FeLV
&
FIV
UPDATE

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FELINE RETROVIRUS INFECTIONS
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Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) are retroviruses which infect domestic cats and produce disease, usually following an asymptomatic period of months to years. The retrovirus family (the *Retroviridae*) uses reverse transcriptase, an RNA-dependent DNA polymerase (*pol*), to produce a double-stranded DNA copy of the virion RNA. The name retrovirus is derived from this "backwards" flow of information from RNA to DNA. The DNA copy, called a provirus, integrates into the host cell chromasomes and thus can replicate along with the infected host cell.

Retroviruses are divided into three subfamilies, the *Spumavirinae*, the *Oncornavirinae*, and the *Lentivirinae*, based on shared physical and biochemical properties. Cats are susceptible to infection by viruses from each of these subfamilies. Feline syncytium-forming virus (FeSFV), a spumavirus or "foamy virus," has been isolated from both healthy and diseased cats. In some cat populations, the infection rate in older cats may be 70% or greater. In general, FeSFV is considered to have little or no pathogenicity in domestic cats. Chronic progressive polyarthritis has been linked with FeSFV infection but the disease has not been reproduced by experimental FeSFV infection.

Many oncogenic animal retroviruses, including FeLV, belong to the oncovirus subfamily. Three types of feline oncoviruses have been described: (1) the endogenous oncoviruses, such as RD114, which are present in all feline cells but do not replicate or cause disease; (2) the exogenous, replication-competent oncovirus, FeLV; and (3) the exogenous, replication-defective oncoviruses, including feline sarcoma virus (FeSV), which rapidly induces fibrosarcomas. Infection with FeLV and its associated viruses is a significant cause of morbidity and mortality in domestic cats.

Feline immunodeficiency virus belongs to the lentivirus subfamily. Lentiviruses infect a broad range of mammals and include human (HIV), simian (SIV), and bovine (BIV) immunodeficiency viruses, equine infectious anemia virus (EIAV), maedi-visna virus (MVV) of sheep, and caprine arthritis-encephalitis virus (CAEV). The immunodefiency disease resulting from FIV infection in domestic cats is similar to human acquired immune deficiency syndrome (AIDS) and thus provides a useful animal model for HIV infection and AIDS.

Clinically, FeLV and FIV infections in cats have very similar presentations, although there are some distinct differences. The following discussion will compare and contrast these 2 important feline retroviruses.

FELINE LEUKEMIA VIRUS

Feline leukemia virus is associated with both neoplastic and nonneoplastic (immunosuppressive) diseases in the cat. Isolates of FeLV can be divided into 3 subgroups (A, B, and C) according to in vitro host-range characteristics. Subgroup A

is found in more than 90% of FeLV-positive cats; it is easily transmitted from cat to cat and causes a rapid viremia after infection. Subgroup A alone is not highly pathogenic in cats, although persistent infection may result in lymphosarcomas after a long incubation time. The FeLV-B and FeLV-C subgroups are the result polymorphism in the envelope protein gp70 because of in vivo mutation or recombination of subgroup A *env* sequences with endogenous retroviral sequences. Subgroup B occurs as a coinfection with subgroup A FeLV in about 50% of infected cats; it is not readily transmitted and is slow to produce viremia. Most cats with myeloproliferative, myelosuppressive, and immunosuppressive diseases are coinfected with subgroups A and B. One isolate, FeLV-FAIDS, induces a rapidly fatal immunodeficiency disease as the result of a subtle mutation in the *env* gene; this isolate is replication-defective due to another mutation in the *gag* gene. Only about 1% of FeLV-infected cats carry subgroup C virus, again as a coinfection with subgroup A; usually, infection with subgroup C FeLV results in persistent viremia only in neonatal kittens. Aplastic anemia is a common result of persistent FeLV-C infections.

Feline sarcoma viruses are mutants of FeLV which arise by in vivo recombination between the genes of FeLV and host cells. The virus:host fusion proteins that result from the genetic recombination in FeSVs are responsible for the relatively rapid and efficient production of fibrosarcomas by these viruses. These viruses are replication-defective and require the presence of replication-competent FeLV in order to produce the proteins necessary for assembly of virions, infection of new cells, and initiation of replication.

Immunogenic Proteins of FeLV

The major core or capsid protein, p27, is the antigen detected in commercial assays for FeLV. Antibodies to p27 are not protective against viremia; in fact, immune complexes of p27 antigen and antibody probably are involved in the pathognensis of immune-mediated disease in FeLV-infected cats. The glycoprotein gp70 is found on the surface of the viral envelope. This protein is involved in binding the membrane receptor on the surface of susceptible cells. The development of virus-neutralizing antibodies to gp70 is believed to play an essential role in a protective immune response. These antibodies may not be necessary or sufficient for protection in some cats; apparently, some persistently viremic cats have gp70 neutralizing antibodies, while a few cats recover from FeLV infection without ever developing detectable titers of these antibodies. The intramembrane protein, p15E, may be associated with the pathogenesis of immunosuppression and nonregenerative anemia of FeLV infection. The importance of p15E in the pathogenesis of FeLV infection is still unclear because the use of vaccines prepared with whole inactivated virus (thus containing p15E) does not result in immunosuppression.

The feline oncornavirus-associated cell membrane antigen (FOCMA) is also of questionable significance. It is expressed on the cell membrane of FeLV- and FeSV-induced tumor cells and is believed to be the product of genetic recombination between FeLV gp70 and endogenous retroviral sequences. Antibodies to FOCMA have some protective activity against the development of FeLV-related neoplasia,

but they do not prevent FeLV-induced nonneoplastic diseases. The presence of FOCMA antibody in nonviremic, FeLV-exposed cats may indicate a persistent latent or low-activity FeLV infection. These cats are more likely to have signs of immunodeficiency than nonviremic, FOCMA-negative cats.

Epizootiology and Transmission of FeLV

Feline leukemia virus infects domestic cats worldwide. In addition, FeLV infection occurs sporadically in some nondomestic cats. An estimated 2 to 3% of cats in the U.S. are infected with FeLV. Sick cats are 3 times more likely than asymptomatic cats to be FeLV-positive. The FeLV antigen-positive male:female ratio is 1.7:1, and the prevalence of FeLV infection is highest for cats between 1 and 6 years of age, with a mean age of about 3 years.

Persistently viremic cats shed large amounts FeLV in their saliva, urine, tears, and milk. Cat to cat transmission occurs through exposure to these fluids by fighting, grooming, or contact with contaminated food, water, or litter pans. Bite wounds are an effecient method of spread, but prolonged, close contact between cats also enhances the likelihood of FeLV transmission. Infection with FeLV results in fetal and neonatal death of kittens from 80% of affected queens; in addition, transplacental and transmammary transmission of FeLV occurs in at least 20% of surviving kittens from infected queens.

Pathogenesis of FeLV Infection

Susceptibility to persistent FeLV viremia is strongly influenced by the age of cats at exposure. The development of age-related resistance is attributed to the increasing immunocompetence of the cat. In adult cats, infection with FeLV may result in persistent viremia or in apparent recovery (no persistent viremia). Some cats never have detectable viremia; other recovered cats may be transiently viremic, develop an immune response, and revert to a seronegative status. Whether these cats are truly virus-free is a topic of debate; rather, the virus may be latent in many of these cats. Latent infection may not be important because aviremic cats rarely progress to viremia or develop neoplastic disease; however, the recent correlation of the presence of antibody to FOCMA with immunodeficiency disease in cats suggests some clinical impact of latency.

The initial pathogenesis of FeLV infection can be divided into 5 partially overlapping stages:

Viral replication in the tonsils and pharyngeal lymph nodes (oronasal exposure) or in regional lymph nodes (inoculation or bite wound exposure)

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Infection of small numbers of circulating lymphocytes (primarily B cells) and macrophages which serve to disseminate the virus throughout the cat's body

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Replication of FeLV in the spleen, gut-associated lymphoid tissues, lymph nodes, intestinal crypt epithelial cells and bone marrow precursor cells

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Release of infected neutrophils and platelets from the bone marrow into the circulatory system

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Infection of multiple epithelial and glandular tissues, including tissues of the salivary gland and urinary bladder, with subsequent shedding of virus into the saliva and urine.

An adequate immune response curtails the progression of infection at stage 2 or 3 (by the first 4 to 8 weeks following exposure) and forces the virus into latency. Cats which become persistently viremic progress through all 5 stages; persistent viremia (stages 4 and 5) frequently develops beginning 4 to 6 weeks after infection. Persistently viremic cats usually succumb to FeLV-related diseases within 2 to 3 years after infection.

Clinical Presentation of FeLV-Associated Diseases

In most cats, the onset of FeLV-associated disease occurs over a period of months to years following infection. The FeLV-associated diseases can be categorized as neoplastic or nonneoplastic in nature, with most of the nonneoplastic or degenerative diseases resulting from immunosuppression. Clinical signs of FeLV-induced immunodeficiency cannot be distinguished from those of FIV-induced immunodeficiency (see Table 1 and the section on FIV-associated diseases). Immune complex diseases such as thrombocytopenia, immune-mediated hemolytic anemia, and glomerulonephritis are more common in FeLV-infected cats than in FIV-positive cats. Thymic atrophy (fading kitten syndrome) is observed in young kittens infected with FeLV; it is rarely associated with FIV infection probably because very few young kittens are infected with FIV. Erythroblastopenia (nonregenerative anemia) is a very common clinical finding in FeLV-infected cats. The bone marrow is most often hypercellular due to an arrest in differentation of erythroid cells., although true aplastic anemia with hypocellular bone marrow may be induced by FeLV-C infection. Some cases of nonregenerative anemia are the result of myeloproliferative disease rather than a manifestation of degenerative FeLV disease.

Lymphoma (lymphosarcoma) is the most common FeLV-associated neoplastic disease. Lymphomas can be classified as thymic, multicentric, alimentary, or miscellaneous according to their location or distribution in the affected cat. Thymic and multicentric lymphomas are highly associated with FeLV infection in cats. Alimentary lymphomas, which arise in the intestinal lymphoid tissues and frequently involve the mesenteric lymph nodes, are associated with FeLV infection in only about 50% of affected cats. Miscellaneous lymphomas are found in nonlymphoid tissues (extranodal origin) and most frequently involve the eye and nervous system of FeLV-positive cats. Lymphoid and nonlymphoid leukemias are less common than solid tumors. Lymphoid leukemia usually develops with the multicentric form of lymphoma, but it occasionally involves only the blood and bone marrow. Nonlymphoid leukemias can involve any of the hemopoietic cell lineages; erythroid and myelomonocytic leukemias are predominant.

Fibrosarcomas (and possibly hemangiosarcomas or melanomas) may develop in cats which are coinfected with FeLV and FeSV, and occur most frequently in young cats.

Prevention and Control of FeLV Infection

The ideal method of FeLV control is to prevent contact between infected and uninfected cats. Test and removal programs have been effective in controlling FeLV-related disease in many catteries and multiple-cat households with a history of enzootic FeLV. A typical program has 4 important requirements: (1) All cats are tested for FeLV, and positive cats are removed from the facility immediately ; (2) The facility and equipment (especially food and water dishes and litter pans) are cleaned and disinfected; (3) All cats are retested at 3 to 6 month intervals until the entire population has tested negative for 8 to 12 months; and (4) Incoming cats are quarantined for at least 4 weeks and tested for FeLV before entry into the cattery.

Vaccination can be used to control the spread of FeLV; it is most effective when it is considered as an adjunct to appropriate husbandry practices. Several vaccines against FeLV infection are available (see Table 2). The efficacy of a FeLV vaccine usually is determined by its ability to prevent persistent viremia in vaccinated cats. Localized replication of FeLV and transient viremia may not be prevented by immunization. Most of the commercial FeLV vaccines induce virus-neutralizing antibodies specific for gp70; however, these antibodies probably are not the only important component of a protective immune response. Several independent or semi-independent vaccine trials of various products have reported inconsistent or conflicting results. The efficacy of most FeLV vaccines is somewhat less than 100%, and apparently none of the vaccines is clearly superior to the other products. Vaccination against FeLV infection is recommended for all cats that are at risk of exposure to FeLV. Cats housed alone indoors and cats in multiple-cat facilities known to be free of FeLV infection may not require vaccination. Most cats should be tested for FeLV p27 antigen prior to initial vaccination; if prevaccination testing is not conducted, clients should be aware that their cats may be already infected with FeLV.

FELINE IMMUNODEFICIENCY VIRUS

Feline immunodeficiency virus infection is associated with an immunosuppressive disease in domestic cats, characterized by fever, lymphadenopathy, leukopenia, anemia, anorexia and cachexia, and chronic secondary infections. The disease is known as feline immunodeficiency syndrome (FIS) or, more commonly, feline AIDS. Like human AIDS, FIS appears to be caused by impairment of immune system function through infection and/or damage of lymphocytes.

Epizootiology and Transmission of FIV

Serologic tests for FIV indicate that the virus is distributed widely throughout North America. In the U.S., the prevalence of FIV infection is estimated to be 1.5 to 3% in the healthy cat population and 9 to 15% in cats exhibiting signs of clinical illness. Antibodies to FIV have also been detected in cats from Japan, the United

Kingdom, the Netherlands, France, Australia, New Zealand, and Taiwan. In addition, retrospective serologic surveys conducted in the U. S., Great Britain, and Japan indicate that FIV infection has been well established in the domestic cat population for more than 20 years.

Infection with an FIV-like lentivirus has been detected by serologic methods in several species of captive and free-ranging nondomestic cats. Lentiviruses have been isolated from several antibody-positive Florida panthers and from a Pallas' cat. The pathogenic potential of feline lentivirus infection in nondomestic cats is unknown.

Male cats are approximately 3 times as likely to be infected with FIV as female cats. Free-roaming cats are much more likely to be infected than cats housed strictly indoors; very few purebred cats housed in catteries are infected with FIV. The prevalence of FIV infection increases with age, with a mean age of about 5 years at the time of diagnosis. Feline immunodeficiency virus is efficiently transmitted through bite wounds, with virus being shed in the saliva of infected cats, possibly in the form of infected white blood cells. Transmission through casual contact is at best inefficient under natural conditions. Although early attempts to demonstrate transmission of FIV through casual or sexual contact among cats were unsuccessful, viral RNA and proviral DNA have been detected in samples from FIV-seronegative cats housed in contact with FIV-infected cats. The significance of this finding is unknown, and additional study will be required to determine the potential for transmission of FIV through casual contact. Placental or colostral transmission for FIV from a queen to her offspring occurs infrequently. In utero and postnatal transmission have been documented experimentally, primarily when the queen's initial exposure to FIV occurred during gestation or lactation. Thus, fetuses or kittens exposed to FIV prior to antibody development in the queen appear to be at highest risk of infection.

Immunogenic Proteins of FIV

When cats are experimentally infected with FIV, neutralizing antibodies appear 3 to 4 weeks after infection; however, virus can be isolated from infected cats in spite of high neutralizing antibody titers. Antibodies to the envelope glycoprotein (gp120) and the major core (*gag*) proteins develop first, with antibodies to the transmembrane protein (gp40) and the *pol* gene products generally appearing 4 to 8 weeks after infection. The time of seroconversion partially depends on the dose of FIV given, with more rapid seroconversion in cats receiving the greater dose of virus. Antibody levels peak after several weeks and remain high for months to years following infection. Although most cats develop high antibody levels within a few weeks after FIV infection, several antibody-negative, virus-positive cats have been identified. Some cats may require months to seroconvert, and FIV antibody levels may decrease in some cats during the terminal stages of disease.

Immunopathogenesis of FIV Infection

The underlying immunopathology of FIV infection appears to be similar to that seen in HIV-infected humans. FIV has been demonstrated to preferentially infect interleukin 2 (IL2)-stimulated peripheral blood mononuclear cells,

presumably T lymphocytes, under laboratory conditions; however, unlike HIV infection of human lymphocytes which is restricted to CD4$^+$ lineages, FIV lytically infects both feline CD4$^+$ (helper) and feline CD8$^+$ (cytotoxic) T lymphocytes. In spite of this ability to infect both CD4$^+$ and CD8$^+$ subsets of T cells in vitro, FIV appears to selectively and progressively decrease feline CD4$^+$ cells in vivo. The inversion of the CD4$^+$:CD8$^+$ ratio becomes significant in cats infected for longer than 18 months, and an absolute decrease of CD4$^+$ T lymphocytes occurs in cats with experimental FIV infections of 25 to 40 months duration. After long term (>25 months) FIV infection, cats may have a decreased ability to respond to T-dependent antigens; however, immunologic responses to T-independent antigens are not impaired.

Feline immunodeficiency virus also infects feline peritoneal macrophages. Infected macrophages are thought to be the main "reservoir" of HIV in infected humans; they may play a similar role in FIV-infected cats. Very little is known about additional target cells for FIV infection. Brain astrocytes and microglial cells can be infected in vitro and may be targets for infection in the cat. Megakaryocytes and mononuclear bone marrow cells may be infected in some cats, while other FIV-positive cats have no evidence of bone marrow infection. Coinfection with FeLV apparently extends the host cell range of FIV to include cells of kidney, brain, and liver. In addition, FIV strain differences may dictate which host cells become infected.

Clinical Presentation of FIV-Associated Diseases

Because of the immunosuppressive nature of FIV infection, clinical signs in domestic cats are diverse. Diseases associated with FIV infection cannot be distinguished clinically from FeLV-associated immunodeficiencies (see Table 1). Feline immunodeficiency virus infection can be divided into stages similar to the acute (first), asymptomatic carrier (AC, second), AIDS-related complex (ARC, fourth) and AIDS (fifth) stages of HIV infection. A state similar to the third clinical stage of HIV infection, persistent generalized lymphadenopathy (PGL) with no other signs of illness, also occurs briefly in cats; however, most cats with PGL show concurrent clinical signs. The acute phase begins about 4 weeks after infection and lasts for up to 4 months. Lymphadenopathy, neutropenia, fever, and diarrhea may be observed; however, many cats exhibit no clinical signs during acute infection. The AC stage (clinically inapparent infection) may last several months to years. A short period (less than 4 months) of PGL follows the AC stage. The ARC and AIDS stages of disease (or FIS) are not clearly defined for FIV infection, but cats with ARC usually suffer from chronic respiratory, gastrointestinal, and skin disorders, accompanied by PGL. The development of opportunistic infections, severe emaciation, and lymphoid depletion signals a progression to AIDS. An estimated life expectancy for cats with AIDS is 1 year or less.

In one study of naturally FIV-infected cats, the rate of disease progression was variable, with death occurring in about 18% of infected cats within the first 2 years of observation (4.5 to 6 years after the estimated time of infection). An additional 18% of infected cats developed increasingly severe disease; however, more than 50% of the infected cats remained clinically asymptomatic during the same time period.

Early lymphadenopathy and PGL is associated with follicular hyperplasia and massive paracortical infiltration with plasmacytes. In some lymph nodes, a mixture of follicular hyperplasia and follicular depletion or involution may be observed. In the terminal stage of disease, lymphoid depletion is the predominant finding.

Abnormal hemograms are common in FIV-positive cats. Clinically ill cats (i.e. cats with FIS) are most likely to have hematologic abnormalities, especially cytopenias. Anemia, lymphopenia, neutropenia, and hypergammaglobulinemia are the most frequent findings; however, neutrophilia and lymphocytosis may be observed in some cats. Thrombocytopenia is often seen in FeLV-infected cats, but it is found in less than 10% of FIV-infected cats. Bone marrow abnormalities in FIV-infected cats may include increased cellularity due to elevated numbers of lymphocytes, plasma cells or eosinophils, myeloproliferative disease, dysmorphic syndromes and neoplasia. Cats infected with FIV may be more susceptible to *Haemobartonella felis*-induced anemia and related disease. Since it can be difficult to detect the organisms, anti-rickettsial therapy may be indicated for any cat exhibiting signs of regenerative hemolytic anemia.

Among the most common clinical findings in FIV-infected cats are gingivitis, stomatitis, and periodontitis. Oral lesions, reported in 25 to 50% of positive cats, may be ulcerative (frequently associated with calicivirus), proliferative, or a combination of both types. These lesions often consist of lymphocytic and plasmacytic infiltrates. The plasmacytic infiltrates may extend to the draining lymph nodes and the spleen of affected cats.

Chronic upper respiratory tract disease occurs in about 30% of FIV-positive cats, and persistent diarrhea due to chronic enteritis occurs in 10 to 20% of infected cats. Feline herpesvirus and calicivirus infections may be partially responsible for upper respiratory disease including rhinitis, conjunctivitis and keratitis. Intestinal lesions similar to those seen with feline parvovirus infection have been observed in several cats with diarrhea. The etiology of the enteritis may be bacterial or fungal overgrowth, parasite-induced inflammation, or possibly inflammation induced by direct infection of the gastrointestinal epithelium with FIV.

Chronic, nonresponsive or recurrent infections of the external ear and skin are commonly seen. Skin lesions and abscesses are often due to *Staphylococcus* or other bacterial infections. Generalized notoedric and demodectic mange, parasitic diseases which are uncommon in otherwise healthy cats, have been reported in FIV-positive cats. Dermatophytosis may be especially difficult to treat in FIV-positive cats. **Severe neutropenias have been induced in several FIV-infected cats treated with griseofulvin.** Although the neutropenia is reversible if the griseofulvin is withdrawn early enough, secondary infections associated with the condition can be life-threatening; therefore, this drug should be avoided or used with extreme caution in FIV-positive cats.

Severe wasting occurs in some cats; the cachexia and the chronic fever seen in FIS may be due to an overproduction of tumor necrosis factor. Abortion, infertility and other reproductive failures have been reported in infected queens; however, reproductive disorders have not been linked statistically with FIV infections. Some FIV-infected cats have experienced seizures, behavioral abnormalities and other neurologic disorders, usually in the terminal stages of disease. FIV-specific

antibodies have been detected in the cerebrospinal fluid of some infected cats, and FIV has been isolated from the brains of a few cats. Some strains of FIV may be more neurotropic than others, resulting in direct or indirect damage to the central nervous system. Brain lesions primarily consist of mononuclear cell infiltration and gliosis of the subcortical structures and basal ganglia.

Three types of ophthalmic disease common in FIV-positive cats are anterior uveitis, pars planitis and glaucoma. Histologic changes may include plasmacytic, lymphocytic infiltrates in the iris and ciliary body similar to the type of infiltrates found in other tissues of FIV-infected cats. The pathogenesis of ocular disease in FIV infection is unknown. The virus may be responsible for direct damage to the uveal or vascular epithelium, resulting in inflammation. Other potential mechanisms of ocular pathogenesis are immune-mediated inflammation and opportunistic infections, such as cytomegalovirus and *Toxoplasma gondii* infections. FIV-positive cats are frequently coinfected with *Toxoplasma*, and reactivation of latent toxoplasmosis is suspected to occur in these cats when they become immunosuppressed. One or more of these factors may be involved in the initiation of ocular disease in an individual cat.

Although lentiviruses are not considered to be directly oncogenic, several types of neoplasia have been reported in FIV-positive cats. Because older cats are most likely to be infected with FIV and also to develop nonretrovirus-related tumors, it is difficult to determine just what role FIV may be playing in the neoplastic process. FIV-infected cats are 5 times more likely to develop leukemia/lymphoma than uninfected cats. This relative risk for development of leukemia/lymphoma increases to 62 times normal for FeLV-infected cats and to 77 times normal for cats with dual FeLV/FIV infections. Lymphomas associated with FIV infection frequently are extranodal in origin. In addition to leukemia/lymphoma, neoplastic diseases which have been reported in FIV-positive cats include fibrosarcoma, mastocytoma, squamous cell carcinoma, and myeloproliferative disease.

Coinfection of cats with FIV and FeLV occurs under natural conditions but infection with one virus does not appear to predispose the cat to infection with the second virus. Researchers at the University of California/Davis have demonstrated that pre-existing FeLV infection acts as a potentiator for FIV-related disease in experimentally infected cats. The increased severity of disease apparently is due to an increased amount of FIV replication in lymphoid tissues (where the virus usually is found in cats infected with FIV alone) and to the presence of FIV in non-lymphoid tissues (where FIV usually does not replicate when alone). Cats with naturally acquired dual infections also suffer from severe disease. Because of the increased severity of FIV-related disease, cats coinfected with FIV and FeLV have an extremely poor prognosis.

Prevention and Control of FIV Infection

Commercial vaccines for protection against FIV infection or disease have not been developed. Prevention of exposure to FIV-infected cats is the only available method of control. Because casual contact between cats and contact with fomites are inefficient methods of transmission, preventing exposure to FIV is relatively

straightforward. Cats should not be allowed to roam free or to interact with feral or free-roaming cats. All new cats should be screened for FIV infection prior to entering an FIV-negative multiple-cat household or cattery. If possible, a 6 to 8 week quarantine period should be enforced to allow time for recently infected cats to develop detectable levels of antibody.

If an FIV-positive cat is identified in an established household, removal of the cat may not be necessary since the likelihood of transmission of FIV by casual contact is slight; however, separation of seropositive cats from seronegative cats probably is advisable. Cats with severe oral inflammation or in the terminal stages of disease shed relatively large amounts of virus and thus may pose a greater threat to uninfected cats than asymptomatic FIV-infected cats. Ultimately, the decision on management of FIV-positive cats in a multiple-cat facility must be made by an informed client based on individual circumstances.

DIAGNOSIS OF FELINE RETROVIRUS INFECTIONS

Feline immunodeficiency virus and FeLV infections can be differentiated only by appropriate laboratory tests. In most circumstances, testing for both viruses is indicated. Certainly, cats with signs of immunosuppression and cats entering multiple-cat facilities should be tested for both FIV and FeLV.

Diagnostic Tests for FIV
The diagnosis of FIV infection usually depends on the detection of FIV-specific antibodies in serum, plasma or whole blood. The presence of FIV antibodies correlates well with persistent FIV infection. Commercial ELISA tests are available for use in veterinary clinics, hospitals, and diagnostic laboratories; some laboratories also offer IFA or immunoblot (western blot) assays for FIV antibodies. In general, FIV ELISAs have similar sensitivites to the IFA and immunoblot procedures; however, false-positives (decreased specificities) with ELISAs may occur due to operator error (especially inadequate washing) or nonspecific reactivity with cell culture components. The likelihood of false-positive results increases when testing cats at low risk for FIV infection, Confirmation of positive ELISA tests for FIV antibody by IFA or immunoblot is recommended when the cat is asymptomatic or at low risk for infection, or when euthanasia of an FIV-positive cat may be considered. The presence of maternally-derived FIV antibody in kittens less than 4 to 5 months of age results in positive tests with any of the antibody assays, whether or not the kittens are actually infected.

Diagnostic Tests for FeLV
Commercial assays for FeLV infection detect the viral group-specific core antigen, p27. The IFA test is available through a limited number of diagnostic laboratories. It identifies p27 in leukocytes and platelets in fixed smears of whole blood or buffy coat preparations; a positive result indicates a productive FeLV infection in the bone marrow cells. Most (97%) IFA-positive cats remain persistently infected and viremic for life. In many cats, p27 antigen can be detected

by IFA by 4 weeks after infection, but some cats may take up to 12 weeks to develop an IFA-positive test. When testing leukopenic cats, buffy coat smears provide a much better substrate for the IFA than whole blood smears.

Enzymatic detection of soluble FeLV p27 antigen is the basis of FeLV testing in most veterinary clinics and hospitals. Several commercial manufacturers produce ELISA tests for detection of FeLV antigen in whole blood, serum, plasma, saliva or tears. These tests are more sensitive than the IFA at detecting early or transient FeLV infections; however, a single positive ELISA test cannot predict which cats will be persistently viremic. False-positive tests or inconsistent results may be common with tests using saliva and tears; cats with positive results should be retested using whole blood (IFA) or serum (ELISA).

Because commercial FeLV tests detect viral antigen rather than antibody, previous vaccination does not interfere with the ability to detect FeLV infection. Assays for antibodies to FeLV gp70 and FOCMA are used occasionally to evaluate the immune status of FeLV antigen-negative exposed cats or to evaluate a response to vaccination.

TREATMENT OF FELINE RETROVIRAL INFECTIONS AND ASSOCIATED DISEASES

Antiviral Therapeutic Agents

Safe and consistently effective antiviral agents are not available for use in FIV- and FeLV-infected cats. Two primary approaches to antiretroviral therapy have been used in cats: (1) Reverse transcriptase inhibitors have been administered to suppress viral replication, and (2) Immunomodulatory drugs have been given to potentiate the cat's immune response against the retrovirus.

In a small field trial, general clinical improvement of FIV-associated stomatitis, gingivitis, and diarrhea was observed after treatment with a reverse transcriptase inhibitor, either 9-2[phosphonomethoxyethyl] adenine (PMEA) or 3'-azido-2', 3'-dideoxythymidine (AZT). Thus administration of AZT or PMEA may reduce the severity of FeLV- and FIV-associated diseases; however, the drugs (especially PMEA) are not readily available and the risks of toxicity often outweigh the therapeutic benefits. If these drugs are used, treated cats should be monitered closely for the development of anemia, cytopenias, and hepatotoxicities, and the dosage should be adjusted as needed.

Immunomodulatory drugs may allieviate some clinical signs associated with retroviral infections. Low dose, orally administered human recombinant alpha interferon (IFN) has been successful in increasing survival rates and improving clinical status of FeLV-infected cats. Oral IFN treatment may act by stimulating the release of soluble cytokines, such as IL1, from oropharyngeal macrophages and lymphocytes; these cytokines then circulate systemically and modulate immune function. Additional promising immunomodulatory drugs include acemannan, Propionibacterium acnes, and staphylococcal protein A (SPA). All of these drugs induce the release of endogenous interferons and IL1. In addition, SPA immunoadsorption (plasmapheresis) has been used to remove circulating immune complexes in FeLV-positive cats.

Perhaps the best strategy for antiretroviral therapy is use of a combination of 2 or more of the drugs mentioned above. Until more extensive field trials of these agents, alone and in combination, have been performed, no single treatment can be recommended as better than the rest. Table 3 outlines treatment regimens for AZT and some of the immunomodulatory drugs.

Treatment of Diseases Associated with FeLV and FIV Infections

Management of secondary and opportunistic infections is a primary consideration in the treatment of cats immunosuppressed by FeLV or FIV. Toxoplasmosis, haemobartonellosis, and cryptococcosis are frequently associated with feline retroviral infections; suggested chemotherapies are outlined in Table 3. Additional supportive therapy, such as parenteral fluids and nutritional supplements, may be required. Yearly vaccination for respiratory and enteric viruses with inactivated vaccines is recommended; MLV vaccines for rabies should never be used in immunosuppressed cats (at present, only inactivated rabies vaccines are approved for use in all cats). The ability of some FIV- and FeLV-infected cats to respond appropriately to vaccination is questionable; the immune response of immunocompromised cats to vaccines, especially rabies virus vaccines, needs further evaluation.

Retrovirus-related gingivitis tends to be refractory to treatment. Antibacterial or antimycotic drugs may be used effectively if the primary lesions are due to overgrowth of bacteria or fungi, but prolonged therapy or increased dosages may be required. Metronidazole or clindamycin may be useful in treating anaerobic bacterial infections. Judicious but aggressive use of corticosteroids or gold salts may be helpful in controlling immune-mediated inflammation; however, response to therapy may decline over time. These immunosuppressive agents should be restricted or avoided in cats with overt signs of opportunistic bacterial or fungal infections. A recent report details the use of a preactivated photoactive compound, merocyanine 540, in 2 cats with severe gingivitis; however, a safe and effective dose range for use of this drug in cats has not been adequately defined.

Bone marrow examination is especially useful when evaluating severe anemias in FeLV-infected cats. *Haemobartonella* infection should be suspected in all cats with regenerative hemolytic anemias; treatment consists of administration of oxytetracycline for 3 weeks with short term use of oral glucocorticoids in severe cases. Blood transfusions can provide emergency support when the cat's hematocrit is less than 10%, but multiple transfusions may be required. Passive antibody transfer may help reduce the level of FeLV antigenemia in some cats; therefore, immunization of blood donor cats with FeLV vaccines is useful when blood transfusions are required for FeLV-associated anemia.

Management of weight loss and cachexia associated with FIV and FeLV infections is critical. Cats with normal appetites should be evaluated for malabsorption and managed accordingly. Anorexic cats may benefit from IV administration of diazepam or oral administration of oxazepam. Anabolic steroids may be useful for more prolonged stimulation of appetite and reversal of cachexia; however, controlled studies on the efficacy and safety of these drugs in retrovirus-infected cats are lacking.

Treatment for anterior uveitis consists of application of topical corticosteroids, but long-term response to therapy may be incomplete or poor. Pars planitis will often regress spontaneously and may recur; topical and systemic corticosteroid therapy may be used but may not stop the progression of the lesions. Systemic corticosteroids should be used with caution considering the potential for further immunosuppression of an already compromised cat. Management of FIV-related glaucoma is the same as for glaucoma due to other causes.

Many cases of lymphosarcoma in FeLV-positive cats have been managed successfully with combination chemotherapy. Regimens using vincristine, cyclophosphamide, and prednisone are most commonly used. Periods of remission average 3 to 4 months, but some cats may remain in remission for a much longer time. Myeloproliferative disease and leukemias are more refractory to treatment. No data are available on the efficacy of antineoplastic therapy in FIV-positive cats. Surgical removal of isolated tumors may be useful but care must be taken to insure proper healing of incisions. Established chemotherapy protocols may be followed for the treatment of lymphoproliferative diseases. Combined therapy with nonspecific immunopotentiators such as *Staphylococcus* protein A or *Propionobacterium acnes*, or IFN may help control FeLV- or FIV-related tumors, but experimental evidence of their efficacy is lacking.

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TABLE 1. DISEASES ASSOCIATED WITH FIV AND FELV INFECTIONS

Immunosuppression with opportunistic infections

Gingivitis/Stomatitis (FIV>FeLV)

Myeloproliferative disease/Erythroleukemia (FeLV>>FIV)

Fibrosarcomas (FELV only - FeSV-related)

Lymphosarcoma/Lymphoid leukemias (FeLV>>FIV)

Diarrhea/Panleukopenia-like syndrome

Weight loss/Cachexia

Chronic fever

Glomerulonephritis

Anterior uveitis/Pars planitis/Glaucoma (FIV>>FeLV)

Behavioral changes/Dementia/Peripheral neuropathies

Hypergammaglobulinemia (FIV>FeLV)

Hemolytic anemias/Aplastic anemias (FeLV>>FIV)

Lymphopenia/Neutropenia

Thrombocytopenia (FeLV>>FIV)

Abortion/Fetal resorptions/Thymic atrophy (fading kittens) (FeLV>>FIV)

Chronic progressive polyarthritis (FeSFV-associated??)

TABLE 2. FELINE LEUKEMIA VIRUS VACCINES

Product Name	Manufacturer	Type of Vaccine
Fel-O-Vax Lv-K	Fort Dodge Laboratories,	K, WV (FeLV-FAIDS strain), w/adjuvant
Fevaxyn FeLV	Solvay Animal Health, Shawnee, KS	K, WV (subgroups A & B), w/adjuvant
GenetiVac FeLV	Pitman-Moore/ Coopers Animal Health, Mundelein, IL	Recombinant SU (subgroup A/gp70 + part of p15E), w/adjuvant
Leukocell 2	SmithKline Beecham Animal Health, Exton, PA	Culture filtrate SU (subgroup A, B, & C/gp70, p15E, others), w/adjuvant
VacSYN/FeLV	Synbiotics, San Diego, CA	K, WV (UCD-1 FeLV substrain), no adjuvant

K = killed (inactivated), WV = whole virus, SU = subunit
Derived from Loar, AS. Feline leukemia virus: Immunization and prevention. **Vet Clinics of North America: Small Animal Practice 23:193, 1993.**

TABLE 3. DRUG APPENDIX

Generic	Trade	Dosage	Route	Frequency	Description
AZT (3'-azido-2',3'- dideoxythidine)	Retrovir	5mg/kg	SQ	q12h for 3 weeks	Antiretroviral dr (moniter for aner
Interferon-alpha (recombinant human IFN)	Roferon	30 IU/cat	PO	Daily - 7 days on; 7 days off	Immunefunction modulator
Propionibacterium acnes	Immunoregulin	0.5 ml/cat	IV	Once or twice weekly	Immunefunction modulator
Acemannan	Carrisyn	100 mg/cat or 2mg/kg	PO or SQ, IV	Daily	Immunefunction modulator
Prednisilone		2 to 4 mg/kg	PO	Daily	Corticosteroid - immunosuppressi
Metronidazole	Flagyl	7 to 15 mg/kg	PO	q8h to q12h	Antimicrobial - anaerobes
Oxytetracycline	Terramycin or Liquamycin	15mg/kg or 7mg/kg	PO or IM, IV	q8h or q12h	Antimicrobial - *Haemobartonell*
Clindamycin	Antirobe	11mg/kg	PO	q12h	Antimicrobial - *Toxoplasma*
Diazepam or Oxazepam	Valium or Serax	0.2mg/kg or 2.5mg/kg	IV or PO	As needed	Appetite stimula (Benzadiazepine