



# 2008 American Association of Feline Practitioners Feline Retrovirus Management Guidelines

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## **ABSTRACT**

Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) are among the most common infectious diseases of cats. Although vaccines are available for both viruses, identification and segregation of infected cats form the cornerstone for preventing new infections. Guidelines in this report have been developed for veterinary practices, breeders, shelters, and cat owners to use for diagnosing, preventing, treating, and managing FeLV and FIV infections. All cats should be tested for FeLV and FIV infection at appropriate intervals based on individual risk assessments. This includes testing at the time of acquisition, following exposure to an infected cat or a cat of unknown infection status, prior to vaccination against FeLV or FIV, prior to entering group housing, and when cats become sick. No test is 100% accurate at all times under all conditions; results should be interpreted along with the patient's health and risk factors. Retroviral tests can only diagnose infection, not clinical disease, and cats infected with FeLV or FIV may live for many years. A decision for euthanasia should never be based solely on whether or not the cat is infected. Vaccination against FeLV is highly recommended in kittens. In adult cats, anti-retroviral vaccination is considered non-core and should be administered only if a risk-assessment indicates it is appropriate. Few large controlled studies have been performed using antiviral or immunomodulating drugs for the treatment of naturally infected cats. More research is needed to identify best practices to improve long-term outcomes following retroviral infections in cats.

## **EPIDEMIOLOGY**

Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) are among the most common infectious diseases of cats. In the United States, prevalence of both infections is less than 2% of healthy cats and 6% to 33% of high-risk cats and cats that are tested during illness. (Levy et al., 2006, O'Connor et al., 1991, Moore et al., 2004) Risk factors for infection include male gender, adulthood, and outdoor access, whereas indoor lifestyle and sterilization are associated with reduced infection rates. (Levy et al., 2006, O'Connor et al., 1991, Hoover and Mullins, 1991, Levy, 2000, Levy JK, 2005)

The prevalence of FeLV infection has reportedly decreased during the past 20 years, presumably as a result of implementation of widespread testing programs and development of effective vaccines. (Levy et al., 2006, O'Connor et al., 1991, Moore et al., 2004) In contrast, prevalence of FIV has not changed since it was discovered in 1986. Testing for FIV infection is less common, and a vaccine against FIV was only recently introduced in 2002. Thus, whether the prevalence of FIV infection will change in the future is unknown.

In a study of more than 18,000 cats tested in 2004, 2.3% were positive for FeLV and 2.5% were positive for FIV. (Levy et al., 2006) For both viruses, prevalence was higher among cats tested at veterinary clinics (FeLV 2.9%; FIV, 3.1%) than among cats tested at animal shelters (FeLV 1.5%; FIV 1.7%) and in pet cats that were allowed outdoors (FeLV 3.6%; FIV 4.3%) than in pet cats that were kept strictly indoors (FeLV 1.5%; FIV

0.9%). Infections were higher among sick cats than healthy cats and was highest in sick feral cats (FeLV 15.2%; FIV 18.2%) followed by sick pet cats allowed access to the outdoors (FeLV 7.3%; FIV 8.0%). In contrast, positivity in healthy feral cats (FeLV 1.0%; FIV 3.3%) was lower than in healthy outdoor pet cats (FeLV 2.6%; FIV 3.2%).

Although infected cats may experience a prolonged period of clinical latency, a variety of disease conditions are associated with retroviral infections, including anemia, lymphoma, chronic inflammatory conditions, and susceptibility to secondary and opportunistic infections.(Hoover and Mullins, 1991, Levy, 2000) Specific diseases are associated with a very high rate of retroviral infections, such as cutaneous abscesses (FeLV 8.8%, FIV 12.7%)(Goldkamp et al., 2007) and oral inflammation (FeLV 7.3%, FIV 7.9%) (Bellows J, unpublished data).

Identification and segregation of infected cats is considered to be the single most effective method for preventing new infections with FeLV and FIV. Despite the availability of point-of-care testing for FeLV and FIV infection and of FeLV and FIV vaccines, less than one quarter of all cats have ever been tested, and infections with these viruses are still common. Although characteristics such as gender, age, lifestyle, and health status can be used to assess the likely risk of FeLV and FIV infections, most cats have some degree of infection risk.

While they can be life-threatening viruses, proper management and treatment can give infected cats longer, healthier lives. The following guide reflects the recommendations of the AAFP on managing these infections.

## **PATHOGENESIS**

### **FeLV Pathogenesis**

FeLV is commonly spread vertically from infected queens to their kittens and horizontally among cats that live together or that fight. The susceptibility of cats to FeLV is believed to be age-dependent, but the degree of natural resistance is unknown. In one study, all newborn kittens and the majority of cats up to two months of age developed progressive FeLV infection, but only 15% of cats inoculated when they were four months or older became infected.(Hoover et al., 1976) More recent studies, however, have demonstrated efficient natural and experimental infection of adult cats.(Grant et al., 1980)(Lehmann et al., 1991)

FeLV pathogenesis has been studied for decades using virus culture, immunofluorescent antibody (IFA) assays, and antigen detection.(Hardy et al., 1976a, Hoover and Mullins, 1991, Hoover et al., 1975, Lutz et al., 1980, Lutz et al., 1983, Pedersen et al., 1977, Rojko et al., 1979, Rojko and Kociba, 1991) In most cats, antigenemia (presence of viral proteins in the blood) correlates with viremia (presence of infectious virus that can be cultured from the blood), although a few cats have circulating virus without detectable antigens or antigens without viremia.(Jarrett et al., 1982) Cats typically acquire FeLV *via* the oronasal route by mutual grooming, but also

through bites. Viremic cats shed infectious virus in multiple body fluids, including saliva, nasal secretions, feces, milk, and urine.(Hardy et al., 1976b, Pacitti et al., 1986) After virus exposure, FeLV can be found first in the local lymphoid tissues and then spreads *via* monocytes and lymphocytes into the periphery.(Rojko et al., 1979)

Outcome of infection with FeLV is currently controversial. In the past, it was believed that approximately one third of cats became persistently viremic and up to two thirds eventually cleared the infection. (Hoover and Mullins, 1991) New research suggests that most cats remain infected for life following exposure, but may revert to an aviremic state (regressive infection) in which there is no antigen or culturable virus present in the blood, but FeLV proviral DNA can be detected in the blood by PCR.(Pepin et al., 2007) (Torres et al., 2005, Hofmann-Lehmann et al., 2001) The clinical relevance of PCR-positive, antigen-negative cats is not yet clear. The provirus is integrated into the cat's genome, so it is unlikely to be cleared over time.(Cattori et al., 2006) Although these cats are unlikely to shed infectious virus in saliva, it is possible that proviral DNA is infectious via blood transfusion. (Chen et al., 1998) The continuous presence of provirus may explain the long persistence of virus-neutralizing antibodies in "recovered" cats. Prior to the development of PCR, a status of "latent" infection was described in which the absence of antigenemia was accompanied by persistence of culturable virus in bone marrow or other tissues but not in blood.(Post and Warren, 1980, Madewell and Jarrett, 1983, Rojko et al., 1982, Hofmann-Lehmann et al., 2007b, Pacitti and Jarrett, 1985, Pedersen, 1984) Now, it seems likely "latent" infection is a phase through which cats pass during regressive infection. (Boretta et al., 2004)

FeLV provirus (DNA) and plasma viral RNA are usually detectable by PCR within one week of FeLV exposure, even if FeLV antigen is not. All cats with progressive and regressive infection seem to undergo this phase and to develop similar proviral and plasma viral RNA loads in the peripheral blood during early infection.(Hofmann-Lehmann et al., 2007a) Following FeLV exposure, it appears there are four possible outcomes of FeLV infection. (Hofmann-Lehmann et al., 2007a, Hofmann-Lehmann et al., 2007b, Torres et al., 2005)

In cats with progressive infection, FeLV infection is not contained at this early stage and extensive virus replication occurs first in the lymphoid tissues and then in the bone marrow and in mucosal and glandular epithelial tissues in most infected cats.(Rojko et al., 1979) The latter is associated with excretion of infectious virus in cats with progressive infection. Progressive infection is characterized by insufficient FeLV-specific immunity, and cats frequently succumb to FeLV-associated diseases within a few years.

Regressive infection is accompanied by an effective immune response, and virus replication is contained prior to or at the time of bone marrow infection. Cats with regressive infection are at little risk of developing FeLV-associated diseases. FeLV is integrated into the cat's genome, but there is not active viral replication or viral shedding.(Flynn et al., 2002, Lutz et al., 1983, Pedersen et al., 1977, Flynn et al., 2000)

Following infection, regressive and progressive infections can be distinguished by repeated testing for viral antigen in peripheral blood. (Torres et al., 2005) Most infected cats initially become antigen-positive within two to three weeks after virus exposure. They may then test negative for viral antigen two to eight weeks later or, in rare cases, even after many months (regressive infection). Both progressive and regressive infections are usually accompanied by persistent FeLV proviral DNA in blood. Some infected cats never develop detectable antigenemia. In this case, real-time PCR is more sensitive than antigen detection to detect FeLV exposure.

Abortive exposure has been observed infrequently following experimental FeLV inoculation and is characterized by negative test results for culturable virus, antigen, viral RNA, and proviral DNA after FeLV exposure. (Torres et al., 2005, Torres et al., 2006)

Focal infections have been reported in early studies. They are rare and occur in cats with FeLV infection restricted to certain tissues, such as spleen, lymph node, small intestine or mammary glands.(Hayes et al., 1989, Pacitti et al., 1986)

### Outcomes of FeLV Infection

Outcome of FeLV infection	FeLV p27 antigen in blood	Viral blood culture	Viral tissue culture	Viral RNA in blood	Proviral DNA in blood	Viral shedding	FeLV-associated disease
<b>Progressive</b>	Positive	Positive	Positive	Positive	Positive	Positive	Likely
<b>Regressive</b>	Negative or transiently positive	Negative or transiently positive	Negative or transiently positive	Transiently or persistently positive	Positive	Negative	Unlikely
<b>Abortive</b>	Negative	Negative	Negative	Not tested	Negative	Negative	Unlikely
<b>Focal</b>	Negative	Negative	Positive	Not tested	Not tested	Variable	Unlikely

### FIV Pathogenesis

FIV is shed in high concentrations in the saliva, which also contains infected leukocytes. The major mode of transmission is *via* bite wounds. Transmission of FIV from infected queens to their kittens has been reported in laboratory-reared cats,(Allison and Hoover, 2003, O'Neil et al., 1995) but it appears to be an uncommon event in nature.(Pu et al., 1995, Ueland and Nesse, 1992) Although transmission among household cats that do not fight is uncommon, it still is possible. In one household of 26 cats that were not observed to fight, FIV infection was originally diagnosed in nine cats, but spread to six other cats during a 10-year observation period.(Addie et al., 2000, O'Neil et al., 1995) Sexual transmission, the most common mode of transmission of HIV, appears to be unusual in FIV, even though the semen of infected cats frequently contains infectious virus.(Jordan et al., 1998)

Acute FIV infection is associated with transient fever, lymphadenopathy, and leukopenia, but frequently goes unnoticed by cat owners. Virus is detected in high concentrations in the circulation by culture and PCR within two weeks of infection. Within the first few weeks of FIV infection, both CD4+ (helper) and CD8+ (cytotoxic-suppressor) T-lymphocytes decline.(Egberink and Horzinek, 1992, Yamamoto et al., 2007) The initial lymphopenia is followed by a robust immune response, which is characterized by the production of FIV antibodies, a suppression in circulating viral load, and a rebound in CD8+ T-lymphocytes that exceeds preinfection levels. This results in inversion of the CD4+:CD8+ T-lymphocyte ratio that is likely to persist for the rest of the cat's life. Over time, both CD4+ and CD8+ T-lymphocytes gradually decline. The immune response is unable to eliminate infection, and cats remain infected for life.

Following the primary illness, cats enter a prolonged asymptomatic period that may last for years. During this time, progressive dysfunction of the immune system occurs. Although chronic inflammatory conditions and opportunistic infections are more common in cats with low CD4+ T-lymphocyte counts, some cats with severe CD4+ T-lymphocytopenia remain healthy. It is generally recognized that cell-mediated immunity is more profoundly affected than humoral immunity. Chronic inflammatory conditions, neoplasia, and infections with intracellular organisms, therefore, are more common than infections controlled by antibodies in FIV-infected cats. FIV-infected cats also appear to respond adequately to vaccination. It is common to observe a polyclonal hyperglobulinemia characteristic of nonspecific stimulation of humoral immunity in cats with chronic FIV infection. In human HIV infections, distinctive clinical stages can be defined based on absolute CD4+ T-lymphocyte counts and plasma viral RNA load. Similar systems have been attempted for staging FIV infections but are not as clearly defined in cats.(Goto et al., 2002, Walker et al., 1996)

## **DIAGNOSIS OF FeLV AND FIV**

The retrovirus status of all cats should be known since there are serious health consequences of infection that influence patient management, both in illness and wellness care. Accurate diagnosis of infection is important for both uninfected and infected cats. Identification and segregation of infected cats is considered to be the most effective method for preventing new infections in other cats. Failure to identify infected cats may lead to inadvertent exposure and transmission to uninfected cats. Misdiagnosis of infection in uninfected cats may lead to inappropriate changes in lifestyle or even euthanasia.

Cats may require retrovirus testing at different times in their lives. For example, cats that meet the following criteria should be tested for FeLV and FIV infection:

- Sick cats should be tested even if they have tested negative in the past.
- Cats and kittens should be tested when they are first acquired.
  - Even cats that do not live with other cats should be tested for several reasons, including the impact on their health, the possibility of other cats

- joining the household, the possibility that cats confined indoors may escape and expose other cats
  - Tests should be performed at adoption, and negative cats should be retested a minimum of 60 days later
- Cats with known recent exposure to a retrovirus-infected cat or to a cat with unknown status, particularly *via* a bite wound, should be tested regardless of previous test results.
  - Testing should be carried out immediately, and if negative should be repeated in a minimum of 30 days for FeLV and in a minimum of 60 days for FIV. When the type of possible viral exposure is unknown, it is most practical to retest for both viruses in 60 days.
- Cats living in households with other cats infected with FeLV or FIV should be tested on an annual basis unless they are isolated.
- Cats with high-risk lifestyles should be tested on a regular basis (*e.g.*, cats that have access to outdoors in cat-dense neighborhoods and cats with evidence of fighting such as bite wounds and abscesses).
- Cats should be tested before initial vaccination against FeLV or FIV.
- Cats used for blood or tissue donation should have negative screening tests for FeLV and FIV in addition to negative real-time PCR test results.
- Intermittent re-testing is not necessary for cats with confirmed negative infection status unless that have an opportunity for exposure to infected cats or if they become ill.

## Diagnosis of FeLV

Routine diagnostic screening for FeLV relies on detection of the core viral antigen p27, which is produced abundantly in most infected cats. In-clinic test kits detect soluble circulating antigen in peripheral blood. In the early days of testing, results were more reliable when serum or plasma was tested rather than whole blood. (Barr, 1996) However, with improvements in test technologies, it now appears that anticoagulated whole blood is also a suitable sample for testing. (Hartmann et al., 2007) Antigen tests should not be performed on tears or saliva as these tests are prone to more errors. (Lutz and Jarrett, 1987, Hawkins, 1991, Hawkins et al., 1986) Soluble antigen tests can detect infection during the early primary viremia phase. Most cats will test positive with soluble antigen tests within 30 days of exposure, (Jarrett et al., 1982) however, development of antigenemia is extremely variable and may take considerably longer in some cats. When the results of soluble antigen testing are negative, but recent infection cannot be ruled out, testing should be repeated a minimum of 30 days after the last potential exposure. Alternatively, PCR can be performed on anti-coagulated whole blood to detect provirus. PCR is usually positive sooner than p27 antigen detection. Kittens may be tested at any time, as passively acquired maternal antibody does not interfere with testing for viral antigen. However, kittens infected by some form of maternal transmission may not test positive for weeks to months after birth. (Levy and Crawford, 2005)

Immunofluorescent antibody (IFA) tests on smears from blood or bone marrow detect viral p27 antigen within infected blood cells. IFA tests do not detect infection until secondary viremia is established once bone marrow is infected. False-negative IFA results may occur in leukopenic cats. Cats that have regressive infection and cats that resist bone marrow infection also have negative IFA test results. False-positive results may occur when smears are too thick, when background fluorescence is high, and when the test is prepared and interpreted by inexperienced personnel.

Since the consequences of a positive screening test are significant, confirmatory testing is recommended, especially in low-risk and asymptomatic patients in which the possibility of a false-positive result is higher (low positive predictive value). (Jacobson, 1991) Negative screening test results are highly reliable due to the high sensitivity of the tests and low prevalence of infection (high negative predictive value).

There are several options for confirmation of a positive screening test. Virus culture is the gold standard for identification of progressive FeLV infection, but is not routinely available in North America. A second soluble antigen test can be performed, preferably using a test from a different manufacturer. (Barr, 1996, Hartmann et al., 2001) Some cats may be only transiently antigenemic and may revert to negative status on soluble antigen tests (regressive infection). (Barr, 1996) A positive IFA test on blood or bone marrow indicates a cat is likely to remain persistently antigenemic.

Discordant antigen test results may occur when results of soluble antigen tests and/or IFA tests do not agree and may make it difficult to determine the true FeLV status of a cat. The most common scenario is with a positive soluble antigen test and a negative IFA test. In most cases, such cats are truly infected. Discordant results may be due to the stage of infection, the variability of host responses, or technical problems with testing. The status of the cat with discordant results may eventually become clear by repeating both tests in 60 days and annually thereafter until the test results agree. Cats with discordant test results are best considered as potential sources of infection for other cats until their status is clarified.

PCR testing is offered by a number of commercial laboratories for the diagnosis of FeLV. Technical errors can reduce the sensitivity and specificity of PCR results. At this time, there are no comparative studies of the diagnostic accuracy of different commercial laboratories offering FeLV PCR. When performed under optimal conditions, real-time PCR can be the most sensitive test methodology for FeLV and can help resolve cases with discordant serological test results. Depending on how the PCR is performed, it can detect viral RNA or cell-associated DNA (provirus) and can be performed on blood, bone marrow, and tissues. In addition, PCR testing of saliva has been shown to have high correlation with blood antigen tests. (Gomes-Keller et al., 2006a, Gomes-Keller et al., 2006b) Recent studies using real-time PCR have shown that 5-10% of cats negative on soluble antigen tests were positive for FeLV provirus by PCR (regressive infection). (Hofmann-Lehmann et al., 2001, Gomes-Keller et al., 2006a) Although the clinical significance of antigen-negative, PCR proviral DNA-positive status is still unknown, it appears that most such cats remain aviremic, nonantigenemic, do not



shed virus, and are unlikely to ever develop FeLV-associated diseases. Since FeLV provirus is infectious, (Chen et al., 1998) it is recommended to test all feline blood donors for both FeLV antigen by serology and for provirus by real-time PCR.

Vaccination against FeLV does not generally compromise testing since FeLV tests detect antigen and not antibodies. However, blood collected immediately following vaccination may contain detectable FeLV antigens from the vaccine itself, so diagnostic samples should be collected prior to FeLV vaccine administration. (Levy J, unpublished data). It is not known how long this test interference persists.

## **Diagnosis of FIV**

Cats infected with FIV have low viral loads throughout most of their lives so that it has not been possible to devise rapid, in-clinic screening assays based on antigen detection. FIV produces a persistent, life-long infection so that the detection of antibodies in peripheral blood has been judged sufficient for routine diagnostic screening if the cat has not been previously vaccinated against FIV. (Levy et al., 2004, Hartmann, 1998) In-clinic test kits detect antibodies to different viral antigens, most commonly p24. Most cats produce antibodies to FIV within 60 days of exposure, but development of detectable antibodies may be considerably delayed in some cats. (Barr, 1996) A recent study showed that the performance of a patient-side FIV/FeLV test kit for the detection of FIV infection was excellent. (Levy et al., 2004) When the results of antibody testing are negative, but recent infection cannot be ruled out, testing should be repeated a minimum of 60 days after the last potential exposure.

Since the consequences of a positive screening test are significant, confirmatory testing is recommended, especially in low-risk and asymptomatic patients where the possibility of a false-positive result is higher. (Jacobson, 1991) Negative screening test results are highly reliable due to the high sensitivity of the tests and the low prevalence of infection in most populations. There are several options for confirmation of a positive screening test. Virus culture is the gold standard for identification of FIV infection, but is not routinely available in North America. A second soluble antibody test can be performed, preferably using a test from a different manufacturer. (Barr, 1996, Hartmann et al., 2001) Western blot and IFA detect antibodies against a range of viral antigens but were found to be less sensitive and specific than in-clinic screening tests in one study. (Levy et al., 2004)

The release of the first FIV vaccine (Fel-O-Vax FIV®, Fort Dodge Animal Health) has complicated the ability of veterinary practitioners to diagnose FIV infections. Vaccinated cats produce antibodies that cannot be distinguished from antibodies induced by natural infection by any current commercially available antibody test. (Levy et al., 2004) These antibodies are usually detected within a few weeks of vaccination. Vaccine-induced antibodies have been shown to persist for more than four years in some cats. (Levy J, unpublished data).

In this situation, it may be difficult to determine if a positive FIV antibody test means the cat is truly infected with FIV, is vaccinated against FIV but not infected, or is vaccinated

against FIV and also infected. Recently, an experimental method of ELISA testing that detects antibodies to multiple FIV antigens has been developed in Japan.(Kusuhara et al., 2007) Using this method, researchers were able to distinguish FIV-vaccinated cats from FIV-infected cats with a high degree of accuracy when testing serum samples from cats in both the United States and Canada.(Levy et al., 2007) This test, however, is not yet commercially available in North America.

PCR has been promoted as a method to determine a cat's true status, but investigation of the sensitivity and specificity of the FIV PCR tests offered by some labs has shown widely variable results.(Bienzle et al., 2004) In one study, test sensitivities (the ability to detect true positives) ranged from 41% to 93%, and test specificities (the ability to detect true negatives) ranged from 81% to 100%.(Crawford et al., 2005) Unexpectedly, false-positive results were higher in FIV-vaccinated cats than in unvaccinated cats. Research is being focused on improving the diagnostic accuracy of PCR for FIV.

Positive FIV antibody tests in kittens under six months of age must be interpreted carefully. Antibodies from FIV-vaccinated queens are passed to kittens that nurse on vaccinated queens.(MacDonald et al., 2004) These vaccine-associated antibodies persist past the age of weaning (8 weeks) in more than half of kittens. Kittens born to infected queens or FIV-vaccinated queens also acquire FIV antibodies in colostrum. Since it is uncommon for kittens to actually become infected with FIV, most kittens that test positive for FIV antibodies are not truly infected and will test negative when re-evaluated several months later. Kittens with FIV antibodies when over six months of age are considered to be infected. Because of this potential test interference, it may be tempting to delay testing of kittens for FIV until they are over six months of age. However, the vast majority of kittens test negative at any age and can be declared free of FIV infection. Although FIV infection of kittens is uncommon, it does occasionally occur. Infected kittens could be a source of infection for other cats if they are not identified and segregated. Also, compliance by both owners and veterinarians with retroviral testing recommendations remains low, and delaying testing of newly acquired kittens would likely result in a large number of cats never receiving FIV tests at all.(Goldkamp et al., 2007)

## **PREVENTION OF FeLV AND FIV**

Maximizing prevention of retrovirus infection can be accomplished through a partnership between veterinarians and pet owners. Testing and vaccination protocols, staff education, client reminder programs, and pet owner educational efforts can help contain the spread of these infections.

Traditionally, FeLV infection has been viewed as primarily a concern for cats that are “friendly” with other cats, as close, intimate contact between cats facilitates transmission. This type of contact occurs among cats as a result of nursing, mutual grooming, and sharing of food, water, and litter pans. In contrast, FIV infection is seen as a concern for cats that are “unfriendly” with other cats, as the major mode of transmission is through bite wounds. In reality, both viruses can be spread among cats

that are not known to fight as well as those that are prone to aggressive behavior.(Addie et al., 2000, Goldkamp et al., 2007)

## **FeLV Vaccination**

Several injectable inactivated adjuvanted vaccines, a nonadjuvanted recombinant vaccine for transdermal administration (available in the United States), and an injectable nonadjuvanted recombinant FeLV vaccine (a different preparation from the US product and available in Europe) are commercially available. Reviews of independent studies of vaccine efficacy indicate that the ability of any particular vaccine brand to induce an immune response sufficient to resist persistent viremia varies considerably between studies.(Sparkes, 1997, Sparkes, 2003) Results of several studies indicate that FeLV vaccine-induced immunity persists for at least 12 months following vaccination, although the actual duration of immunity is unknown and may be longer.(Harbour et al., 2002, Hoover et al., 1996) (Hofmann-Lehmann et al., 1995)

Because sufficient protection is not induced in all vaccinates, vaccination against FeLV does not diminish the importance of testing cats to identify and isolate those that are viremic. Therefore, the FeLV infection status of all cats, including vaccinated cats, should be determined. In addition, cats should be tested for FeLV infection before initial vaccination and when there is a possibility that they have been exposed to FeLV since they were vaccinated. There is no value in administering FeLV vaccines to cats confirmed to be FeLV-infected.

FeLV vaccines should be considered as noncore vaccines and are recommended for cats at risk of exposure (e.g., cats permitted outdoors, cats residing in multiple-cat environments in which incoming cats are not tested prior to entry, cats living with FeLV-infected cats). However, vaccination of all kittens is highly recommended because the lifestyles of kittens frequently change after acquisition and they may subsequently become at risk of FeLV exposure.(Richards et al., 2006) Kittens are also more likely than adult cats to develop progressive infections if exposed to FeLV.

When FeLV vaccination is determined to be appropriate, a two-dose primary series is recommended, with the first dose administered as early as eight weeks of age followed by a second dose administered three to four weeks later. A single booster vaccination should be administered one year following completion of the initial series and then annually in cats as long as they remain at risk of exposure.

Of note, although FeLV vaccines have been shown to protect against progressive infection to various degrees, they do not appear to prevent infection. Using real-time PCR, vaccinated cats were found to become positive for circulating proviral DNA as well as plasma viral RNA subsequent to FeLV exposure, even though they did not develop persistent viremia. (Torres et al., 2005, Hofmann-Lehmann et al., 2007b, Hofmann-Lehmann et al., 2006) Thus, FeLV vaccination does not necessarily induce sterilizing immunity. Nonetheless, efficacious FeLV vaccines are of great clinical importance, since protection against persistent viremia may prevent FeLV-associated fatal diseases.

## **FIV Vaccination**

FIV has proven to be a difficult agent to immunize against, in part because FIV vaccines do not induce broad cross-protective immunity against viruses from other strains or clades. Only a single vaccine is currently available for prevention of FIV infection. The vaccine is a whole-virus, dual subtype (clades A and D), inactivated product combined with an adjuvant. The vaccine is licensed for the vaccination of healthy cats eight weeks of age or older as an aid in the prevention of infection with FIV. In licensing trials required by the USDA, when cats were challenged with a heterologous clade A FIV subtype one year after the initial vaccination series, the vaccine yielded a preventable fraction (defined as the proportion of cats protected by vaccination in excess of the proportion that is naturally resistant) of 82%. Results of two subsequent studies indicate 100% protection against infection with two subtype B FIV strains. (Kusuhara et al., 2005, Pu et al., 2005) Results of a third study in which cats were challenged with subtype A FIV indicated that all vaccinated cats and control cats became infected. (Dunham et al., 2006)

FIV vaccines are noncore vaccines and may be considered for cats whose lifestyles put them at high risk of infection, such as outdoor cats that fight or cats living with FIV-infected cats. An initial series of three doses is administered subcutaneously two to three weeks apart; annual revaccination is recommended subsequent to the initial series if the risk of infection continues.

Clients should be informed that vaccinated cats will develop positive FIV test results, and the decision to vaccinate should be reached only after careful consideration of this implication. If the decision falls in favor of vaccination, cats should test negative immediately prior to vaccination. A permanently placed identification microchip and collar are recommended for all cats to increase the chance of returning lost cats to their owners. Microchip databases can also record FIV vaccination histories. This information can be used by animal shelters to help assess the significance of positive FIV test results when shelters screen cats prior to adoption.

## **Limiting Transmission in the Veterinary Practice**

Retroviruses are unstable outside their host animals and can be quickly inactivated by detergents and common hospital disinfectants. (Francis et al., 1979, August, 1991, Kramer et al., 2006, Moorer, 2003, Terpstra et al., 2007, van Engelenburg et al., 2002) However, retroviruses in dried biological deposits can remain viable for more than a week. Simple precautions and routine cleaning procedures will prevent transmission of these agents in veterinary hospitals. All infected patients should be housed in individual cages and may be maintained in this manner in the general hospital population. Because they may be immune-suppressed, they should not be housed in an isolation ward with cats carrying contagious diseases.

Animal caretakers and other hospital staff members should wash their hands between patients and after handling animals and cleaning cages. Both FeLV and FIV can be transmitted in blood transfusions; therefore, all blood donors should be confirmed free of infection.(Wardrop et al., 2005)

Dental and surgical instruments, endotracheal tubes, and other items potentially contaminated with body fluids should be thoroughly cleaned and sterilized between uses.(Druce et al., 1997) Fluid lines, multi-dose medication containers, and food can become contaminated with body fluids (especially blood or saliva), and should not be shared among patients.

### **Limiting Transmission at Home**

FeLV-infected cats should be confined indoors so they do not pose a risk of infection to other cats and so that they are protected against infectious hazards in the environment. If a FeLV-positive cat is identified in a household, the best method of preventing spread to other cats in the household is to isolate the infected cat in a separate room and to prevent the infected cat from interacting with its housemates. A simple screen or chain-link barrier is adequate to prevent viral transmission in the laboratory setting. (Levy J, unpublished data).

If owners choose not to separate housemates, uninfected cats should be vaccinated against FeLV in an attempt to enhance their natural level of immunity. The cats should be kept separated until at least two months after completion of the primary immunization series to allow time for effective immunization. However, it should be understood that no FeLV vaccine protects 100% of cats against FeLV infection. FeLV can be transmitted vertically from an infected queen to her kittens *in utero* or *via* infected milk. Infected queens should not be bred and should be spayed if their condition is sufficiently stable to permit them to undergo surgery.

Generally, cats in households with stable social structures where housemates do not fight are at a low risk for acquiring FIV infection, but a high rate of transmission within a household without observed fighting has been reported.(Addie et al., 2000) Therefore, separation of infected cats from uninfected housemates is recommended to eliminate the potential for FIV transmission. If separation is not possible, no new cats should be introduced in the household to reduce the risk of territorial aggression. Experimentally, FIV has been shown to be vertically transmitted by infected queens to their kittens. Although this is apparently true only for a few specific strains of FIV and is uncommon in nature, infected queens should not be bred and should be spayed if their condition is sufficiently stable to permit them to undergo surgery.

### **CONSIDERATIONS FOR BREEDING CATTERIES**

The prevalence of retrovirus infections in the controlled environments of catteries appears to be low, particularly with the advent of test and removal programs for FeLV many years ago. However, ongoing vigilance is required to prevent introduction of FeLV

or FIV into the cattery. Certain circumstances in catteries facilitate transmission of infectious diseases, such as group-living, mingling of kittens with older cats, close contact of cats during mating, the occasional introduction of new cats, and the practice of sending queens to other catteries for breeding.

Only healthy cats should be used for breeding and the retrovirus status of all cats in the cattery should be known (whether breeding or non-breeding). When testing is performed in the cattery for the first time, all cats should test negative on two tests, 60 days apart. Infected cats should be removed from the cattery. All newly acquired kittens and cats should be placed in isolation and tested for FeLV and FIV on arrival. Ideally, they should remain isolated until a second negative test is obtained 60 days later, particularly if they originate from a cattery with unknown retrovirus status.

Queens sent to another facility for mating should be tested before leaving the cattery and should only be sent to mate with a tom that has tested negative for FeLV and FIV. Upon return to the home cattery, the queen should be kept in isolation and re-tested.

Cat shows are not significant sources of retrovirus infection since cats on exhibition are housed separately and the viruses are susceptible to the routine disinfectants that are commonly employed. In addition, environmental contamination of surfaces is not a risk due to the fragile nature of retroviruses. Therefore, there is no need to test cats that have left the cattery solely for the purpose of a cat show.

In catteries that follow testing guidelines and maintain retrovirus-negative status, vaccination against FeLV or FIV is not necessary, as long as no cats have access to the outdoors. Time and resources should be focused on maintaining a retrovirus-negative cattery through testing. Some catteries do not maintain breeding toms, and rely totally on stud services from other catteries. In such circumstances, vaccination of queens against FeLV may be considered, in addition to testing queens that leave the cattery for stud service. Vaccination against FIV is not recommended because the infection is uncommon in catteries, and vaccination interferes with current test methodologies.

## **CONSIDERATIONS FOR CAT SHELTERS**

Although prevalence of FeLV and FIV in shelters mirrors the relatively low rates found in pet cats, thousands of infected cats are likely to pass through shelters each year. Shelters should have policies in place for testing, prevention, and responding to positive test results.

The sheltering industry is currently in a state of flux as growing support for “No Kill” policies stimulates discussion about what constitutes an “untreatable” or “unsavable” animal. Using the strictest definition of euthanasia as an act of mercy for alleviating unremitting suffering, a growing number of shelters are classifying healthy FeLV-infected and FIV-infected cats as adoptable. This has created new challenges for shelter facilities, as it often takes longer to find homes for infected cats. When shelter space is limited, longer resident times may lead to lower overall adoption success.

Sanctuaries devoted to long-term care of infected cats have been developed as an alternative and present their own set of challenges for optimal care and environmental enrichment.

Although this document broadly recommends testing all cats for retroviral infection, an exception exists for feral cats in trap-neuter-return programs. The prevalence of infection is similar in outdoor pet cats and feral cats, so feral cats do not present an increased threat to pets. Additionally, neutering reduces two common modes of transmission: queen to kitten for FeLV and fighting among males for both FeLV and FIV. Since population control of feral cats requires commitment to neutering the largest number of cats possible, many trap-neuter-return programs do not routinely test feral cats.(Wallace and Levy, 2006)

### **Testing for FeLV and FIV in Shelters**

Diagnosis of FeLV and FIV in shelter situations follows the same principles as in pet cats. Ideally, all cats would be tested upon entry to the shelter or prior to adoption. All cats entering shelters should be considered potentially infected, regardless of the environment from which they originated. Because the background of most shelter cats is unknown, it is advisable to retest cats 60 days after the initial test in case of recent exposure. This also applies to unweaned orphaned kittens, which may have been infected from the queen or another cat, but test negative at the time of admission to the shelter. These kittens should be retested prior to adoption. Cats that are returned to the shelter following a failed adoption should also be retested.

Although screening tests are commonly used in shelters, confirmatory tests pose a greater challenge. Increased costs, delays, and difficulty in interpreting discordant results are reasons many shelters do not pursue confirmatory testing. Currently, the inability to distinguish FIV-vaccinated cats from those that are infected or both vaccinated and infected is a major concern for shelters.

Testing at admission is optional for cats that are housed in single-cat cages. It is common for some shelters to test cats at the time of adoption instead of at admission, particularly if a substantial proportion of cats are not expected to be adopted. In some situations, limited shelter resources do not permit testing of all cats for both FeLV and FIV prior to adoption. In such cases, shelters may place priorities on testing higher-risk cats such as sick cats, adult males, and cats suspected to be exposed to infected cats. If limited testing or no testing is employed, it is advisable to house cats singly and to recommend testing post-adoption. In such cases, it should be clearly explained and documented to the adopter that the AAFP recommends testing of all newly adopted cats. Arrangements should be made by the adopter to have the new pet tested by their own veterinarian as soon as possible. The new pet should be kept separate from other cats until the test result is known, and preferably until a second test is performed 60 days later. Although the vast majority of sheltered cats are free of infection, post-adoption testing is likely to result in some new pet owners confronting difficult decisions about what to do with a newly adopted cat that is subsequently diagnosed with a

retrovirus infection. If one cat in a litter or group is later reported to be infected, the adopters of other cats with exposure to the infected cat should be contacted and informed.

Cats should have negative test results for both FeLV and FIV prior to being introduced to group housing. It is ideal to quarantine and retest 60 days later prior to group housing, but this is not always practical in a shelter setting. Resident cats in foster homes should be tested before foster cats are added to the household.

In shelters or sanctuaries that group-house large numbers of cats long-term, it is a good practice to retest resident cats annually. Cats held in multi-cat environments with cats of unknown background constitute a high-risk population even if all of the cats are tested when they are first added to the group. Since tests are not 100% accurate it is possible for a cat to be admitted to the group with an undiagnosed infection.

The presence of infection varies within individual litters, feral cat colonies, and households. Some shelters attempt to conserve resources by testing only a queen and not her kittens or test only a few members of a litter or household, but it is inappropriate to test one cat as a proxy for another. Because prevalence's of retroviruses are low, even among feral cats, it is also inappropriate to test a small number of cats within a colony if the intent is to determine whether FeLV or FIV is present. Medical records in shelters should individually identify each cat and accurately reflect the actual testing procedures performed.

Since there are currently no tests that distinguish FIV antibodies induced by infection compared to those induced by vaccination, shelters have the difficult task of determining the true infection status of stray cats that are admitted without medical histories and that test positive for FIV antibodies. In some cases, the history of FIV vaccination may be recorded in a microchip database that can be accessed if the cat is microchipped. However, even if it is known that cats have been vaccinated against FIV, it is not usually possible to determine if the cats are not also infected. This is a challenge for shelters for which there is no current solution.

Test procedures must be performed as indicated by the manufacturer to maintain accuracy. Procedures such as pooling multiple samples for use in a single test reduce test sensitivity and should not be performed.

#### Testing Recommendations:

- As for pet cats, it is ideal for all cats in shelters to be tested for FeLV and FIV.
- Testing at admission is optional for singly-housed cats.
- Testing is highly recommended for group-housed cats.
- If not performed prior to adoption, testing should be recommended to the new owner before exposure to other cats.
- Testing should be repeated 60 days after the initial test and annually for cats kept in long-term group housing.



- Each cat should be individually tested. It is inappropriate to test one cat as a proxy for another or to pool samples for testing.
- Both foster families and adopters should have their own resident cats tested prior to fostering or adopting a new cat.
- Testing is optional in feral cat trap-neuter-return programs.

## **Prevention of FeLV and FIV Transmission in Shelters**

FeLV and FIV differ from other infectious diseases of importance in shelters, such as panleukopenia virus, calicivirus, and herpes virus, because the retroviruses are easily inactivated with routine disinfection and are not spread by indirect contact. However, FeLV and FIV are efficiently transmitted iatrogenically by small amounts of contaminated body fluids, particularly blood and saliva.(Druce et al., 1997) For this reason, surgical instruments and needles should never be shared between cats without effective sterilization, even within the same litter. Similarly, all endotracheal tubes, breathing circuits, dental instruments, and other potentially contaminated equipment should be disinfected between each patient, even among cats from the same environment or litter.

Vaccination against FeLV is generally not recommended in shelters in which cats are individually housed because of the low risk of viral transmission. In such shelters, resources are generally better spent on testing, and the decision to vaccinate is best left to the adopter based on the cat's risk profile in its new home. In facilities in which cats are group-housed, such as in some shelters and foster homes, FeLV vaccination is highly recommended. High turnover of cats from multiple unknown backgrounds make group-housing and foster homes a higher risk for FeLV transmission, especially when quarantine and retesting at a later time is not possible.

For the same reason, vaccination against FIV is not generally recommended in typical single-cat housing. In addition, vaccine-induced positive antibody test results make it difficult for shelters to confirm the true FIV infection status of vaccinated cats in the future.

### **Control Recommendations:**

- FeLV vaccination is optional for singly housed cats.
- FeLV vaccination is highly recommended for all cats housed in groups and for both foster cats and permanent residents in foster homes.
- Cats should be tested negative for FeLV prior to vaccination.
- Vaccination is not 100% effective and should never be used in place of a test and segregate program.
- In contrast to the case for feline panleukopenia, herpesvirus, and calicivirus vaccines, the value of a single FeLV vaccine has not been determined. Therefore, FeLV vaccination is not recommended for feral cat trap-neuter-return programs if program resources are needed for higher priorities.
- FIV vaccination is not recommended for use in shelters.

- Strict adherence to universal precautions is required to prevent iatrogenic transmission of retroviruses in the shelter environment *via* contaminated equipment and secretions.
- Cats used for blood donation in shelters should be proved free of retroviral infection prior to donating blood.

## **MANAGEMENT OF RETROVIRUS-INFECTED CATS**

Both FeLV-infected and FIV-infected cats can live many years with proper care and may succumb at older ages from causes unrelated to their retrovirus infections. Long-term monitoring of a 26-cat household with endemic FeLV and FIV revealed that all FeLV-infected cats died within five years, but FIV infection did not affect survival in this group.(Addie et al., 2000) A large study compared the survival of more than 1,000 FIV-infected cats to more than 8,000 age- and sex-matched uninfected control cats.(Levy, 2006) Of cats that were not euthanized around the time of diagnosis, median survival of FIV-infected cats was 4.9 years compared to 6.0 years for control cats. A comparison between more than 800 FeLV-infected cats and 7,000 controls revealed that the median survival of FeLV-infected cats was 2.4 years compared to 6.3 years for controls. With proper care, many retrovirus-infected cats may live for several years with good quality of life. Thus, a decision for treatment or for euthanasia should never be based solely on the presence of a retrovirus infection.

It is important to recognize that FIV- and FeLV-infected cats are subject to the same diseases that befall cats free of those infections, and that a disease diagnosed in a retrovirus-infected cat may not be related to the retrovirus infection.(Levy, 2000, Levy JK, 2005) However, in all cats, healthy or sick, FIV and FeLV status should be known because the presence of a retrovirus infection impacts their health status and long-term management.

Cats infected with FIV, FeLV, or both should be confined indoors to prevent spread to other cats in the neighborhood and exposure of affected cats to infectious agents carried by other animals. Good nutrition, husbandry, and an enriched lifestyle are essential to maintaining good health.(August, 1991, Overall et al., 2005) The cats should be fed a nutritionally balanced and complete feline diet. Raw meat and dairy products should be avoided because the risk of food-borne bacterial and parasitic diseases is greater in immunosuppressed individuals. A program for routine control of gastrointestinal parasites, ectoparasites, and heartworms, where applicable, should be implemented.(Companion Animal Parasite Council, 2007)

Cats infected with a retrovirus should receive wellness visits at least semi-annually to promptly detect changes in their health status. Veterinarians should obtain a detailed history to help identify changes requiring more intensive investigation and perform a thorough physical examination at each visit. Special attention should be paid to the oral cavity because dental and gum diseases are common in retrovirus-infected cats. Lymph nodes should be evaluated for changes in size and shape. All cats should receive a thorough examination of the anterior and posterior segments of the eye.(Willis, 2000)

The skin should be examined closely for evidence of external parasitic infestations, fungal diseases, and neoplastic changes. The body weight should be accurately measured and recorded, because weight loss is often the first sign of deterioration in a cat's condition.

A complete blood count should be performed annually for FIV-infected cats and at least semi-annually for FeLV-infected cats because of the greater frequency of virus-related hematologic disorders in FeLV-infected cats. Serum biochemical analyses and urinalyses should be performed annually; urine samples should be collected by cystocentesis so that bacterial cultures can be performed if indicated. Fecal examinations should be performed for cats with a history of possible exposure to gastrointestinal parasites or pathogens.

“Routine vaccination” of retrovirus-infected cats is a subject of debate. Although there is little evidence that modified live-virus vaccines are problematic, inactivated vaccines are recommended as live-virus vaccines may theoretically regain their pathogenicity in immune-suppressed animals.(Buonavoglia et al., 1993, Reubel et al., 1994, Richards et al., 2006) Healthy FIV-infected cats have been shown to have similarly adequate immune responses to vaccination compared to uninfected cats.(Fischer et al., 2007, Dawson et al., 1991) (Lehmann et al., 1991) Vaccination of FIV-infected cats may lead to stimulation of the immune system and subsequent increased FIV replication, although the clinical significance of this observation is unknown.(Reubel et al., 1994, Lehmann et al., 1992) Some cats infected with FeLV may not adequately respond to vaccination.(Franchini, 1990) In general, it is recommended that vaccine selection and immunization intervals for cats with FeLV or FIV infection be selected based on individual risk assessments using guidelines developed for cats in general.(Richards et al., 2006)

Sexually intact male and female cats should be neutered to reduce stress associated with estrus and mating behaviors. Neutered animals are also less likely to roam outside the house or interact aggressively with their housemates. Surgery is generally well-tolerated by infected cats that are not showing any clinical signs of disease. A thorough examination and ideally pre-anesthetic blood testing should be performed before surgery. Perioperative antibiotic administration should be considered for infected cats undergoing dental procedures and surgeries, due to their potentially immunosuppressed state. Appropriate analgesia should be administered not only to cats undergoing invasive procedures, but also to cats with chronic pain due to retroviral-associated conditions such as stomatitis, uveitis, and neoplasia.(Hellyer et al., 2007)

Clinical illness in cats with FeLV or FIV infection may be a primary effect of retroviral infection (such as lymphoma or pure red cell aplasia), a secondary disease associated with immune dysfunction (such as opportunistic infections or stomatitis), or be unrelated to the viral infection. Prompt and accurate diagnosis is essential to allow early therapeutic intervention and a successful treatment outcome. Therefore, more intensive diagnostic testing should proceed earlier in the course of illness for infected cats than might be recommended for uninfected cats. Many cats infected with FeLV or FIV

respond as well as their uninfected counterparts to appropriate medications and treatment strategies, although a longer or more aggressive course of treatment may be needed.

Corticosteroids and other immune-suppressive drugs should be administered only to those patients with a clear indication for their use. In severe stomatitis that commonly occurs in retrovirus-infected cats, full-mouth extraction is preferred over long-term use of corticosteroids. Griseofulvin has been shown to cause bone marrow suppression in FIV-infected cats and should not be used for treatment of fungal infections. (Shelton et al., 1990)

Highly active antiretroviral therapy (HAART) cocktails are the mainstay of treatment in HIV-infected patients and result in longer survivals and improved quality of life. Antiviral therapy has also been used in retrovirus-infected cats, although the drugs available to cats are limited and tend to be more toxic in cats than in humans. (Hartmann, 2006) Drugs aimed at modulating the immune system are commonly used in cats and are proposed to restore compromised immune function, thereby allowing the patient to control viral burden and recover from associated clinical syndromes. Unfortunately, there are only a few large long-term controlled studies in naturally infected cats that have shown durable benefit using either antiviral drugs or immunomodulators.

The only antiviral compound routinely used in both retrovirus infections is zidovudine (AZT), a nucleoside analogue (thymidine derivative) that blocks the viral reverse transcriptase enzyme. It has been shown that AZT effectively inhibits FeLV and FIV replication *in vitro* and *in vivo*. It can reduce plasma virus load, improve immunological and clinical status, particularly in cats with neurological signs or stomatitis. It is used at a dosage of 5-10 mg/kg q 12h PO or SC. The higher dose should be used carefully in FeLV-infected cats as side effects, particularly non-regenerative anemia, can develop. (Hartmann et al., 1995a, Hartmann et al., 1995b, Hartmann, 2005, Hartmann et al., 1992)

Feline interferon- $\omega$  (Virbagen Omega, Virbac) has been available for use in a few countries for several years. In a placebo-controlled field study, FeLV-infected cats treated with interferon- $\omega$  ( $10^6$  IU/kg SC q 24 h for five consecutive days repeated three times with several weeks between treatments) were more likely to be alive at one year compared to placebo-treated cats. (de Mari et al., 2004) The mechanism for the survival advantage is undetermined, as no virological parameters were measured. There was no effect on survival in FIV-infected cats.

Natural human interferon- $\alpha$  (Alfaferone, Alfa Wasserman, Italy) was used in clinically-ill cats naturally infected with FIV (50 IU on the oral mucosa daily for seven days on alternating weeks for six months, followed by a two-month break, and then repetition of the six-month treatment). Supportive treatments (e.g., antibiotics and parasiticides) were allowed. Of the 53 cats that entered the study, results were reported for 30 of the cats. Three cats were co-infected with FeLV. All but one of the 24 cats in the treatment group for which results were reported were alive at 18 months compared to only one of

the six placebo-treated cats. There were no improvements in viral burden, CD4+ T-lymphocyte counts, or hematological results to explain the apparent survival benefit associated with interferon- $\alpha$  treatment. (Pedretti et al., 2006)

1 **Drugs Used in the Treatment of FeLV and FIV Infections**

2

<b>Drug</b>	<b>Category</b>	<b>Target virus</b>	<b>Controlled trials in naturally infected cats</b>
Zidovudine	Antiviral	FeLV	Improved stomatitis score, reduced p27 antigenemia(Hartmann et al., 1992)
Zidovudine	Antiviral	FIV	Improved stomatitis score, improved CD4+:CD8+ ratio(Hartmann et al., 1992)
Didanosine	Antiviral	FeLV, FIV	No trials reported
Suramin	Antiviral	FeLV, FIV	No trials reported
Feline interferon- $\omega$	Antiviral, Immunomodulator	FeLV	Improved survival(de Mari et al., 2004)
Feline interferon- $\omega$	Antiviral, Immunomodulator	FIV	No effect vs. placebo(de Mari et al., 2004)
Recombinant human interferon- $\alpha$	Antiviral, Immunomodulator	FeLV	No effect vs. placebo(McCaw et al., 2001)
Natural human interferon- $\alpha$	Antiviral, Immunomodulator	FIV	Improved survival(Pedretti et al., 2006)
<i>Staphylococcus</i> Protein A	Immunomodulator	FeLV	No effect vs. placebo(McCaw et al., 2001)
<i>Staphylococcus</i> Protein A	Immunomodulator	FIV	No trials reported
Pind-avi, Pind-orf	Immunomodulator	FeLV	No effect vs. placebo(Hartmann et al., 1998)
Pind-avi, Pind-orf	Immunomodulator	FIV	No trials reported
Acemannan	Immunomodulator	FeLV, FIV	No trials reported
Bacille Calmette-Guérin	Immunomodulator	FeLV, FIV	No trials reported
Diethylcarbamazine	Immunomodulator	FeLV, FIV	No trials reported
Lymphocyte T-Cell Immunomodulator	Immunomodulator	FeLV, FIV	No trials reported
Levamisole	Immunomodulator	FeLV, FIV	No trials reported
<i>Propionibacterium acnes</i>	Immunomodulator	FeLV, FIV	No trials reported
<i>Serratia marcescens</i>	Immunomodulator	FeLV, FIV	No trials reported
Bovine lactoferrin	Immunomodulator	FeLV, FIV	No trials reported

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