Feline immunodeficiency virus infection – update on diagnosis and treatment

K. Hartmann
Medizinische Kleintierklinik, LMU Munich, Germany

Introduction

Although feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) are both retroviruses, they differ in their potential to cause disease. FeLV is much more pathogenic to cats than FIV.

FIV can cause an acquired immunodeficiency syndrome in cats with increased risk for opportunistic infections, neurologic diseases, and tumors. However, in most naturally infected cats, FIV does not cause a severe clinical syndrome. With appropriate health care, FIV-infected cats can live many years and will die from causes unrelated to their FIV infection. Therefore, overall survival time is not shorter than that of uninfected cats. Quality of life is usually fairly high over an extended period of time. This is why a decision for treatment or euthanasia should never be based only on the presence or absence of FIV infection.

What clinical signs do FIV-infected cats develop?

FIV is a lentivirus that shares many properties with human immunodeficiency virus (HIV). It can cause an acquired immune deficiency syndrome, which predisposes cats to other infections and diseases, such as stomatitis, neurologic problems, or tumors. Although secondary infections are common in FIV-infected cats, specific opportunistic infections or acquired immunodeficiency virus- (AIDS-) defining infections typically occurring in HIV-infected humans are not commonly reported in FIV-infected cats.

In most naturally infected cats, FIV does not cause a severe clinical syndrome. However, FIV-infected cats are 5 times more likely to develop lymphoma than non-infected cats (compared to an about 60 times higher likelihood of lymphoma in progressively FeLV-infected cats). Most of the aspects of clinical signs in FIV-infected cats are related to pathogenesis of secondary diseases, such as infections and neoplasms to which FIV-infected cats are more susceptible.

With proper health care, FIV-infected cats can live many years and, in fact, die at older age from causes unrelated to their FIV infection. In a follow-up study in naturally FIV-infected cats, the rate of progression was variable, with death occurring within the first 2 years of observation (about 5 years after the estimated time of infection) in 18% of infected cats. An additional 18% developed increasingly severe disease, but more than 50% remained clinically asymptomatic during an observation period of 2 years. FIV infection has little impact on a cat population and does not reduce the number of cats in a household.

What is the best test to diagnose FIV infection?

Diagnosis of FIV infection is most commonly made by detection of FIV-specific antibodies in blood. In addition, PCR is widely used as direct virus detection method.

How good are antibody tests to predict infection?

FIV produces a persistent infection from which cats do not recover, and infected cats usually develop high amounts of FIV-specific antibodies. Therefore, detection of antibodies has historically been synonymous with infection. In veterinary practice, antibodies are usually detected by either ELISA or rapid immunomigration-type assays that are widely available and easy to use. These in-clinic test kits detect antibodies to different viral antigens, such as p24 and gp40. Most cats produce antibodies within 30 days, at the latest 60 days after infection. Currently available in-clinic FIV tests are highly sensitive and specific. Several recent studies documented an excellent performance of in-house FIV/FeLV test kits for the detection of FIV infection. Since the consequences of a positive test are potentially clinically important, confirmatory testing is still recommended, especially in asymptomatic or indoor cats for which the risk of a false positive result is higher. False positive results can still occur, e.g. through technical error. Negative 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 in-house test. Western blot is the gold standard confirmatory test for antibody detection.

Although very convenient and highly reliable in most situations, antibody testing yet has some disadvantages. First, antibody tests have to be interpreted carefully in kitten less than 6 months of age. Kitten up to 6 months can have passively acquired anti-FIV antibodies from infected or vaccinated queens. Under natural circumstances, kitten rarely acquire the infection from their mothers. Therefore, most kitten that test positive initially will eventually turn negative when maternal antibodies wane. Retesting these kitten after the age of 6 months of age is advised. If the second test is negative, the earlier positive result was likely the result of the presence of maternal antibodies. If still positive, the kitten is likely to be infected. If a kitten less than 6 months is antibody-negative, it is likely to be not infected.

Second, cats in an early phase of infection can be antibody-negative. When results of antibody testing are
negative, but recent infection cannot be ruled out, testing should therefore be repeated a minimum of 60 days after the last potential exposure. Although most cats develop a detectable antibody response within 60 days of initial infection, in some cats antibody development has not been observed until 70 days after inoculation, and has even required 6 months or longer in few animals in experimental studies. In very rapidly progressive infections, antibody development might also not occur at all.

Third, throughout the asymptomatic phase of infection, FIV-specific antibodies are readily detected in blood of most cats, but asymptomatic kitten with very low antibody concentrations or no detectable antibodies have been observed after experimental infection. In these kitten, evidence of FIV infection could only by demonstrated by virus culture or PCR. In addition, some cats entering the terminal phase of infection might become negative in antibody tests due to debilitation of their immune system (although this situation is very unlikely in natural infections). For such cats, Western blots can show FIV-specific antibodies not detected by some if the in-house tests.

Fourth, the release of a FIV vaccine in the United States, Australia, and Japan has complicated the ability of veterinarians to diagnose FIV infections based on antibody detection. Vaccinated cats produce antibodies that cannot be distinguished from antibodies induced by natural infection by commercially available antibody test, including Western blots. Antibodies can usually be detected within a few weeks after vaccination, and it has been shown that they persist for more than 3 years in some cats. Antibodies are also passed to kitten that nurse on vaccinated queens. In more than half of those kitten, passively acquired vaccine-associated antibodies persist at least until the age of 8 weeks. It depends, however, on the in-house test used, and some of the in-house tests will turn negative about 6 months after the vaccination.

What is the role of PCR in FIV diagnosis?
With the introduction of the FIV vaccine and the emerging associated problems of interpreting antibody test results in vaccinated animals, other methods of detecting FIV infection are now more frequently used. In order to determine a cat’s true status, detecting infection by direct diagnostic methods, such as PCR, has been suggested. PCR is a very sensitive and specific method when used in experimentally infected cats. If appropriately inactivated, vaccines do not result in provirus production and thus, do not interfere with PCR assays detecting viral DNA. However, PCR requires specialized equipment and is therefore currently only performed in specialized laboratories. The marked variability of the FIV genome has raised concerns about the ability of the PCR to detect all FIV variants. Selection of PCR reagents, including primer and probe sequences, is often based on genetic sequences of a few well-characterized FIV strains and therefore does not detect all isolates. Additionally, some laboratory cats with documented FIV infection have insufficient circulating provirus copies for detection by conventional PCR. Investigation of sensitivity and specificity of the FIV PCR tests offered by some labs has shown widely variable results, including false positive and false negative results. In one study, sensitivities of PCR performed in different laboratories ranged from 41% to 93%, and specificities ranged from 81% to 100%. Failure to identify infected cats can lead to inadvertent exposure and transmission of FIV to uninfected cats.

How should FIV-infected cats be treated?
Treatment of secondary or unrelated diseases is the most important aspect in treatment of FIV-infected cats. In some rare situations, antiviral chemotherapy is indicated.

Which general management is recommended?
FIV-infected cats must be kept strictly indoors. This is the most important life-prolonging advice for FIV-infected cats. This avoids spread of infection to other cats in the neighborhood. Equally important, exposure of the immunosuppressed cat to infectious agents carried by other animals is prevented. In FIV-infected cats, secondary infections can cause clinical signs and can also lead to progression of the FIV infection.

“Routine vaccination” of FIV-infected cats is subject to much discussion. Although there is no scientific proof that retrovirus-infected cats are at increased risk from modified-life virus (MLV) vaccines, inactivated vaccines are recommended out of concern that MLV vaccines given to immunosuppressed animals will regain pathogenicity. FIV-infected cats are susceptible to secondary infection. In an early stage of infection, they are able to mount appropriate levels of protective antibodies after vaccination; therefore, regular vaccination seems indicated. However, cats kept strictly indoors should not be vaccinated, since immunosuppression and immune stimulation can both lead to progression of FIV infection by altering the balance between immune system and virus. Stimulation of FIV-infected lymphocytes is known to promote virus production in vitro. In vivo vaccination of chronically FIV-infected cats with a synthetic peptide was associated with a decrease in the CD4/CD8 ratio. Thus, the potential trade-off to protection from infection with vaccination is progression of FIV infection secondary to increased virus production. If FIV-infected cats are kept strictly indoors, the risk of secondary infections should be lower than the possible adverse effects of vaccination. FIV-infected cats should receive routine health care at least semiannually to promptly detect changes in health status. A complete blood count, biochemistry profile, and urinalysis should be performed at least annually. Intact male and female cats should be neutered to reduce stress associated with estrus and mating behavior and the desire to roam outside the house and interact aggressively. In general, surgery is well tolerated by asymptomatic FIV-infected cats, but perioperative
antibiotic protection is needed for all surgeries and dental procedures. FIV survives for only minutes outside of the host and is susceptible to all disinfectants (including common soap). Hence, simple precautions and routine cleaning procedures prevent transmission in the hospital. FIV-infected cats can be housed in the same ward as other hospitalized patients but in individual cages. They might be immunosuppressed and should be kept away from cats with other infectious diseases. For this reason, they should not be placed in a “contagious disease ward” with cats suffering from infections such as respiratory viruses.

When FIV-infected cats show signs of clinical sickness, prompt and accurate identification of the causative secondary condition is essential. In most cases, clinical signs in FIV-infected cats are not caused by FIV and intensive diagnostic testing for secondary diseases should proceed early in the course of illness to facilitate appropriate therapeutic intervention. Many cats with a FIV infection respond as well uninfected cats to appropriate medications, although a longer or more aggressive course of therapy (e.g., antibiotics) might be needed. Glucocorticoids or other immunosuppressive should be avoided. Griseofulvin has been shown to cause bone marrow suppression in FIV-infected cats and should not be used for this reason.

Which antivirals can be used in FIV-infected cats?

Most antivirals used in cats are licensed for humans and are hence intended specifically for treatment of HIV infection. Some can be used to treat FIV infection because most enzymes of FIV and HIV have similar sensitivities to various inhibitors. All antiviral compounds interfere with one or more steps of the virus replication process. Based upon this, the drugs can be assigned to different drug classes. Potential targets in the retroviral replication process for antiviral drugs include (1) binding of virus to specific cell surface receptors, (2) entry into the cell and uncoating of the virus, (3) reverse transcription of viral genome, (4) integration of proviral DNA into host genome, (5) viral protein processing, (6) virion assembly and maturation, and (7) virion release. Currently, there are 26 compounds that have been formally approved by the Food and Drug Administration (FDA) for treatment of HIV infection and these drugs are generally classified as (1) reverse transcriptase inhibitors (including nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), and nucleotide synthesis inhibitors (NSIs)), (2) protease inhibitors (PIs), (3) entry inhibitors (EIs) (including fusion inhibitors (FIs) and receptor inhibitors (RIs)), and (4) integrase inhibitors (INIs). Interferons also belong to antiviral compounds and interact with several steps in the viral replication cycle. Efficacy against FIV of several compounds from most of these drug classes have been evaluated, at least in vitro.

NRTIs were the first drugs approved for the treatment of HIV. NRTIs are analogues of endogenous 2´-deoxynucleosides. Nucleosides are the building blocks of nucleic acids and composed of a nitrogenous base and a five-carbon sugar (ribose or deoxyribose). Like natural nucleosides, NRTIs require intracellular enzymatic activation through 3 phosphorylation steps to their 5´-triphosphate form (nucleotide). In their active form, they compete with endogenous nucleotides at the catalytic, i.e., substrate-binding site of RT and they are incorporated into the elongating proviral deoxyribonucleic acid (DNA) strand, thus functioning as competitive substrate inhibitors. However, in comparison to the natural nucleotides, NRTIs lack the 3´-hydroxyl group on the deoxyribose moiety and this leads to strand termination as the subsequent nucleotide cannot form the next 5´-3´ phosphodiester bond necessary to extend the DNA strand.

Zidovudin: Zidovudine (3´-azido-3´-deoxythymidine, AZT) is a thymidine analogue. In 1987, it was the first drug approved by the FDA for treatment of HIV infection. Anti-FIV activity of zidovudine has been proven in numerous in vitro studies. Zidovudine also inhibits FIV replication in vivo; it reduces plasma viral load, improves the immunologic and clinical status of FIV-infected cats, increases quality of life, and prolongs life expectancy. In placebo-controlled trials, zidovudine improved stomatitis and increased the CD4/CD8 ratio in naturally FIV-infected cats. Neurologic abnormalities also tend to respond favorably to treatment with zidovudine. In some cats with FIV-associated neurologic signs, a marked improvement occurs within the first days of therapy. As in HIV, evidence exists that FIV can become resistant to nucleoside analogues. Zidovudine-resistant FIV mutants can arise after only 6 months’ use, with a single-point mutation in the FIV gene being responsible for the resistance.

Stavudine: Stavudine (2´,3´- didehydro -2´,3´-dideoxythymidine, d4T) is another drug with efficacy against HIV. Stavudine is active against FIV in vitro. Mutants of FIV which are resistant to stavudine and cross-resistant to several other antivirals, including zidovudine, have also been detected. No in vivo data in FIV-infected cats are published.

Didanosine: Didanosine (2´,3´-dideoxyinosine, ddI) is also used to treat HIV infection in humans. Didanosine is active against FIV in vitro. In one experimental study, FIV replication was significantly suppressed in animals treated with didanosine, but treatment contributed to the development of antiretroviral toxic neuropathy. Lamivudine (2R,cis-4-amino-l-(2-hydroxymethyl-l,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one, 3TC) is also an approved anti-HIV drug. Lamivudine is active against FIV in vitro. Combination of zidovudine and lamivudine had synergistic anti-FIV activities in cell culture. FIV mutants resistant to lamivudine with a point mutation in the RT gene were found in vitro and showed cross-resistance to zidovudine.
resistance to zidovudine. In one in vivo study, experimentally FIV-infected cats were treated with a high-dose of a zidovudine/lamivudine combination. This combination of drugs protected some cats when treatment was started before infection, but zidovudine/lamivudine treatment had no anti-FIV activity in chronically infected cats. Severe side effects, including fever, anorexia, and marked hematologic changes were observed in some of the cats with the described high-dose dual-drug treatment.

NtRTIs also interact with the catalytic site of the RT and are incorporated into the elongating proviral DNA strand, subsequently causing strand termination. They compete with the natural nucleotides and thereby also function as competitive substrate inhibitors. However, in contrast to NRTIs, NtRTIs contain a phosphate group and therefore only 2 intracellular phosphorylation steps are needed to convert them into their active forms. This circumvents the first and often rate-limiting phosphorylation step.

**Adefovir:** Adefovir (2-(6-amino-9H-purin-9-yl)-ethoxy-methyl-phosphonic acid, PMEA) is not licensed as HIV drug, but is currently approved in an orally available formulation (bis-POM PMEA) for treatment of chronic hepatitis B. Adefovir belongs to the acyclic nucleoside phosphonates. This phosphonate bond is non-hydrolyzable which makes it more difficult to cleave off these compounds once they have been incorporated at the 3'-terminal end of the elongating proviral DNA strand. Adefovir inhibits FIV replication in vitro. Several studies have investigated the efficacy of adefovir in either experimentally or naturally FIV-infected cats. Some of these studies showed some efficacy, but severe side effects were also reported, mainly in the form of non-regenerative anemia. In a recent study, adefovir was used in FIV-infected cats in a 6-week placebo-controlled, double-blinded clinical trial; 10 cats received adefovir (10 mg/kg SC twice weekly), another group of 10 cats received placebo. There was no decrease in proviral or viral loads in treated cats and they developed a progressive, life-threatening anemia, which is a common adverse effect of nucleotide analogs.

**Tenofovir:** Tenofovir (2R-1-(6-amino-9H-purin-9-yl)-propan-2-yl-oxy-methyl-phosphonic acid, PMPA) has an antiviral spectrum that is narrower than that of adefovir, with no effect on herpesviruses, but confinement to hepadna- and retroviruses. Tenofovir is licensed for treating HIV infection. It is currently the only approved NtRTI for HIV therapy and marketed as the prodrug tenofovir disoproxil fumarate (TDF). Tenofovir is effective against FIV in vitro, but in vivo studies have not been published so far.

NNRTIs are, with few exceptions, highly specific for HIV. Unlike NRTIs and NtRTIs which bind to the catalytic site of RT, NNRTIs interact with an allosteric site of the enzyme and are not incorporated into the proviral DNA strand. They are classified as non-competitive inhibitors of RT and do not require intracellular activation to inhibit the enzyme. The interaction with the allosteric site, which is located in close proximity to the catalytic site, leads to a number of conformational changes within the RT. Amongst other effects, these changes cause a decrease in the interaction between the DNA primer and the polymerase domain of the enzyme and thereby result in inhibition of virus replication.

**Suramin:** Suramin (1-(3-benzamido-4-ethylbenzamido)-naphthalene4,6,8-trisulfonic acid sym-3'-urea sodium salt) is an old NNRTI that has been used in veterinary medicine. Suramin inhibits RT by interacting with the template-primer binding site of the enzyme. Although not being a nucleoside analogue, it competitively binds to the primer binding site and inhibits the template-primer binding that is necessary for DNA prolongation, and thus, suramin can be classified as NNRTI. Suramin is used as antitrypanosomal agent, and also for treatment of some tumors, such as prostate cancer. It shows an inhibitory effect on the RT activity of retroviruses and has also been used in humans with HIV infection. Suramin is associated with a significant number of severe side effects, such as nausea and anaphylactic shock as immediate reactions during administration in humans. Further, in part protracted side effects are peripheral neuritis leading to palmar-plantar hyperesthesia, photophobia, skin reactions, agranulocytosis, hemolytic anemia, and destruction of the adrenal cortex. The efficacy of suramin against FIV is unknown. Suramin was used in FeLV-infected cats with questionable efficacy.

NSIs interfere with DNA and RNA synthesis, however not by mimicking nucleosides. They usually have a broad spectrum but also exhibit marked toxicity. The 2 NSIs foscarnet and ribavirin have been used in veterinary medicine.

**Foscarnet:** Foscarnet (phosphonoformic acid, PFA) has a wide spectrum against DNA and RNA viruses, including retroviruses. Foscarnet interferes with exchange of pyrophosphate from deoxynucleoside triphosphate during viral replication by binding to a site on RT or DNA polymerase. Foscarnet is only virustatic, and after treatment is discontinued, viral replication is re-activated. Foscarnet is mostly administered IV by continuous infusion because of its short half-life, the same has also been found in cats. Oral application is possible but can cause irritation of mucous membranes and oral bleeding. Foscarnet has many side effects in
both humans and cats, such as nephrotoxicity and myelosuppression. It is also toxic to epithelial cells and mucous membranes, and gastrointestinal side effects and ulcerations of genital epithelium can occur. In addition, it also chelates divalent cations, such as calcium, so that hypocalcemia, hypomagnesemia, and hypokalemia can develop. In vitro, foscarnet was shown to be active against FIV, but foscarnet-resistant FIV strains can develop. No in vivo studies have been published.

**Ribavirin:** Ribavirin (1-β-D-ribofuranosyl-1 H-1,2,4-triazole-3-carboxamide, RTCA) has marked in vitro antiviral activity against a variety of DNA and RNA viruses. Systemic application, however, is limited because of its side effects. Side effects in cats (even using low doses) include hemolysis and toxic effect on bone marrow. An approach to decrease the toxicity of ribavirin by incorporating it into lecithin-containing liposomes and administering it at lower doses was not successful. Ribavirin is active against FIV in vivo. In vivo, therapeutic concentrations are difficult to achieve because of its toxicity. Also, cats are extremely sensitive to side effects.

RIs either bind to the virus or to the cellular receptor, and in effect lead to inhibition of binding of the virus to the cell surface. Most of these receptor antagonists/homologues are highly selective for HIV and are hence not useful for veterinary medicine. One exception that can be used in cats with FIV infection are bicyclams. The reason for this is the similarity between HIV and FIV infection concerning chemokine receptor usage for infection. Chemokine receptors belong to the group of seven transmembrane receptors that replicate in silkworms after in vitro infection. Chemokine receptors that belong to the group of seven transmembrane proteins, in which signal transmission is afforded through rapid influx of calcium into the cell. Chemokine receptors are essential coreceptors for HIV and FIV in the infection of CD4+ lymphocytes. CXCR4 is the major receptor for FIV infection, but other receptors have been shown to mediate viral binding. By binding to CXCR4, bicyclams prevent interaction of CXCR4 with other ligands, thereby inhibiting the entry of HIV or FIV into the cell.

**Plerixafor:** Plerixafor (1,1’-(1,4-phenylenbis(methylene)-bis(1,4,8,11-tetraazacycletetradecane)-octachlo-ride dehydrate, AMD3100) is the prototype compound among the bicyclams. It is not on the market as anti-HIV drug, but is used in humans for stem cell mobilization. Plerixafor is administered to cats in a concentration of 0.5 mg/kg every 12 hours. Magnesium and calcium levels should be monitored regularly during treatment. Plerixafor is active against FIV in vitro. The efficacy of plerixafor against FIV was investigated in naturally FIV-infected cats in a placebo-controlled double-blind clinical trial. Treatment with plerixafor resulted in a significant decrease in provirus load, but also a decrease in serum magnesium levels, which, however, did not result in any clinical consequences. No development of resistance of FIV isolates to plerixafor was found during treatment.

INIs inhibit the enzyme integrase which catalyzes strand transfer (3’-end joining) that inserts both viral DNA ends into a host cell chromosome. The high degree of conservation of integrase active sites across many retroviruses suggests that FIV might be sensitive to integrase inhibitors. The mechanism of their action is inhibition of integration of the proviral DNA produced by reverse transcription of the viral RNA genome.

**Raltegravir:** Raltegravir is used as anti-HIV compound. Efficacy of raltegravir against FIV has not been investigated so far, but raltegravir is effective against FeLV.

**Human interferon-α:** Recombinant human interferon-α (IFN-α) has antiviral and immunomodulatory activity. IFN-α is active against many DNA and RNA viruses. There are two common treatment regimens for use of rHuIFN-α in cats. One is SC injection of high-dose (10^{5}-10^{6} IU/kg q 24 h) IFN-α, the other oral administration of low-dose (1-50 IU/kg every 24 hours) IFN-α. When given parenterally to cats, human IFN-α becomes ineffective after 3 to 7 weeks because of development of neutralizing antibodies that limit its activity. IFN-α can be given orally for a longer period as no antibodies will develop during oral treatment. Given orally, IFN-α is inactivated by gastric acid and destroyed by trypsin and other proteolytic enzymes in the duodenum. Thus, direct antiviral effects are unlikely after oral application. However, oral IFN-α still seems to have immunomodulatory activity. This is due to the fact that after oral application, IFN-α can bind to mucosal receptors in the oral cavity stimulating the local lymphoid tissue leading to cytokine release on lymphatic cells in the oral or pharyngeal area triggering a cascade of immunologic responses that finally act systemically. Human IFN-α is active against FIV in vitro. Although frequently used in the field for treating FIV-infected cats, no controlled studies evaluating the effect of high-dose parenteral human IFN-α in FIV-infected cats have been conducted. Use of low dose oral human IFN-α in sick, naturally FIV-infected cats (50 IU/kg placed on the oral mucosa daily for 7 days on alternating weeks for 6 months, followed by a 2-month break, and then repetition of the 6-month treatment) resulted in improvement of clinical signs in a placebo-controlled double-blind study.

**Feline interferon-ω:** Feline interferon-ω (IFN-ω), the corresponding feline interferon, is licensed for use in veterinary medicine in Japan, Australia, Europe. Feline IFN-ω is a recombinant product which is produced by baculoviruses containing the feline sequence for this IFN that replicate in silkworms after infection. Feline IFN-ω can be used in cats for long periods without antibody...
development. In FIV infection, a treatment protocol of $10^6$ IU/kg SQ q 24 h on 5 consecutive days is recommended. No major severe side effects have been reported in cats. IFN-ω inhibits FIV replication in vitro. One study investigated efficacy of feline IFN-ω against FIV infection in 62 naturally FIV-infected cats treated with high dose IFN-ω at $10^6$ IU/kg SQ q 24 h on 5 consecutive days in a placebo-controlled multi-center trial. This study did not show significant changes in survival rate in treated cats when compared to a placebo group, although some clinical improvement was noted. In another study evaluating naturally FIV-infected cats housed in a shelter, some clinical improvement was seen with treatment of IFN-ω used in the licensed protocol, but in this study, there was no placebo control. Hematologic values remained within reference ranges, and there were no biochemical abnormalities associated with IFN-ω treatment. Another study evaluated the use of oral administration of an intermediate dose of IFN-ω for the treatment of symptomatic, client-owned, naturally FIV-infected cats. The treatment protocol comprised $10^5$ U/cat PO q 24 h for 90 consecutive days, administered by the cats’ owners. A historical group treated SC with the high dose licensed protocol was used as a control for comparison, but no placebo group was included. Treatment resulted in significant improvement of clinical scores between pre- and post-treatment values and there was no significant difference between the SC historical control group and the PO group, suggesting PO administration of low-dose IFN-ω could be used as an alternative to the licensed protocol at significantly reduced costs. In a further study assessing viremia, provirus load, and blood cytokine profile in naturally FIV-infected cats treated either with oral or subcutaneous feline IFN-ω (in the same dosages as described above), but again without placebo control, there was no change in viremia and most of the cytokine levels measured. This questions the efficacy found in previous clinical trials conducted without placebo control. The fact that virus load remained unchanged in the cats, but some clinical improvement could be observed, invites the conclusion, that IFN-ω rather might have an effect on secondary infections than on FIV itself. In summary, there are differences in the outcome of the different studies on feline IFN-ω in FIV-infected cats so far, and definitive conclusions cannot be drawn without the results of additional studies including sufficiently high numbers of naturally infected cats evaluated in randomized, placebo-controlled, and double-blinded studies.

**Suggested Reading References**


Other references can be provided by the author on request.