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Feline Immunodeficiency Virus Infection

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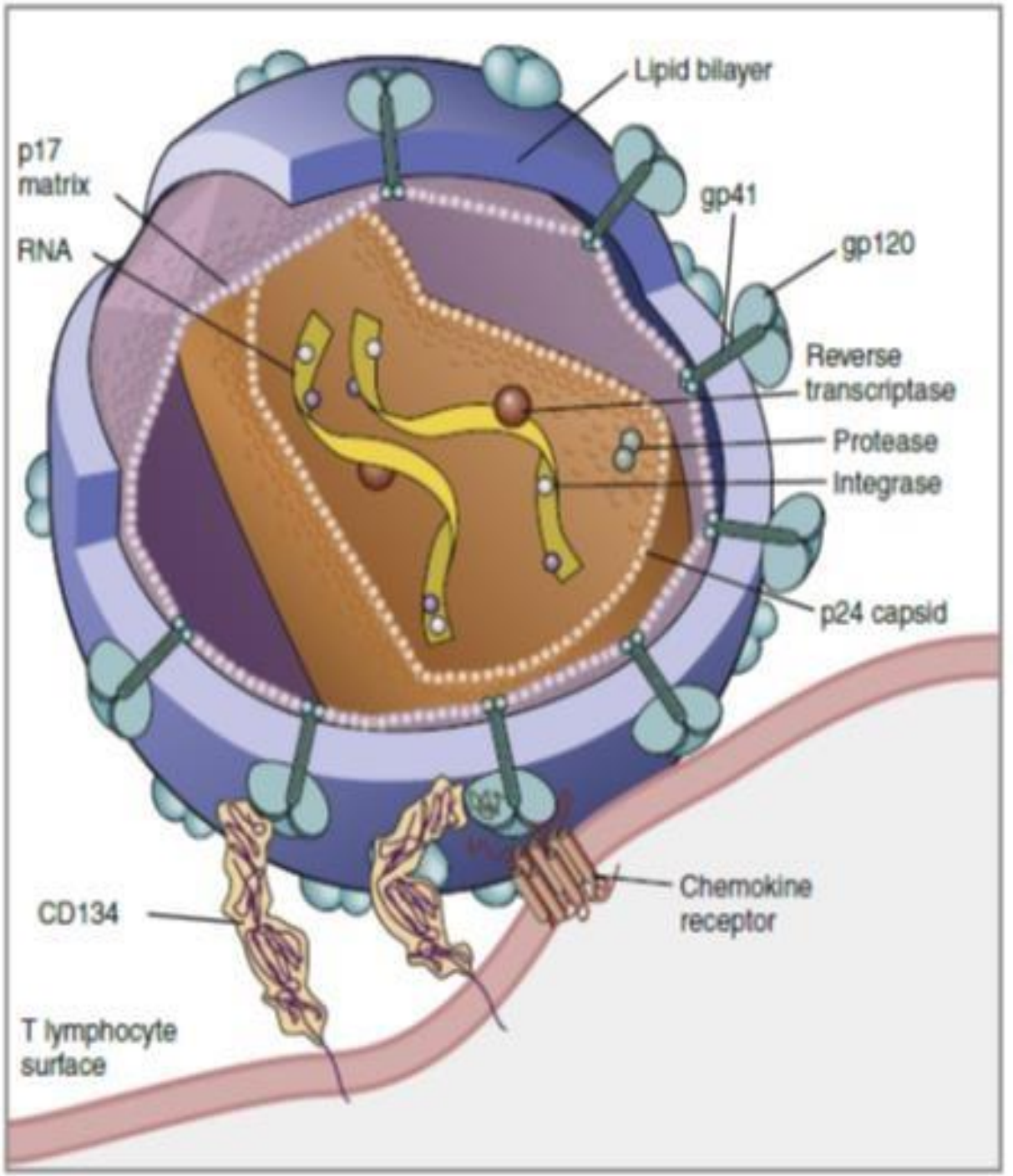
- Feline immunodeficiency virus (FIV: Feline immunodeficiency virus) is a contagious retrovirus = Chronic and persistent infection that can lead to immunodeficiency.
- Subclinical, systemic, neoplastic, neurological, and opportunistic infections due to immunosuppression are all recognized presentations of the disease.
- Although often compared to infection with the human immunodeficiency virus (HIV), the degree of immunosuppression in infected cats is generally much lower.

Etiology

- FIV is an enveloped RNA virus belonging to the Retroviridae family, subfamily Orthoretrovirinae, genus Lentivirus, sharing many properties with other retroviruses such as HIV.
- Based on the sequence diversity of the env gene, there are 6 different subtypes of FIV, A to F.
- Subtypes A and B are the most widely distributed, followed by subtype C.

- Other recombinant subtypes have been recognized = A/B, A/C, B/D, B/E and A/B/C as well as other subtypes.
- The heterogeneity of the virus complicates the design of molecular diagnostic tests and vaccines against HIV.
- The question of whether differences in the clinical manifestations of the disease are linked to infection by different subtypes requires further study.

- HIV virion is shown adjacent to the surface of a CD4+ T cell.
- Lentiviruses contain 2 identical strands of RNA (the viral genome) + associated enzymes, which include reverse transcriptase, integrase, and protease, surrounded by a capsid (p24 protein) and a matrix (p17 protein), all surrounded by a phospholipid membrane envelope derived from the host cell.
- Viral membrane proteins (gp41 and gp120) are embedded in the envelope.
- CD134 and CXCR4 (chemokines) receptors = receptors for HIV.



- The virus is very labile in the environment, surviving only a few minutes, and is sensitive to any type of disinfectant.
- The virus invades the cells and integrates into the host's genome.
- The transcription of DNA leads to the synthesis of new viral components, and the assembly and budding of the virus occur at the cellular surface.

Epidemiology

- FIV has a worldwide distribution in domestic cats.
- Domestic and wild cats; hyenas
- The prevalence of serologically positive animals varies from 1% to 14% in cats without clinical signs and exceeds 44% in sick cats.
- Although cats of any age or sex can be infected, the majority of cats (80–90%) are 2 years or older (adult age) at the time of diagnosis of the disease (averaging 5 to 10 years for other authors 6-8 years).

- Living outdoors and intact male sex increase the risk of infection = More common in unneutered adult male cats.
- FIV is associated with a higher risk of FeLV, and vice versa.
- Bites are the main mode of transmission, due to the high viral concentration in saliva (virus or infected cells).
- Transmission can also occur through blood donation (transfusion).

- Vertical transmission (via the placenta), during parturition and via lactation is possible:
  - A low percentage of kittens remain infected.
  - This percentage depends on the viral load of the mother during gestation or at birth.
  - If the mother has active immunodeficiency, more than 70% of the kittens will be persistent carriers of the virus, whereas if the mother is asymptomatic, almost no kitten will be infected.
- Viral presence in semen has been experimentally documented, but this has not been confirmed in naturally infected cats.
- Unlike HIV, sexual transmission is rare.

Pathogenesis

- The main cellular target of FIV = CD4+ T lymphocytes = play an important role in the development of cellular and humoral immunity, leading to the destruction and reduction of the production of these cells and, consequently, immunodeficiency.
- However, FIV also infects CD8+ T lymphocytes, B lymphocytes, macrophages, dendritic cells, microglia, and astrocytes.
- The subsequent effects of the virus on the immune system are complex, incompletely understood, and seem to lead to both immune suppression and activation.
- Cats remain infected for life due to the integration of FIV into the host cell genome = FIV-infected cats are persistently infected, despite all the animal's immunological mechanisms to fight the infection.

❑ Phase 1 = Acute viremia phase

- ✓After inoculation with FIV, the virus replicates in T and B lymphocytes and macrophages of the lymph nodes, and in the lymphoid tissues of other organs such as the spleen and thymus, leading to an acute viremia phase that can last from 6 to 10 weeks post-infection.
- ✓The clinical signs are non-specific: Anorexia, Lethargy, lymphadenopathy, leukopenia.

- ✓This initial viremia causes the spread of the virus in the bone marrow, and in other lymphoid tissues: of the intestine, lungs, kidneys, and nervous system.
- ✓After dissemination of the virus, the viremia decreases due to the development of cellular and humoral immunity, although this response is insufficient to inactivate the virus.

❑ Phase 2 = Subclinical Phase

- ✓Asymptomatic phase that can last from several months to the entire life of the animal.
- ✓The production of the virus continues at low levels; a slow and progressive decline in the number of CD4+ T lymphocytes.
- ✓Despite the absence of clinical signs, the immune system gradually weakens, with decreases in the population of CD4+ T lymphocytes and the CD4+/CD8+ ratio.

❑ Phase 3 = Immunodeficiency Phase = terminal phase

- ✓When the CD4+/CD8+ ratio is so low that it indicates the death of CD4+ lymphocytes, the immunodeficiency phase begins =
- ✓This is the period during which opportunistic infections develop.
- ✓The immune system is unable to mount an effective response.

Cat infected with FIV in the immunodeficiency phase with severe myiasis (larval parasitism).

- In FIV, the role of passive immunity, by which an animal acquires antibodies (Ab) through the colostrum of vaccinated or FIV-infected mothers, remains uncertain.
- It has been suggested that passive immunity may provide protection against FIV.

Clinical study

- Many cats infected with FIV show no clinical signs for weeks or years post-infection and may eventually die from causes unrelated to FIV.
- The terminal stage is most often recognized and clinically diagnosed.
- Three phases of the disease have been described:

- **Acute viremia phase**
- **Subclinical phase**
- **Immunodeficiency phase = terminal phase**

Stages of feline immunodeficiency virus infection

STAGE	DESCRIPTION
Acute	Fever, anorexia, diarrhea, stomatitis, lethargy, weight los and/or lymphadenomegaly may be observed, although this is transient and often unrecognized by owners
Subclinical	Cats may remain subclinically infected for years, or even for life, or may progress to the terminal (sick) stage
Terminal	Clinical signs occurring in the terminal phase of FIV vary widely, and reflect clinical disease seen with opportunistic bacterial, viral or parasitic/protozoal infections, neoplastic disease, myelosuppression, neurologic and ophthalmic disease. Many infected cats never develop FIV-related clinical signs, and instead die from other causes. Infections in FIV-positive cats may be less responsive to treatment, and exaggerated, when compared with those in immunocompetent cats

- Cats infected with FIV exhibit a wide variety of nonspecific clinical signs; the most common during the terminal phase of the infection are:

- Oral diseases (Example: periodontal disease, gingivitis, lymphoplasmacytic stomatitis, and feline odontoclastic resorption lesions).

- Peritonitis in 25%-50% of cases.
- Chronic or recurrent ocular and upper respiratory tract involvement often associated with feline herpesvirus and calicivirus infections (rhinitis, conjunctivitis, keratitis in 30% of cases, uveitis, hyphema, chorioretinitis, and glaucoma).

- Acute or chronic dermatological manifestations (Example: Otitis externa, dermatitis and pyoderma, dermatophytosis, mycobacterial and fungal infections [such as cryptococcosis and sporotrichosis], parasitic infestations such as demodicosis and myiasis agents).

- Multisystemic diseases (mycoplasmosis, other opportunistic infections.)

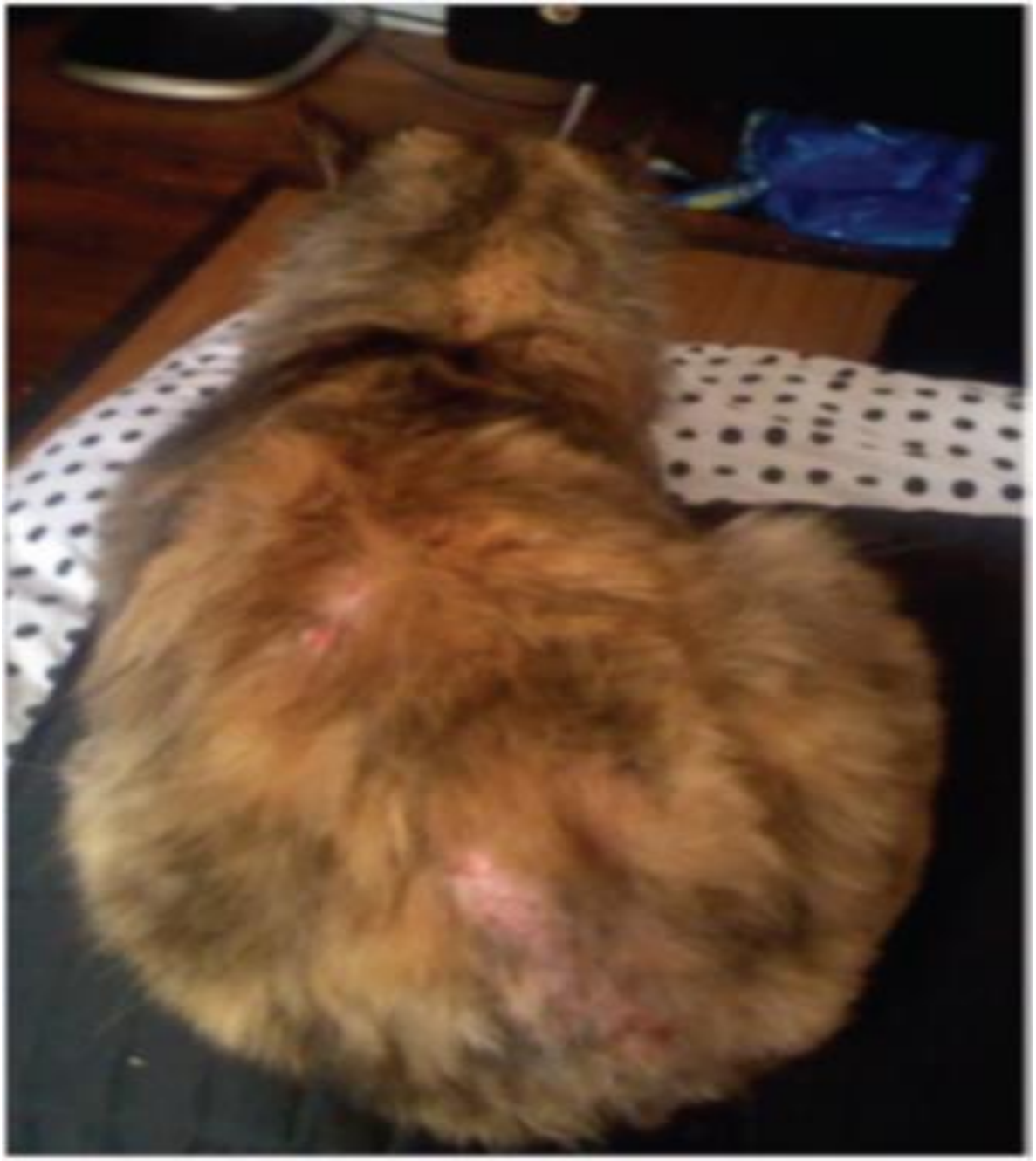
toxoplasmosis) and

- Neoplasia, particularly lymphomas.
- Myelodysplasia.

- Neurological impairments (aggressiveness, cognitive dysfunction, tremors, seizures, delayed reflexes or abnormal functioning of cranial nerves, and possibly urinary and fecal incontinence).
- Various immune-mediated and inflammatory disorders (Example: immune-mediated glomerulonephritis, cardiac inflammation, and other myopathies).
- Chronic renal failure associated with immune-mediated glomerulonephritis; a gastrointestinal syndrome resembling panleukopenia may occur.

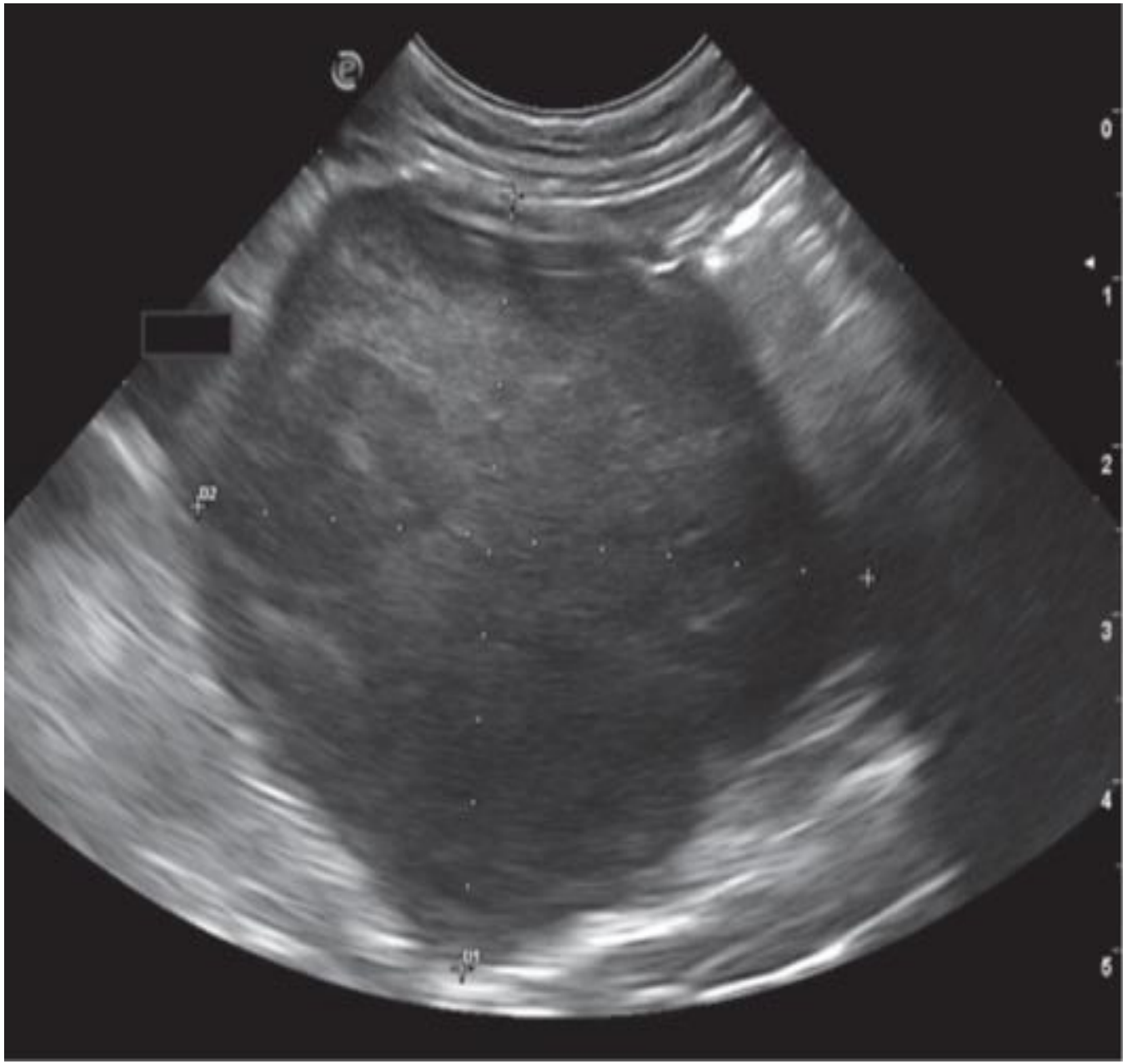
- Persistent diarrhea in 10 to 20% (chronic) + weight loss and poor physical condition = Bacterial or fungal proliferation or parasitic inflammation + direct effect of FIV infection on the gastrointestinal tract epithelium.
- Lower urinary tract infections.
- Mild non-regenerative anemia, neutropenia, lymphopenia, and hyperproteinemia (hypergammaglobulinemia) are commonly noted biological signs in the routine hematology and serum biochemistry of FIV-affected animals.

An inflammatory dermatosis chronic is diagnosed in someti mes infected with FIV. cats



Chronic stomatitis in a cat with FIV.

Abdominal ultrasound image of an enlarged lymphatic node associated with lymphoma in a FIV-positive cat.



Diagnosis

Clinical and differential diagnostics

- Any adult cat presented for a chronic or debilitating illness, fever, or weight loss must be routinely tested for FIV as well as FeLV.
- Cats suffering from anemia, neutropenia, stomatitis, glossitis, lymphoma, or chronic upper respiratory infections should also be tested for FIV infection.

The differential diagnosis of FIV infection includes numerous diseases, such as:

- FeLV infection.
- PIF; cats infected with FIV exhibit significant hypergammaglobulinemia.
- Bartonellosis and other causes of stomatitis such as feline calicivirus infection.
- Immune-mediated diseases, other chronic inflammatory and neoplastic diseases in cats that occur in the absence of detectable FIV infection.

Paraclinical diagnosis

➢ Hematological abnormalities

- ❑The most common hematological abnormalities are neutropenia (leukopenia), mild anemia, and lymphopenia.
- ❑Severe anemia, thrombocytopenia, or thrombocytosis may also occur.
- ❑Hyperproteinemia is common.
- ❑Other abnormalities may be present depending on co-infection or concurrent disease.

- **Urinalysis**

Proteinuria may be present with = glomerulonephritis.

➢ Serological tests (antibody search)

- ❑Serology (IFA, ELISA) = Method of choice for the initial diagnosis in a cat that has not been vaccinated and is over 6 months old.
- ❑The detection of specific FIV antibodies is done on = Blood, serum, plasma.
- ❑Rapid tests (ELISA tests for example) at healthcare locations are highly specific and sensitive for the detection of anti-FIV antibodies.

- Most cats produce antibodies within 60 days of exposure, but the development of detectable antibodies may be significantly delayed in some cats.
- Severe immunosuppression and inability to develop an antibody response can also lead to falsely negative results.
- Falsely negatives are rare in kittens under 6 months of age.

- Any positive result found during the screening (rapid test) of a healthy cat must be confirmed using: ELISA (rapid) from another manufacturer, PCR, Western Blot.
- Kittens with positive rapid ELISA test results must be retested after 6 months of age.
- Falsely positive results due to the presence of antibodies may occur in cats vaccinated against FIV or in kittens under 6 months of age (maternal antibodies).

- Cats previously vaccinated against FIV may remain seropositive for 1 year and possibly more than 4 years.
- A test must also be done prior to FIV vaccination and before cats can become blood or tissue donors (kidneys for example).
- Seronegative cats with a recent risk of exposure should be retested 2 to 3 months later.

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➢PCR

- The sensitivities and specificities of available PCR tests vary and can range from 40% to 100%.
- It is important to combine the interpretation of results with serology.
- Negative PCR results do not necessarily mean that the cat is not infected, as the primers used in the test may not detect all field strains.

Treatment

- Clinically normal patients do not require treatment.
- The use of nucleoside analogs such as AZT and PMEA produces short-term clinical improvement and an increase in the CD4+/CD8+ ratio = Significant side effects, especially anemia.

- Human recombinant alpha interferon or feline omega interferon (106 U/kg SC once daily) can be used in immunocompromised cats following a retroviral infection (FIV or FeLV).
- Any underlying disease or opportunistic infection must be identified and treated (stomatitis for example).
- Symptomatic treatments, such as fluid therapy and nutritional support, may be necessary.

- **Treatment protocols in the management of clinical signs of feline infections by FeLV and/or FIV.**

Immunomodulation therapy

- Staphylococcal protein A (SPA, Kabi Pharmacia, Inc) (10 µg/kg IP twice weekly). Continue as needed. The drug has been used in cats for periods of up to 8 weeks. No improvement in humoral immunity has been documented
- Acemannan (Carrisyn, Carrington Laboratories) (2 mg/kg IP once weekly for 6 weeks). No improvement in clinical outcome or CD4/CD8 ratios was documented following 8 weeks of treatment
- *Propionibacterium acnes* (Immunoregulin, ImmunoVet) (0.5 ml per cat IV once or twice weekly as needed). Clinical improvement has been anectodally reported
- Human recombinant interferon-alpha (rHuIFN) (Roferon-A, Hoffmann LaRoche). (The availability of this drug varies.) Various dosing regimens are described:
  - High dose: 1,000–10,000 U/kg IM q24h for 3–7 weeks. Treatment beyond this period is associated with anti-interferon antibody
  - Low dose: 30 U PO q24h for life

Antiviral therapy

- Azidothymidine (formerly called AZT; now, Retrovir, GlaxoSmithKline) (5 mg/kg PO q8h for periods of up to 4–6 weeks depending on degree of bone marrow toxicity [anemia]). Alternatively, administered at 15 mg/kg PO q12h
- 9-(2-Phosphonylmethoxyethyl) adenine (PMEA) (2.5 mg/kg SC q12h [duration not stipulated]). Availability is limited

FeLV-associated lymphoma/lymphosarcoma

Single-agent glucocorticoids are minimally effective and, therefore, are reserved for palliative management. Combination drug therapy is recommended:

- Induction (weeks 1–4):
  - Cyclophosphamide (Cytoxan, Bristol-Myers) (300 mg/m² PO given once on weeks 1 and 4 only);
  - plus vincristine (Oncovin, Eli Lily) (0.75 mg/m² IV given once weekly on weeks 1, 2, 3, and 4);
  - plus prednisone (2 mg/kg PO q24h for 4 weeks)
- Maintenance (beyond 4 weeks):
  - Discontinue the cyclophosphamide and vincristine
  - Continue the prednisone daily as outlined above. Once the cat is determined to be in remission, the drug dose is gradually reduced over 3 weeks then stopped
  - Beginning with week 7, administer doxorubicin (25 mg/m² IV once every 3 weeks) until it is determined the cat is in remission

Cytopenia

- Human recombinant erythropoietin (100 IU/kg SC q48h for 2 weeks or until the desired hematocrit is reached)
  Anti-erythropoietin antibody may develop against exogenous and endogenous erythropoietin
- Granulocyte-colony stimulating factor (G-CSF) (5 µg/kg SC q12h 1–2 weeks)

Stomatitis

- Metronidazole (5 mg/kg PO q8h 2–4 weeks as needed)
- Clindamycin (12.5 mg/kg PO q8h 2–4 weeks)
- Prednisone (5 mg per cat PO q12h 2–4 weeks)
- Bovine lactoferrin (available from chemical suppliers only) (40 mg/kg applied directly to the oral mucosa, q24h as needed)

Prognosis

- Infected cats (subclinical phase) with FIV can live for many years if they have an excellent quality of life.
- The prognosis is bleak during the terminal phase of the infection.
- The owner's commitment to treating opportunistic infections can influence the prognosis.
- Very young and geriatric cats may have a more severe and progressive disease progression = Poor prognosis.

Prophylaxis

Health prophylaxis

The most effective prophylactic measures to prevent FIV infection are:

- Cleaning and disinfection: FIV is sensitive to all disinfectants, including soap; therefore, routine cleaning and disinfection procedures prevent the transmission of the virus within feline communities, clinics, etc.
- FIV transmission is reduced when cats are kept indoors.

- Limit exposure and encounters with cats infected with FIV (potential transmission through bites) = It is important to determine the FIV status before cats are introduced to one another.

- FIV positive and negative cats must be separated.
- If a positive cat is identified in a multi-cat home, all other cats must be tested and new cats should not be introduced.

Vaccination

Vaccination against FIV is controversial and is considered a non-essential vaccine for several reasons:

- Vaccination only offers partial protection against infection.
- Existing serological tests do not differentiate between natural infection and vaccination.
- Increased risk of vaccine-associated sarcoma formation with adjuvants.

- An inactivated virus (FIV) vaccine with adjuvant (double-clade vaccine: subgroups A and D of FIV) is available in some countries; however, it is not authorized by some authors.
- The primary vaccination is done with 3 doses spaced 2 to 4 weeks apart.

- The initial vaccination may lead to a falsely positive FIV test result (rapid ELISA, for example) for many years.
- Kittens that have nursed from a vaccinated mother may also have a falsely positive test result if tested before 6 months of age.

Guidelines for Vaccination of Individual Pet Cats

Vaccine	Initial Vaccination		Booster Schedule	Comments
	Age ≤ 16 Weeks	Age > 16 Weeks		
FIV (I, SC)	Three doses, 3 weeks apart, starting at 8 weeks of age	Three doses, 3 weeks apart	Annual	Not generally recommended. Immunization does not provide complete protection and interferes with interpretation of antibody test results, and PCR is insufficiently sensitive for accurate diagnosis. The first dose should only be given to FIV-negative cats. Antibodies may also be passed to kittens in colostrum and interfere with testing up to 12 weeks of age.

I, inactivated ;SC, subcutaneous

Public health

- FIV poses no known health risk to humans.