Feline Immunodeficiency Virus

To promote education about feline immunodeficiency virus (FIV), IDEXX Laboratories sponsored a Feline Immunodeficiency Virus Forum* in July 2000 at the American Veterinary Medical Association annual convention. This panel of academic experts and prominent feline practitioners was assembled from all over the United States to collect the latest thinking on feline immunodeficiency virus from a broad range of authoritative sources. The goal was to help veterinarians make informed choices on diagnostic testing for this disease. The research presented, as well as the opinions expressed, shed new, important information on the clinical significance and diagnosis of this disease.

History

Dr. Niels Pederson and his group from the University of California Davis in 1986 discovered feline immunodeficiency virus in a no-kill shelter facility near Petaluma, California. FIV has been detected worldwide and has been found in stored samples as far back as 1966 in Europe, 1968 in the United States, and 1972 in Australia. Although it is a recently discovered virus, it has been present in the feline population for much longer.

Understanding the Disease Process

There are five major subtypes of FIV, and more are emerging. There is a tremendous amount of virus variability within an individual and between individuals. Researchers have never identified a single identical isolate.

The genomic structure of the virus is most similar to the maedi/visna virus of the Lentivirus group, and there is a cross-reactivity between the P24 antigen of the FIV virus and the P26 antigen of equine infectious anemia virus, so there is some cross-reactivity with some of the other Lentiviruses. FIV is composed of a spherical to ellipsoid type virion of 105 to 125 nm.

During the acute phase of infection, lymphocytes are the primary targets of the virus. Then there is an infection of macrophages and a drift from a lymphocytotropic to a monocytotropic strain. This also may have an impact on the differences in transmissibility in various strains that have been isolated from the various populations of cats.

The virus isolation from lymphocytes can occur as early as 10 to 14 days after infection. The viremia will increase in intensity up to about 3 weeks after infection; it peaks at about week 7 and 8 and then tends to decrease.

Antibody production may appear as early as 2 weeks after infection. Two to 4 weeks is the range that is described in most references. The envelope antibody develops first, which is followed by antibody generated against the core proteins. However, some cats may not have antibody present for up to 1 year after infection in some of the experimental studies and some may never develop detectable levels of antibody, though virus can be recovered from peripheral blood lymphocytes.

In general, FIV is not considered oncogenic. However, in a recent study in which lymphoma was invoked in cats...
experimentally infected with FIV, the diseases that occurred in the laboratory in specific pathogen free (SPF) cats were different than the diseases that occurred in random source cats. Conditions that seem to be purely attributable to FIV are ocular disease, central nervous system disease, lymphoma, and sometimes wasting syndromes if the cats live 10 years more. However, if random source cats are experimentally infected, other chronic diseases occur, such as stomatitis, respiratory disease, and skin disease, which are probably diseases that require cofactors of the virus to express themselves.

Lymphoma definitely occurs in the laboratory as a result of FIV infection. FIV-associated lymphomas tend to be B-cell lymphomas and occur frequently in extranodal sites such as the eye, the kidney, the nose, or as a nasal-renal combination. However, these tumors seem to be somewhat indolent compared with the more aggressive FeLV-associated ones. Human immunodeficiency virus (HIV) is also associated with B-cell lymphomas.

There are four stages of FIV infection. In stage 1—the acute stage of infection—the following can be detected in some individuals: a decreased number of polymorphonuclear neutrophil leukocytes (PMNs), lymphadenopathy, and fever. Acute stage signs seem to be most prominent in kittens and geriatric cats. Lymphadenopathy is particularly persistent in kittens that are infected perinatally or prenatally. The acute stage of infection may last for days, weeks, or months.

Stage 2—the asymptomatic stage—is where most clinicians detect infection by routine testing. These cats have no obvious clinical signs or laboratory evidence of infection other than the presence of FIV antibodies.

Stage 3 is characterized by nonspecific clinical signs. There may be lymphadenopathy, fever, apathy, leukopenia, and inflammatory eye diseases. Stomatitis or behavioral changes may develop in this stage.

Stage 4 is the terminal AIDS-like stage. This stage is characterized by the classic AIDS-related complex, wasting, immunodeficiency-type problems with many secondary infections (i.e., severe stomatitis), neoplasia, and neurologic abnormalities. This stage usually lasts only a few months.

Prevalence
The incidence of FIV in various populations varies greatly (Figure 1). The incidence in sick cat populations is about 2% in Germany and The Netherlands, about 33% in the United Kingdom, and 44% in Japan. The differences are probably related to husbandry practices in the various countries as well as the maintenance of animal health in the feline populations in those countries. Although it is primarily a domestic cat virus, evidence of infection has been found in exotic cat species as well. Several studies show that FIV has a male cat predominance.

Transmission
Vertical transmission of FIV occurs; however, bite wounds among male cats are considered to be the primary mode of transmission. FIV also has been detected in semen, so a few cases may occur secondary to coital transmission. This has not been shown to occur in natural breeding but has been shown experimentally. It would be difficult to prove in the natural setting because cats are not tested until they are sick. Once FIV is introduced into a population, it seems to be maintained at a relatively stable status between susceptible and infected individuals.

Dr. Wolf: One of the points for our discussion is Dr. Hoover’s group article on the vertical transmission of FIV. What does his article mean to you, Dr. Richards?

Dr. Richards: I think it’s very interesting. The amount of research dollars available to study FIV far exceeds that of other infectious agents in cats primarily because FIV looks an awful lot like HIV. Because vertical transmission is a characteristic of HIV, it’s useful to find a strain of FIV that does the same thing. We can learn

Figure 1—Map showing cat population and the incidence of feline leukemia virus and feline immunodeficiency virus in the United States.
more about the human disease, theoretically, by studying cats.

So we certainly know vertical transmission can happen. However, the question remains as to how often it happens in nature.

**Dr. Ford:** It’s difficult to translate the findings of Dr. Hoover’s study into how they might affect the practitioner. I find vertical transmission intriguing. One thing that impresses me about retroviruses, and particularly FIV, is that it is not a static environment. These viruses are constantly changing, and we probably aren’t doing the level of surveillance that we could do.

**Dr. Wolf:** One study showed that antibodies protect kittens.\(^1\) So if the queen was chronically infected and she transmitted maternal antibodies to her kittens, infections could be prevented. Three other studies show no vertical transmission in chronically infected colonies of cats.\(^2\)\(^-\)\(^4\) So I think there’s a lot of conflicting evidence, and the studies that show vertical transmission are in a rather artificial setting. But maybe that point is totally moot; if it occurs at all, then perhaps we ought to be looking for it.

**Dr. Levy:** I think, experimentally, we’ve shown really well that acute infection of the queen is the highest risk of transmission to the kitten. So acute, primary infection during pregnancy or at the time of delivery is most likely to result in vertical transmission. And that probably, just statistically, is a pretty rare event in nature, which is one reason why we don’t see a lot of truly infected kittens. Most young kittens that initially test positive on the antibody test ultimately prove to be uninfected. It is believed that FIV can survive outside of the body for only a few minutes in ideal conditions. Nevertheless, there may be practices in veterinary clinics that are responsible for some of the unexplained cases of FIV (e.g., using a single spay packet for several cats, or using the same fluid bag for multiple patients and switching the needle only).

**Concurrent Infection with FeLV**

**Dr. Ford:** What I’d like to know from the group is what is the incidence of concurrent infection with FIV and FeLV. I realize most practitioners use a combo test. Diane, are you seeing FeLV antigen positive and FIV antibody positive cats?

**Dr. Eigner:** Actually, no. We only use the combo tests when we’re testing for FIV, at least as our initial test, and very few cats have been positive with both—most of the cats I see are positive for FIV only.

**Dr. Wolf:** The data from our feral cat study are rather interesting. We’ve studied close to 300 cats now. Of those, only one had both infections. The rest had either one or the other.

**Dr. Levy:** I’ve got similar data from feral cats from the North Carolina program and the Florida program. We’ve only had six dual-positive cats (all male) out of 1876 that have been tested.

**Dr. Lappin:** We can add another 206 cats to that. We just published a paper on enteric zoonosis in cats with diarrhea in Colorado. We found one dual-positive cat. About one-third of the sample was shelter cats and two-thirds were pet cats.

**Dr. Wolf:** I think that probably speaks a lot to the transmission and the differences: FeLV tends to be a disease of friendly cats and FIV is a disease of unfriendly cats.

**Lymphomas**

**Dr. Ford:** Obviously, FeLV is oncogenic, and FIV generally is not considered oncogenic. Is there a link between FIV and lymphoma?
infection. If the presence of antibodies is tested periodically, they will disappear at various times during the course of infection, which causes problems in diagnosing FIV. Because retroviruses like FIV are constantly adapting, research to aid diagnosis can quickly become outdated.

The IFA and ELISA are the screening standards for FIV. The Western blot is the gold standard of confirmatory tests because it has the advantage of looking for multiple antibody specificity rather than a single antibody class. However, these tests only indicate the presence of antibodies— they do not prove that there is an active infection. A research laboratory can do virus isolation or RT-PCR of some type, but it is generally not available to a practitioner or even to commercial veterinary laboratories. CD4 and CD8 ratios do not correlate with clinical stage or help predict the course of the disease. A diagnostic test that predicts the disease course of the cat for clients would be helpful.

The most recent sensitivity/specificity of the FeLV-FIV combination snap test was 98% to 99%. Test reliability in the sick cat population, depending on the prevalence of FIV (between 15% to 30%), is closer to 80% to 95%.

A kitten with a negative FIV test is likely to be uninfected, but the absence of antibody is not always indicative of being infection free. Conversely, the presence of FIV antibodies does not always indicate that that virus is present. Kittens may have detectable maternal antibodies for up to 6 months of age. There is also a slight risk that the untested kitten may transmit FIV to another cat in a household. A positive test result in a sick cat does not necessarily mean that the illness is due to FIV alone.

Although we are not sure how many cats are tested more than once for FIV, based on the numbers of tests sold, we know that less than approximately 16% of cats in the United States have been tested since 1991.

**Confirming FIV Tests**

**Dr. Levy:** I test all cats at the first visit. In my shelter work, all cats have a combo test regardless of their age. The value of testing kittens is that they’re almost always negative. The strength of that negative test is very powerful. I am concerned that delaying testing until 6 months means a lot of cats will never actually be tested.

I’ve seen very few FIV positive kittens, even though I’ve tested more than 800 kittens a year for shelter programs. All of the FIV “positive” kittens that I have seen, which is only a few litters, have seroconverted to negative over a couple of months. But I have taken consult calls from other veterinarians on a handful of kittens that ultimately did prove to be persistently infected. Delaying testing until 6 months would allow these infected kittens to remain in a household, possibly exposing other cats.

I would like to see the American Association of Feline Practitioners and the whole feline health profession move toward more comprehensive testing of all cats.

**Dr. Ford:** We might be missing something by teaching veterinarians not to test cats younger than 6 months for FIV. If there are more cats that sustain their FIV antibodies and are infected, would there not be reason to consider earlier testing? For example, can we see if these kittens have profoundly low CD4s and determine very early on if they are infected or not instead of waiting until 6 months? The longer we wait to test, the less chance we have to actually test a cat.

**Dr. Wolf:** Should we test all kittens, regardless of age, when we first see them, and then retest them after 6 months of age?

**Dr. Richards:** Sure. But I think one of the things that perhaps wasn’t clearly stated in the guidelines is that if we have just one shot at testing a kitten, then do it at 6 months of age. And, if we do test a kitten younger than this, regardless of the result, retest it when it is 6 months old. This is because if we get a positive test result in a kitten younger than that age, we are probably just detecting maternal antibody, so we’re going to have to retest that kitten again anyway once we’re certain that maternal antibody is no longer present. It will be cleared by 6 months of age, so any FIV antibody detected by that age or older would indicate that it’s the result of the kitten’s own infection. A potential advantage in knowing that a kitten less than 6 months is antibody positive is that if it is one of the unlucky few who does get infected from its mother, it will likely be in this sort of case. Obviously the queen must be infected in order to pass on the antibody to the litter, and she might then transmit the infection as well.

On the other hand, if we have an FIV antibody-negative kitten younger than 6 months, it might make us feel a bit more certain that it is going to sustain that negative status. If the kitten doesn’t have any maternally derived FIV antibodies, it’s a possibility that the queen didn’t have any antibodies either, meaning that she probably wasn’t infected. But we’ve had some concern about delayed conversion in cats and recognizing that antibodies may not be detectable for some time in a cat that’s infected at
birth. So a cat that tests negative early on may be infected but hasn’t seroconverted yet. That was another reason why we wanted to test at 6 months of age.

Even without retesting at 6 months of age I’d feel reasonably comfortable assuming that the kitten that tests negative is truly uninfected. But I certainly agree with Julie about not being cavalier about positive-tested kittens. Most of the time the cat will be fine—as in the case of my office cat, which was one of those kittens younger than 6 months of age that tested positive—but the rare one ultimately may be infected.

In general, we’re going to be more comfortable with the negative tests being predictive of the truly uninfected status because most cats aren’t infected. This is always a point of confusion when discussing sensitivity and specificity because those terms apply to the percentage of infected animals that test positive and the percentage of uninfected cats that test negative, respectively. In practice we’re more interested in predictive value; that is, is a cat that tests positive truly infected or is a cat that tests negative truly uninfected?

**Dr. Lappin:** I believe in confirming all positive ELISA, particularly in low-risk groups. If the incidence of FIV in a group is 1% and the false positive test rate is 5%, there will be more false positive results than true positive results.

Other reasons for confirming all positive ELISA test results are that the clinical syndromes associated with FIV are diverse via direct virus effects or opportunistic infections and antibody tests results don’t prove disease. By way of antibody tests we are not assessing predictive value for disease; we are assessing predictive value for infection.

A positive test result in a sick cat doesn’t necessarily mean the cat is sick due to FIV. A good reference is Richard Malik’s article on nasal cryptococcosis in Australia. Of the 29 cats, nine were FIV seropositive, all of which responded well to fluconazole. Thus, it is likely these FIV positive cats were immune competent, emphasizing that antibody tests are not immune function tests.

**Dr. Wolf:** Have we reached a consensus on confirmatory testing? Should all positive FIV ELISA tests be confirmed with another test?

**Dr. Richards:** Yes.

**Dr. Ford:** Yes. Absolutely, yes.

**Dr. Levy:** I guess I’ve been a little negligent in confirming tests that were from classic cases like the outdoor tomcat that comes in with stomatitis. Perhaps I shouldn’t be. I certainly wouldn’t have an argument with saying we should confirm every single test. However, we’re going to end up with the same situation once we confirm that infection: the disease the cat has may or may not be related to the virus. Even in a confirmed case, we still need to treat the disease, not the FIV status.

**Dr. Eigner:** I think we do that in private practice, and we confirm the tests. I definitely recommend confirming the tests. In private practice we try to remember that the cat still may have a problem that is not related to FIV status.

**Dr. Levy:** Although you do that in your practice, which is a high-end cat practice, I know that a lot of practices recommend euthanasia simply because of a positive test, whether or not the
cat’s sick, and that’s the end of the discussion. The clients often don’t even realize they have a choice about that decision or that the cat’s illness could be related to a disease other than FIV.

Dr. Eigner: My only comment is that a lot of times FIV may not be causing the symptoms that the cat has at presentation.

Dr. Lappin: I guess the way I look at it is that the standard of care is not what the client does, it’s what the veterinarian offers the client. So we should be recommending the best. The client may not be able to afford to confirm a positive test, but that shouldn’t change our recommendation. My most recent false positive was FIV seropositive with nosebleeds. We thought it was possibly an FIV coagulopathy. I worked up a coagulopathy part before I confirmed the test, and it turned out the cat was hypertensive and hyperthyroid and not FIV positive, by Western blot confirmation.

Dr. Richards: A completely asymptomatic cat with a positive test result has less of a chance of being truly infected than a cat with a positive test that has multiple abscesses and a fever, yet the possibility is still there. We’re playing the odds. It’s probably more important, odds-wise, to confirm those positive test results on the asymptomatic cats, but it’s important in all cases.

Dr. Wolf: So basically you’re talking about the reliability of the test in an asymptomatic population, where the incidence is 1% or less?

Dr. Richards: Yes.

Dr. Wolf: The reliability of a positive test, using methodology with 98% specificity and sensitivity, is only 33% when you are testing a population that has only a 1% true prevalence of the disease.

Dr. Richards: ...Specifically, the reliability of the positive test results. I’m really comfortable with the reliability—in other words, the predictive value—of the negative test results in that population with such a low prevalence of infection.

Dr. Wolf: And in either case, in either population, it’s going to be close to 98% or 99% reliability for results that are negative. In the sick cat population, depending on what the incidence is, reliability of a positive test will be anywhere between 15% and 30%. Reliability goes up closer to 80% or 95% in those populations of sick cats.

Antigen Testing

Dr. Ford: A lot of practitioners ask why there isn’t an antigen test for FIV. FIV, like HIV, changes so dramatically it’s difficult to develop an antigen-specific test that will be consistent with the variant strains. Are there other reasons?

Dr. Levy: I think maybe the more important reason is that the level of antigens is so extremely low after the acute phase that the virus is undetectable. If the antigen test were sensitive enough, the virus could be detected. Also, a culture can be obtained and FIV-detected very easily with the currently available antigen tests from IDEXX. Because it’s present in very low amounts, the virus must be amplified through a culture system to detect it with the current antigen test.

Supplemental Testing

Dr. Lappin: I think that it would be very nice to have a standardized PCR and/or affordable virus isolation to do follow-ups on the seropositive kitten.

Dr. Levy: We need that for those cats with negative test results that look like they have FIV.

Dr. Lappin: Exactly. One standardized PCR test would be a big help in determining whether treatment is effective. Virus isolation is commercially available but it’s not cheap. I believe standardization is the key.

Testing Recommendations

Dr. Wolf: Dr. Lappin, do you want to toe the mark on testing recommendations?

Dr. Lappin: I would be very interested in changing the recommendation for an initial testing age and test all kittens when first examined. If we go with the philosophy of standard of care—forgetting about having only one choice—the guidelines should state what we should do. Then if the client needs an alternative due to financial constraint, we could say, "Alternatively, test your cat in 6 months." I would rather segregate a colostrum-positive kitten than not detect a kitten that is truly infected. Not detecting the rare case of vertical transmission, which we agreed does occur, is dangerous in a multi-cat household.

Disease Management

The potential benefits of interferon and other antiviral treatments for FIV-positive cats are not known and are limited to the few high-end practices that are not concerned about their client’s price sensitivity. Fortunately, the basic management protocol for the FIV-positive cat is relatively inexpensive and euthanasia is not necessary in...
most instances. Management of the FIV-positive cat should include providing a stress-free environment, educating the client about secondary infections and the role of nutrition in immune system health, keeping the cat indoors, and possibly more regular check ups (e.g., every 6 months).

Dr. Wolf: Let’s say we get a positive test in an asymptomatic animal, and it’s confirmed. How do we manage that animal? What are your recommendations to the client at this point?

Dr. Lappin: Clinicians at CSU have stopped short of recommending antiviral treatment and/or cytokine therapy for the asymptomatic single-cat household. If they are kept indoors, they’ll probably live for a long time.

What to do with a single FIV seropositive cat in the multiple-cat household is more difficult. Ultimately, it’s the client’s decision. I tell the client that most cats that live passively with others will not transmit the virus to others. I explain the facts to them so that they can make the decision on whether to segregate the cats or maintain an integrated household. The majority of my clients in that situation have continued to integrate the cats.

Dr. Wolf: Dr. Eigner, I know that you don’t have a lot of cats with FIV in your practice. What are your recommendations to clients?

Dr. Eigner: We do not counsel them to get rid of the cat if it’s in a multi-cat household, provided all the cats live in a pretty harmonious situation. I strongly recommend annual visits and, as Dr. Lappin said, I recommend that the client keep the cat indoors to help prevent potential exposure to infection, whether it’s parasitic or from fight wounds. We also stress dental care because we feel that periodontal disease is probably the number-one problem of cats as they age.

Something we do that may or may not have scientific support, is that when we do dental work on FIV-positive cats, we administer a prophylactic antibiotic before and after dentistry. We treat them a little differently than we do our regular dental care patients. They also receive only killed-virus vaccines. I vaccinate my FIV-positive patients the same way I vaccinate my regular patient population, performing a risk-assessment each time. We have been following the CD4/CD8 constants of a few of the FIV-positive cats, and I don’t know that it’s made a big difference, but it has confirmed that CD4/CD8 constants are low in patients that have already deteriorated. So we stress really good basic wellness and low stress. We put FIV-positive cats on interferon (30 international units a day).

Dr. Wolf: Dr. Richards, do you make recommendations from the Cornell Feline Health Center?

Dr. Richards: Yes, and the recommendation depends on the situation. In a multi-cat household the likelihood of a cat contracting FIV from an infected housemate is pretty low, but we know it can happen. In a recent study from the UK, a couple of cats in an endemic environment were infected, even though there was no evidence of biting. It makes me wonder if that has something to do with the strain of the virus. In that case it was probably an oral rather than a bite-induced inoculation. Maybe that particular strain of virus had tropism for certain cells, which made it more transmittable across the mucous membrane.

We talk to the client about the potential risks to the other cats, and in most situations they choose to keep the cats together. We certainly recommend that FIV-positive cats stay indoors to avoid some of the things that can endanger their health and to ensure that they don’t endanger the health of neighborhood cats. Because many FIV-positive cats live very long lives and there is a low likelihood of infecting other cats in the household, we don’t recommend making a lot of changes in the environment of the FIV-positive cat.
can be devastating to the health of the cat and to the health of those cats to which it’s exposed.

**Summary**
- Feline immunodeficiency virus is currently underdiagnosed.
- Although studies show that FIV predominantly affects male cats, female cats are not excluded from the risk of infection.
- Vertical transmission of FIV occurs; however, bite wounds between adult cats are considered to be the primary mode of transmission.
- Conditions that seem to be purely attributable to FIV are ocular disease, central nervous system disease, lymphoma, and sometimes wasting syndromes if the cats live 10 years more. However, if random source cats are experimentally infected, other chronic diseases occur, such as stomatitis, respiratory disease, and skin disease, which are probably diseases that require cofactors of the virus to express themselves.
- FIV-associated lymphomas tend to be B-cell lymphomas and occur frequently in extranodal sites such as the eye, the kidney, nasal cavity, and skin.
- If the presence of antibodies is tested periodically, they will disappear at various times during the course of infection, which causes problems in diagnosing FIV.
- The IFA and ELISA are the screening standards for FIV. The Western blot is the gold standard of confirmatory tests.
- The most recent sensitivity/specificity of the FeLV-FIV combination snap test was 98% to 99%. Test reliability in the sick cat population, depending on the incidence of FIV (between 15% to 30%), is closer to 80% to 95%.
- Cats younger than 6 months that are tested for FIV should be tested again at 6 months of age, if possible. All cats should be tested at the first visit to the veterinarian regardless of age.
- There is an antigen test for FIV; however, the virus must usually be amplified through tissue culture because of the low levels of circulating antigen in the cat’s system.
- Keeping an FIV-positive cat indoors helps prevent fight wounds and helps prevent the spread of the disease among other outdoor cats.
- FIV testing is recommended for other cats in a multiple-cat household when the FIV status of one cat has been confirmed.
- Annual FIV testing of at-risk cats throughout their lifetimes has beneficial value in preventing the spread of FIV.
- Veterinarians need to make a strong effort to know the FIV status of all cats, especially sick cats and those at risk for FIV infection.

**Prevention**
Annual FIV testing of indoor-outdoor cats throughout their lifetimes may help prevent the spread of FIV by enabling us to identify infected cats and advocate their confinement to reduce exposure to other cats. Prevention of infection by FIV can only be accomplished by preventing exposure to infected cats.

**Dr. Ford:** I think the term “immune suppression,” as we use it, lacks definition. Cats with FIV and humans with HIV tend to still have a good immune response to vaccination. Current standards state that in HIV-infected humans, with rare exception, vaccination is still indicated. But, for the most part, humans are still vaccinated with modified live virus vaccines, and on a regular schedule.

**Dr. Richards:** There is a danger in practitioners thinking that FIV infection is rare and saying, “Why should I bother testing for it?” I still cling to the belief that we need to know the FIV infection status of every cat. And I think there are lots of reasons for that. Asymptomatic cats, healthy cats, sick cats—I think every cat needs to be tested to clarify its infectious status. And that’s not influenced at all by how uncommon infection appears to be. It

**References**