Feline Immunodeficiency Virus

Current Knowledge and Future Directions

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INTRODUCTION

Overview

Feline immunodeficiency virus (FIV) is a ubiquitous pathogen of domestic cats. Transmission occurs primarily via biting during territorial fights and results in persistent lifelong infection. Although progressive decline of CD4\textsuperscript{+} T cells is a hallmark of FIV infection, clinical manifestations in naturally infected cats are often inapparent. Many infected cats have treatable medical problems that are common in cats irrespective of their retroviral status. In those cats that do develop immunodeficiency-associated diseases, it is often difficult to assign clinical relevance to their FIV status. The initial diagnosis is based on detection of circulating antibodies to the viral capsid protein p24. Although different strains of FIV circulate among wild Felidae and Hyaenidae, the virus presents no known zoonotic risk.

Background

FIV was first isolated from cats in 1986 during the height of the human immunodeficiency virus (HIV)-AIDS pandemic in the Western world, at a time when licensed HIV treatments were not yet available. This historical context provides insight into the intensity of the research effort that has been focused on FIV. FIV causes...
immunodeficiency in infected cats that closely resembles that seen in human HIV infection. Hence experimental infection of cats with FIV was widely adopted as a model to develop an HIV vaccine. This research program provided new tools to investigate the feline immune response, which benefited our understanding greatly. A commercial FIV vaccine became available 2 decades ago, but this vaccine has limited availability and its efficacy in the field is poor.

In the 35 years since the discovery of FIV, it has become apparent that the immunodeficiency that accompanies natural infection is often subclinical, contrasting starkly with the predictable decline to terminal AIDS in untreated HIV-infected patients. Perhaps the area in greatest need of research is the outcomes associated with natural FIV infection. Which cats progress and why? Which features of the infecting virus, the individual cat, or the environment contribute to clinical outcome? Can we predict the outcome in an individual cat? Are we recognizing subtle or unexpected consequences of FIV infection?

THE VIRUS

Discovery and Origins
- FIV was discovered in Petaluma, California, USA in 1986 in group-housed cats displaying signs suggesting an underlying immunodeficiency [1].
- FIV originated among wild felids in Africa between 5 and 2.5 million years ago, disseminated through the Panthera lineage and ancestors of the African lion, then globally among New World cats as species-specific strains [2].
  - FIV-Fca (the FIV strain infecting domestic cats, Felis catus), as inferred by comparative genomic analyses, has a more recent evolutionary origin, having been in coexistence with its host for much shorter period than FIV strains infecting wild cats (eg, FIV-Pca, FIV-Ppa).
- FIV is genetically more closely related to ungulate retroviruses (equine infectious anemia virus, bovine immunodeficiency virus, caprine arthritis and encephalitis virus), but resembles primate lentiviruses in its ability to cause a clinical immunodeficiency [1].

Virion Structure and Genomic Organization
- FIV belongs to the family Retroviridae, subfamily Orthoretrovirinae, genus Lentivirus.
- The FIV virion is an enveloped, spherical particle that contains 2 copies of a positive-stranded RNA within the viral core (Fig. 1).

- The genome contains approximately 9400 nucleotides comprising 3 major genes: gag, pol, and env [3] (Fig. 2).
  - Additional accessory and regulatory genes (vif, orf-A, and rev) have a role in viral replication, trafficking of viral RNA from the nucleus to cytosol, virus release, and defense against host restriction factors.
- The envelope bears heavily glycosylated proteins (Env) that interact with cellular receptor for the virus. Mutations within the env gene facilitate immune evasion [4].

Viral Diversity on the Population Level
- FIV-Fca forms a phylogenetically diverse group of viruses distributed among domestic cats worldwide [2]. Based on sequence diversity of a highly variable V3-V5 region of env, FIV is classified into 5 subtypes (clades), A to E [5]. Diversity can reach 26% between isolates and likely reflects independent viral coevolution in different geographic areas (Fig. 3).
  - Clinical significance of specific subtypes has not been determined in natural infections. There is no convincing evidence that one subtype is more pathogenic than the other.
  - Genetic diversity is generated by point mutations, introduced by an error-prone reverse transcriptase (RT) and recombination between viral variants [6,7].
    - Recombination can occur between viral variants of the same or different subtypes. Recombination is facilitated by the (1) presence of 2 RNA molecules within each virion and (2) the ability of RT to switch between the 2 RNA genomes during provirus formation.
    - Concurrent infection of the host with different strains of the virus may lead to the emergence of novel variants with altered properties such as pathogenicity or infectivity.

Intrahost Viral Diversity and Intrahost Evolution
- FIV exists within the host as closely related variants referred to as viral quasi-species that collectively contribute to the characteristics of the viral population [8].
  - The intrahost diversity and rate of intrahost evolution of FIV env is relatively low when compared with that of HIV [7].
  - When contrasted with pathogenic and rapidly evolving human HIV counterparts, and compared with less pathogenic bovine immunodeficiency virus (BIV), which exhibits little sequence variation [9],
the relative genetic stability of FIV likely reflects a long period of coexistence between the virus and the host; this may contribute to lower pathogenicity and explain why many FIV-infected cats do not progress to the terminal-stage disease [7].

EPIDEMIOLOGY

Prevalence
- FIV is distributed globally with a seroprevalence ranging between less than 2.5 and greater than 14% [10].
- Risk factors for FIV seropositivity are presented in Table 1.
- Average age at the time of diagnosis is 6 years, with male cats being almost 5 times more likely to be seropositive than females [11].

Transmission
- Horizontal transmission via inoculation of virus in saliva or blood during aggressive territorial fights is predominant [12].
- Vertical, perinatal, and postnatal queen to kitten transmission is rarely documented, unless the queen becomes infected during pregnancy [13].
  - Perinatal infection of 1 kitten does not imply infection of the whole litter.
- Virus can be isolated from semen, but natural sexual transmission of FIV has not been documented [14].
- Transmission of FIV among naturally infected cats cohabiting in stable households is infrequent [15].
- Cats used as blood donors must be free from FIV infection because iatrogenic transmission by this route is inevitable [16].

PATHOGENESIS

Cell Tropism
- Infection commences with binding of the viral Env to the viral receptor on susceptible cells.
  - FIV preferentially targets CD4+ T cells, CD4+CD25 regulatory T cells, macrophages, monocytes, neuroglia, CD8+ T cells, and B cells.
  - The virus uses feline CD134 as its primary receptor [17] and CXCR4 as a coreceptor [18].
  - CD134 is expressed on feline CD4+ T lymphocytes consistent with progressive depletion of CD4+ lymphocytes during disease progression [17].
  - Structurally, the extracellular domain of CD134 is composed of 3 cysteine-rich domains (CRD-1, CRD-2, and CRD-3) (Fig. 4).
  - Understanding the structure of CD134 is important in deciphering the nature of virus-host interaction, because different strains of FIV have

FIG. 1 Schematic representation of FIV virion. The virion is a spherical particle of approximately 120 nm in diameter. The virion contains 2 copies of single-stranded, positive-sense viral RNA (vRNA) surrounded by the nucleocapsid (NC), p24 capsid (CA), matrix (MA), and heavily glycosylated envelope glycoprotein (Env). Reverse transcriptase (RT), integrase (IN), and protease (PR) enzymes are responsible for DNA synthesis from viral RNA, integration of proviral DNA into the DNA of the host cell, and cleavage of precursor protein products, respectively.

FIG. 2 Genomic organization of FIV (simplified). The genome consists of 3 major genes: (1) gag, which encodes core proteins: matrix (MA), capsid (CA, p24), and nucleocapsid (NC); (2) pol, which encodes key enzymes: integrase (IN), protease (PR), and reverse transcriptase (RT); and (3) env, which encodes envelope glycoprotein (Env), one regulatory (rev), and 2 accessory genes (vif, orf-a). The genes are bordered by long terminal repeats (LTRs) within the provirus.
different affinity for the primary entry receptor [19] (see Fig. 4).

- Some strains of the virus (often referred as “early” variants), require stringent interaction with determinants on both cysteine-rich domains (CRD-1 and CRD-2) of CD134 to achieve productive infection [20]. In contrast, “late” variants can infect susceptible cells via interaction with a first cysteine-rich domain (CRD-1) alone [20].

- Data from experimental [20] and natural infections [21] reveal that the virus changes the way it interacts with its primary receptor during the course of disease, similar to the receptor switch observed during progression of HIV infection [22].

- In naturally infected cats, CRD-2-dependent viral variants dominate in early infection, and evolve toward CRD-2 independence during disease progression (late infection) [21].

- Emergence of “late,” CRD-2 independent viral variants segregates with declining clinical status and onset of immunodeficiency [21,23].

**Correlates of Immune Protection**

FIV infection elicits a robust innate immune response, followed by cell-mediated and humoral adaptive responses. However, sterilizing immunity is not achieved and persistent infection is established. Subsequent progressive depletion of CD4+ lymphocytes and paradoxic global immune activation and immune suppression leads to immune dysfunction [24].

- Cell-mediated immunity is governed by cytotoxic CD8+ T lymphocytes (CTLs). This immunity develops within weeks postexposure and is responsible for the subsequent decline in plasma viral load seen during the “asymptomatic” stage of infection [25,26].

- The antiviral activity of CD8+ T cells is mediated through (a) noncytotoxic, non-antigen-specific CD8+ T cells [26] and (b) major histocompatibility complex (MHC) class I-restricted CTLs [27].

- Nonspecific CD8+ T cells appear approximately 1 week postexposure and target the virus via contact-dependent or contact-independent noncytotoxic mechanisms.
Typical MHC class I-restricted CD8+ T cells are primed against specific viral proteins (Gag, Pol, and Env) and are detectable as early as 2 weeks postexposure.

- CD8+ T-cell numbers increase throughout infection and decline only at the terminal stage [24].

- Humoral, B-cell-mediated immunity elicited against Gag and Env viral proteins, and manifested by increased IgG immunoglobulin plasma levels, is detectable within 2 to 4 weeks postinfection [28,29].

- Additional immunity is provided by virus-neutralizing antibodies (VNABs), which, although detectable within 30 days postinfection, take several months to fully develop [30].

- VNABs’ interaction with epitopes on the Env interferes with, or blocks, cellular entry of the virus, thus preventing the infection (antibody-mediated viral neutralization).

- Autoantibodies against the primary receptor for FIV, CD134, provide additional protection against the virus in some infected cats [31].

- Although presence of VNABs can be beneficial, or at least neutral, antibody-dependent enhancement has also been documented [32].

- Intrinsic immunity represented by cellular-based antiviral restriction factors provides additional protection that controls almost every stage of retroviral life cycle. Intrinsic retroviral restriction factors encoded by the feline genome include APOBEC3G [33] and Tetherin/BST-2 proteins [34].

  - APOBEC3G (apolipoprotein B messenger RNA [mRNA]-editing enzyme catalytic polypeptide-like 3 G) operates during reverse transcription causing accumulation of guanosine to adenosine substitutions in a positive-strand viral DNA, subsequent accumulation of premature stop codons and inhibition of viral replication by hypermutation, and degradation of viral genomic material.

  - Feline Tetherin/BST-2 retains the FIV virion on the cell surface preventing its release, but not the cell-to-cell spread of the virus.

Despite vigorous responses, innate, intrinsic, and adaptive immunity fail to clear the virus, and FIV infection eventually leads to variable degrees of immune dysfunction. Although depletion of CD4+ T cells plays an important role, long-standing immune activation and impaired regenerative capacity of the bone marrow progenitor cells seems to be equally important in development of immunodeficiency.

The Course of Feline Immunodeficiency Virus Infection and Clinical Signs

Infected cats are often normal on clinical examination, and it can be difficult to assign the significance of retroviral status to presenting clinical signs. Nevertheless, it is plausible to attribute FIV’s role in cases with refractory infections, which fail to respond to standard and prolonged therapies. The disease course is characterized by 3 distinct stages [35] (Fig. 5):

- Acute, primary stage, which is defined by a rapid viral replication and subsequent viremia. The virus replicates in CD4+ T cells, macrophages, and dendritic cells. Plasma viral load peaks at 8 to 12 weeks postinfection.

  - Transient nonspecific clinical signs such as lethargy, inappetence, and pyrexia may be detected. Generalized lymphadenopathy and
neutropenia may occur and persist for several months [12].

- Rapid depletion of CD4+ T cells and subsequent excessive production of CD8+ T cells results in an inversion of the CD4:CD8 ratio, which is often lifelong.
- The immune response curtails viral replication but fails to clear virus.

- Silent, subclinical stage with mild or inapparent clinical signs.
  - Plasma viral loads are suppressed.
  - CD4+ T lymphocyte numbers, after an initial rebound, continue to decline progressively.
  - Combination of immunosuppression and immune hyperactivation contributes to FIV-induced immune dysregulation, which variably affects individual cats. Transient nonspecific clinical signs include hyporexia, lethargy, intermittent pyrexia, and lymphadenopathy.
  - Feline chronic gingivostomatitis, which has a complex and multifactorial cause, is frequently seen in infected cats [36,37] (Fig. 6).
  - Declining numbers of CD4+ T cells, and subsequent decreased production of cytokines such as interferon (IFN)-γ, interleukin (IL)-2, IL-10, and IL-12 contribute to impaired immunity and opportunistic infections [38]; more pronounced clinical signs associated with pathogens as documented for Toxoplasma gondii [39], and Listeria monocytogenes [40]; and indirect predisposition for neoplasia [41].
- Owing to incompletely understood reasons, some infected cats remain in this phase for life, whereas others progress to the terminal stage of disease [38].

- Terminal stage is characterized by progressive immune depletion, subsequent escape of the virus from the immune surveillance, and onset of clinical signs compatible with a profound}

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**FIG. 5** Clinical course of FIV infection. Following infection, there is an acute stage, which is characterized by peak viral replication. Pyrexia, lymphadenopathy, and other nonspecific clinical signs may coincide. The subsequent robust immune response suppresses viral replication, and infected cats enter the chronic stage of infection. Sometimes referred as “asymptomatic” this stage is accompanied by a sustained cytotoxic T lymphocyte response (CTL), emergence of neutralizing antibodies, suppressed plasma viral load (PVL), and a progressive depletion of CD4+ T cells. It is unknown why some cats remain well in this stage of infection, whereas others progress to profound immunodeficiency and eventually succumb. Env, envelope glycoprotein; p24, viral capsid protein.

**FIG. 6** Feline chronic gingivostomatitis (FCGS). Although not causal, FIV may contribute to the severity of FCGS with infected cats having significant differences in their oral microbiota when compared with uninfected ones [37]. (Courtesy of Matthew Oxford, BVM&S GPCert (SAS) MRCVS, Winchester, Hampshire, UK.)
immunodeficiency. Persistent neutropenia is frequently documented [42,43], and increases the risk of atypical and refractory bacterial, viral, fungal, and parasitic infections. Some cats develop neoplasia and neurologic disease.

- Weight loss, resembling HIV-associated “wasting syndrome,” is frequently observed [44]. The underlying cause is multifactorial with altered hypermetabolism, cytokine effects, and hyporexia being quoted as the main contributors.
- Concurrent infections include bacterial pyoderma, demodicosis, disseminated cowpox, cryptococcosis, mycobacteriosis, and lungworm [28,45–47]. These infections tend to be more severe and more difficult to treat than in immunocompetent cats.
- Neuropathogenesis is attributed to actions of monocytes and macrophages, which carry the virus across the blood-brain barrier resulting in progressive encephalitis. Stereotypic behavioral and circadian rhythm changes, aggression, tremors, and delayed pupillary light reflexes have all been attributed to FIV-induced neuropathogenesis [48].
- Nephropathy and presence of proteinuria, but not renal azotemia, have been reported [49]. Potential underlying mechanisms include glomerular deposition of viral-antibody immune complexes, direct viral infection of renal epithelial cells, and thrombotic microangiopathy.
- FIV-associated impairment of the antineoplastic immune control capacity and its consequences are the most likely reason why infected cats are 5 to 6 times more likely to develop lymphoma when compared with their FIV-negative counterparts [41].
  - Chronic hyperstimulation of the B-cell compartment is another mechanism rendering cells more prone to neoplastic transformation [50].
  - Furthermore, FIV-induced immune dysregulation may reveal oncogenic potential of other viruses. Any role for recently discovered Felis catus gammaherpesvirus 1 in lymphomagenesis in FIV-infected cats remains to be established [51–53].

**PROGNOSIS**

In contrast to HIV infection, surrogate markers to monitor disease progression or response to treatment are not well established for FIV infection. Although many infected cats achieve similar life spans to their uninfected counterparts [42,43,54], it remains unknown why some cats progress to the terminal-stage disease, whereas others remain asymptomatic.

- In a study examining the long-term outcome of natural retroviral infections, the survival rate for FIV-infected cats at 6 years postdiagnosis was 65%, compared with 90% for uninfected control cats [54]. The decision on euthanasia around the time of diagnosis of FIV infection is one of the main reasons for reported decreased survival of infected cats. In the same study, after exclusions of cats that were euthanized or died within 100 days postdiagnosis, the survival rate for FIV-infected cats at 3 and 6 years was 94% and 80%, respectively, when compared with controls [54].
- There is no justification for euthanasia of healthy cats based on their FIV status.
- CD4:CD8 ratio, a well-established surrogate marker to monitor progression of HIV infection, is not of diagnostic value because no correlation between inversion of CD4:CD8 and disease progression in FIV-infected cats has been found [55,56].
- The plasma viral load is suggested to be a promising prognostic marker [57], but its potential clinical utility remains to be established.

**DETECTION AND DIAGNOSIS**

The retroviral status of every feline patient should, ideally, be known to improve their individual health care and to prevent spread of the virus to other cats [58]. FIV infection can be diagnosed by (1) serology, followed by (2) polymerase chain reaction (PCR).

- Serologic, point-of-care (POC) screening tests using lateral flow immunochromatography or bidirectional-flow enzyme-linked immunosorbent assay (ELISA) technologies, and laboratory-based ELISA assays that detect antibodies against nucleocapsid, p24 capsid, or Env viral proteins can be reliably used for diagnosis in most cases and are the diagnostic tests of choice [58].
- Although antibodies to the virus can be detected approximately 2 to 4 weeks postexperimental infection [28], in most cases seroconversion occurs within 60 days postexposure [59].
- Maternal-derived antibodies (MDAs) from FIV-infected or vaccinated queens can persist for up to 5 months and could be responsible for false-positive serology results in young kittens [60].
In such cases, cats should be retested after 6 months of age.  
- Fel-O-Vax FIV (Boehringer Ingelheim Pty Limited, NSW, Australia) vaccine-induced antibodies can confound the serologic diagnosis and differentiation between infected, vaccinated, and vaccinated and infected cats [61].
  - In cats with prior FIV vaccination history, it is important to select the serologic test that can distinguish between natural infection and vaccine-induced antibodies.
  - The SNAP Combo FeLV Ag/FIV Ab Test (IDEXX Laboratories, Inc, Westbrook, ME, USA) is highly sensitive and specific but does not differentiate between the antibodies induced by natural infection and those induced by the vaccination.
  - Anigen Rapid FIV Ab/FeLV Ag Test Kit (Bionote, Inc, Hwaseong-si, South Korea) and WITNESS FeLV-FIV Test Kit (Zoetis, Inc, Florham Park, NJ, USA) seem to differentiate FIV-infected cats from annually vaccinated cats with 100% specificity [62]. However, caution is still needed in interpretation of those 2 POC test results in cats with a recent history of primary vaccination (3 doses, 2–4 weeks apart). Some immunized cats can potentially return false-positive results up to 22 weeks after receiving the final dose of primary vaccination [62].

- Additional serologic assays include Western blot and immunofluorescent antibody assay. These assays are technically demanding, potentially less sensitive, and more challenging to interpret than ELISA assays [63].
- Molecular PCR tests detect integrated DNA provirus or plasma viral RNA.
  - PCR is not recommended as a screening test, but as an adjunct to serology in doubtful situations. PCR can be useful in determination of true FIV status in
    - seropositive cats that have been vaccinated against FIV,
    - seropositive kittens, where presence of anti-FIV MDAs is suspected, and
    - seronegative cats that may have been recently infected but where not enough time has lapsed for seroconversion to occur.
  - Variable performance of FIV PCR tests has been reported [64]. The overall sensitivity has been estimated 5% to 15% lower than that of serologic assays [65].
- Lower sensitivity can be attributed to inability of the primers to detect all field isolates, poor sample quality, and low viral and provirus load [66].

**MANAGEMENT OF INFECTED CATS**

**Environment and Housing Conditions**

Predicting the outcome for individual FIV-infected cats is challenging because the relationship between FIV infection and various clinical presentations is unclear.
- There are several studies that demonstrated that FIV infection does not adversely affect the longevity of infected cats [42,43,67].
- Housing conditions, appropriate nutrition, and husbandry are crucial to maintain FIV-infected cats in good health [44].
  - Stable, indoor households, are most suitable. Low-density housing not only seems to reduce the risk of disease progression but also lowers the risk of transmission to other cats.
  - Overcrowded shelter conditions, environmental stress, and exposure to infectious agents can have a significant negative impact on FIV-infected cats leading to onset of the terminal-stage disease.
  - Cats should be fed complete, balanced diets matched for the age and nutritional needs imposed by concurrent medical conditions. Raw diets are discouraged to avoid exposure to foodborne infectious diseases.
  - Neutering is crucial in reducing roaming and aggressive behaviors.

**HEALTH CARE**

**Preventive Health Care**

FIV-infected cats should ideally undergo a thorough routine clinical examination every 6 to 12 months.
- Hematology, biochemistry, and full urine analysis should be performed annually [58] and any problems investigated.
- Routine, ectoparasite and endoparasite prophylaxis, including heartworm control, is crucial.
- Recommendation for vaccination of immunocompromised cats has been clarified by the most recent ABCD guidelines [68].
  - Booster vaccinations for previously vaccinated FIV-infected cats that live indoors are not recommended.
Outdoor cats that are at risk of exposure to infectious diseases should be considered for vaccination, ideally with inactivated formulations classified as “core” vaccines.

- Where surgery is indicated in FIV-infected cats, perioperative antibiotics should be reserved for cats with persistent neutropenia, or those at moderate to high risk of bacterial contamination of the surgical site.[69]
- Infected cats should not be hospitalized in isolation wards to minimize their risk of exposure to communicable infectious diseases.
- Given very low environmental persistence, there is a minimal risk of hospital-acquired virus transmission as long as standard biosecurity protocols are followed.

**Supportive Treatment**

FIV-infected cats often have treatable diseases. As such, their medical problems need to be approached and investigated with this mindset, but a higher consideration is given for differentials concerning ectoparasites and endoparasites, unusual opportunistic infections, and neoplasia.

- The response of FIV-infected cats to medical therapy is often similar to that of negative cats, but more aggressive or a longer course of treatment is sometimes needed. Antibiotic choice, when indicated, needs to be guided by culture and susceptibility results[69].
- Treatment with griseofulvin has been associated with myelosuppression and severe neutropenia[70] in FIV-infected cats.
- Use of glucocorticoids seems counterintuitive, because they have the potential to exacerbate the lentiviral infection. However, their judicious use in some circumstances for treatment of immunemediated conditions can be beneficial[71].
- Cats diagnosed with lymphoma seem to respond to multigene chemotherapy in a similar way as retrovirus-negative cats[72]. Cytotoxic treatments should therefore not be discouraged, but patients need to be more closely monitored for chemotherapy-induced myelosuppression.
- Treatment of FIV-associated neutropenia has been attempted with a recombinant human G-CSF (granulocyte colony-stimulation factor)[73]. Although associated with a short-term positive response, G-CSF tends to promote viral replication and enhancement of infection[74]. The safe use of G-CSF is further impeded by development of antibodies to human G-CSF, which could cross-react with endogenous feline G-CSF to cause refractory agranulocytosis[73].
- Although studies in FIV-infected cats are lacking, anemia can be treated with darbepoetin[75], which is less antigenic than previously recommended erythropoietin[74].
- Insulinlike growth factor 1 (rHuLGF-1) has been shown to stimulate thymic function, and increase the number of circulating T lymphocytes in juvenile experimentally infected cats[76], but there are no studies assessing its efficacy in naturally acquired infections.

**Immunomodulatory and Specific Antiviral Therapies**

Clear clinical guidelines as when to start immunomodulatory and specific antiretroviral treatments are not available for cats. However, in patients whose health status is clearly adversely affected by FIV infection, and where recurrent infections are persistent despite aggressive conventional therapies, it is reasonable to consider these treatment options. The expectations and potential benefits of antiviral therapies need to be carefully balanced against the risk as well as monetary considerations.

- Interferon therapy has both immunomodulatory and antiviral effects[77–79]. Although in vivo data documenting treatment benefit are limited, IFNs can be considered for some infected cats.
  - Recombinant human interferon-α (rHuIFN-α) has been shown to have antiviral activity against FIV in vitro.[80] rHuIFN-α can be administered as subcutaneous (SC) injection at 10^4 to 10^6 U/kg every 24 hours. However, within 3 to 7 weeks, treated cats develop anti-human IFN antibodies, rendering rHuIFN-α ineffective[81].
  - Recombinant feline interferon-ω (rFeIFN-ω, Virbagen Omega, Virbac) is not antigenic, and prolonged therapy is not associated with any major side effects[82]. rFeIFN-ω can be given at 10^6 U/kg SC every 24 hours on 5 consecutive days for 3 series starting on days 0, 14, and 60. An alternative protocol also exists where rFeIFN-ω is administered orally at 10^6 U/cat SC every 24 hours for 90 consecutive days[83]. Although IFN-ω suppresses FIV replication in vitro,[80] its efficacy in vivo is much more variable; some studies reported an improvement of clinical scores and laboratory parameters, whereas others failed to demonstrate a clear benefit[80,83,84].
Antiviral therapies consist of an impressive arsenal of drugs specifically designed for treatment of HIV infection. Although most are either noneffective or toxic for cats, 2 groups: 1) nucleoside analogue reverse transcriptase inhibitors (NARTIs) and 2) receptor antagonists, can be considered for off-license treatment of some infected cats.

- Zidovudine (3'-azido-2',3'-dideoxythymidine, AZT) has been studied as a potential therapeutic for FIV infection [85–87].
  - Zidovudine, a NARTI, inhibits viral replication in vitro and in vivo, with resultant decrease in plasma viral load and improvement of clinical status. The recommended dosage is at 5 to 10 mg/kg every 12 hours orally or SC.
  - Zidovudine can lead to myelosuppression. Nonregenerative anemia is one of the most common side effects. Complete blood cell count should be therefore monitored initially every week, and if no concerns are identified during the first month of treatment, once monthly thereafter. In cats that have developed drug-induced anemia, discontinuation of treatment results in a prompt improvement of hematocrit values.
  - Other limiting side effects include gastrointestinal disturbances and anorexia.
  - Although some cats can tolerate treatment beyond 2 years, resistance to zidovudine can develop as early as 6 months after initiation of treatment [88].
- Receptor antagonists bind to either the cell surface receptor or the virus itself, thus inhibiting the virus receptor interaction and virus entry. Of receptor antagonists identified for HIV, only bicyclams have been investigated as a potential treatment of cats.
  - Plerixafor (1,1(1,4-phenylenbisphenylene)-bis(1,4,8,11-tetraazacyclotetradecane)-octachloride dehydrate, AMD3100) is a selective CXCR4 antagonist, which is licensed as a stem cell activator for human patients undergoing bone marrow transplant. Plerixafor has been studied in vitro and in vivo in FIV-infected cats. Based on a study of 40 cats, treatment at 0.5 mg/kg every 12 hours SC for 6 weeks was associated with decreased viral loads and improvement in clinical parameters with no apparent side effects [89].

VACCINATION

Since its discovery FIV served as a valuable animal model in pursuit of a safe and efficacious lentiviral vaccine. This global research effort culminated in the release of the first commercial FIV vaccine in 2002. The vaccine was licensed in the United States based on 80% efficacy against homologous and heterologous challenge [92]. Twenty years later, multiple studies that examined its efficacy under experimental and field conditions suggest that full protection remains elusive.

Although not what we have hoped for, lessons learned along the way, briefly reviewed in the following points, will inform development of a new generation of vaccines.

- Development of lentiviral vaccine is associated with several major obstacles:
  - Remarkable genetic diversity of the viral env gives virus a tremendous populational antigenic plasticity, making it difficult to design one vaccine that would protect against all strains worldwide.
  - Potential superinfection events, error-prone nature of RT, and its propensity for recombination are additional mechanisms indirectly responsible for the enormous plasticity of the virus and resultant immune evasion.
  - The ability of lentiviruses to establish latent infection in nondividing cells, where integrated provirus is inaccessible to the immune system until the cell becomes activated, provides an additional escape mechanism.
○ Vaccine-induced enhancement of infection has been described in multiple studies where prototypic vaccines instead of protecting, render immunized subjects more susceptible to infection [93].

- Multiple studies informed development of a commercial dual subtype inactivated vaccine (Fel-O-Vax FIV).
  ○ The vaccine consists of inactivated FIV Petaluma (clade A) and FIV Shizuoka (clade D)-infected whole cells [92].
  ○ Fel-O-Vax FIV was licensed based on encouraging efficacy data. However, it has been shown that the protection achieved in initial reported studies [94–96] did not extend to experimental challenge with a primary, virulent UK strain of the virus [97]. The vaccine was never licensed in Europe.
  ○ Cats vaccinated against FIV and subsequently diagnosed with infection are reported [98–100]. The efficacy of the vaccine in Australia is estimated at 56% [99].
  ○ The FIV vaccine, which is regarded as “noncore” by the WSAVA, is still available in Australia, New Zealand, and Japan but has been discontinued in North America since 2015.

### SUMMARY

Over the last 20 years it has become increasingly evident that the FIV vaccine, which stood behind this unprecedented research effort, is far from being fully efficacious. Lessons learned from the cat helped us to better understand its immune system and the immunodeficiency virus at a level not available for any other feline pathogen. Data gained along the way has influenced our current clinical decision making when approaching FIV-infected patients in a hospital setting. Knowledge of the viral and host factors helps to better understand and substantiate clinical observation that many naturally FIV-infected cats remain healthy and do not progress to terminal disease during their often-normal life spans. Although a safe and fully efficacious lentiviral vaccine is not within our reach yet, the vast knowledge about viral immunology learned from the feline model will inform efforts in the development of next-generation lentiviral vaccines. In the next 20 years, an improved understanding of outcomes in naturally infected cats will assist in designing evidence-based interventions to improve the quality of life of millions of FIV-infected cats worldwide.

### REFERENCES


