIV-1. This chimeric virus is a form of SIV with the gp120 coat of HIV-1.<sup>66,106,113</sup> This virus was developed in order to establish a primate system for the evaluation of viral envelope targeting vaccines, anti-HIV-1 envelope glycoprotein antiserum, monoclonal antibodies, and anti-HIV-1 drugs designed to inhibit the functions of the tat, rev, and env viral proteins. Additionally, a simian model system intended to recapitulate viral drug resistance has also been created utilizing a chimeric virus.<sup>140</sup> Simian models utilizing this transgenic virus have received increasing attention in hopes that this may lead to the formulation of preventative treatment strategies.

## **7. CONCLUSION**

Most lentiviruses are species specific, and disease manifestations do not necessarily parallel HIV infection in its human host. This suggests that HIV infections of humans need be studied to fully realize the goal of effective vaccine prevention of viral infection. Nonetheless, HIV does not infect animals easily including nonhuman primates. Although several other





**FIGURE 5.** SIV Pathology. Tissues derived from monkeys with SIV show disease consequences. Panel A illustrates the presence of *pneumocystis carinii*, a common opportunistic infection in lung during advanced HIV and SIV infections. Panel B depicts an SIV encephalitic brain with a multinucleated giant cells encephalitis and astrogliosis. Lung and brain tissue were stained with Luxol Fast Blue and is at 20X. Panels C shows disorganized architecture of the lymph node at 10X magnification and stained with hemotoxylin and eosin. Contributed by Dr. Howard Fox.

lentiviruses, similar in many respects to HIV, have been discovered, including SIV and FIV; where correlations in disease pathogenesis are manifest, these species-specific viruses are genetically distinct.

Presently, no animal system exists that is completely representative of the human disease process. However, each animal model can recapitulate some manifestations of human disease. In order to construct a model of the human lentiviral infection, an animal would have to be genetically altered so that the virus could affect it in a manner similar to what is found in man. Progress has been made in this direction, though it is by no means complete, and currently no “completely relevant” model of AIDS have been produced.

In summary, the ideal animal model system would involve the study of HIV-1 and be based in a relevant small animal model. However, this is currently not possible. Animal models remain the sole means to vigorously examine the effects of disease-preventative regimens that would have a profound effect on reversing the suffering manifest worldwide as a result of HIV disease.

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