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The Veterinary Journal 1998, **155**, 123–137

Review

Feline Immunodeficiency Virus Infection: an Overview

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SUMMARY

In 1987, Pedersen *et al.* (1987) reported the isolation of a T-lymphotropic virus possessing the characteristics of a lentivirus from pet cats in Davis, California. From the first report onwards, it was evident that in causing an acquired immunodeficiency syndrome in cats, the virus was of substantial veterinary importance. It shares many physical and biochemical properties with human immunodeficiency virus (HIV), and was therefore named feline immunodeficiency virus (FIV). This article reviews recent knowledge of the aetiology, epidemiology, pathogenesis, clinical signs, diagnosis, prevention, and treatment options of FIV infection.

KEYWORDS: FIV; feline immunodeficiency virus; feline acquired immunodeficiency syndrome.

AETIOLOGY

Classification

Feline immunodeficiency virus (FIV) is a member of the family of retroviruses. Due to its morphological and biochemical characteristics, cell tropism, Mg^{2+} dependent reverse transcriptase (RT), genetic organization and antigenic properties, it is classified as a lentivirus (Pedersen *et al.*, 1987; Olmsted *et al.*, 1989a,b; Talbott *et al.*, 1989; Yamamoto *et al.*, 1989). The genomic structure of FIV, especially in the intergenomic region, is more closely aligned with visna maedi virus than with other lentiviruses (Pedersen & Torten, 1995). Western blot analysis using a rabbit serum directed against p26 of equine infectious anaemia virus (EIAV) reveals cross-reactivity with p24 of FIV. Serum of FIV-infected cats also recognizes p26 of EIAV, indicating a reciprocal cross-reactivity (Egberink *et al.*, 1990b; Steinman *et al.*, 1990).

Morphology

FIV morphology is very similar to the structure of other lentiviruses (Fig. 1). The complete virion is 105–125 nm in diameter, spherical to ellipsoid in shape, and possesses short, poorly defined envelope projections (Pedersen *et al.*, 1987). The gene structure has the typical organization of retroviruses, and the size of lentiviruses of about 9400 base pairs. In addition to the major structural genes (*env, gag, pol*), the FIV genome contains open reading frames that potentially encode for two large and five small proteins (Olmsted *et al.*, 1989a,b; Talbott *et al.*, 1989, Miyazawa *et al.*, 1991; Maki *et al.*, 1992).

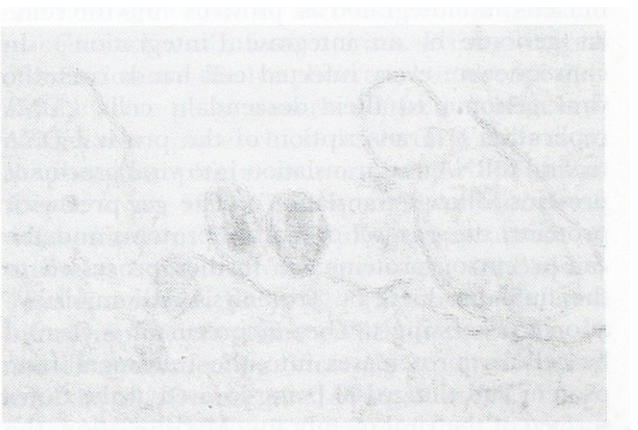

Fig. 1. Electron micrograph of FIV particles (kindly provided by Dr. H. Egberink, University of Utrecht, The Netherlands).

Replication

Like all retroviruses, FIV follows a typical life cycle of 10 steps similar to the replication of cyto-

1090/0233/98/020123-15/$12·00/0

lytic RNA viruses. Differences consist of the reverse transcription and integration steps in which viral RNA is converted into DNA and subsequently integrated in the cellular genome. The first step during infection of the target cell is the attachment of the virion to the cell surface ('adsorption'), and the V3 loop of FIV gp120 surface glycoprotein has been shown to be important for viral binding (Lombardi *et al.*, 1994). Recently it was demonstrated that the binding of FIV gp120 is not to a CD4 receptor, as in human immunodeficiency virus (HIV) infection, but to another receptor on the cell surface. This receptor is similar to the human CD9 but is missing a glycosylation in the first extracellular loop (Willett *et al.*, 1994). Following fusion of the virus envelope with the cell membrane ('virus cell fusion') the nucleocapsid is released intracellularly ('uncoating').

A unique step in the replication cycle of retroviruses is the integration of the viral genome, whereby the viral enzyme RT transcribes the RNA into double-stranded DNA ('reverse transcription'), which is then transported in the nucleus and integrated as 'provirus' into the cellular genome by an integrase ('integration'). In consequence, every infected cell hands over the viral genome to their descendant cells ('DNA replication'). Transcription of the proviral DNA to viral mRNA and translation into viral precursor proteins follow ('translation'). The *gag* precursor proteins, the *gag–pol* precursor proteins and the *env* precursor proteins are further processed to the final products by proteolysis and myristoylation ('processing'). The *env* precursor is cleaved by cellular proteinases into the transmembrane protein and the gp120 being located at the outer surface of the viral membrane. Myristoylation, the translational attachment of a C14 fatty acid, is a prerequisite for proper membrane targeting of the *gag* proteins (Elder *et al.*, 1993).

The last phase of the FIV replication cycle consists of the assembly of virions ('assembly') and their release ('budding') from the cells, during which the virus receives its envelope consisting of parts of the cell membrane and viral glycoproteins (Haase, 1986; Goff, 1990; Egberink, 1991; Haseltine, 1991).

EPIDEMIOLOGY

Geographic distribution

FIV has been detected worldwide. In Europe, prevalences range from 2% in Germany and The Netherlands to 33% in the United Kingdom (Gruffydd-Jones *et al.*, 1988; Lutz *et al.*, 1988, 1990; Hartmann & Lutz, 1989; Kirstensen *et al.*, 1989; Kölbl & Schuller, 1989; Neu *et al.*, 1989; Moraillon, 1990; Hartmann & Hinze, 1991; Bandecchi *et al.*, 1992; Ueland & Lutz, 1992). In the United States, infection percentages vary from 1–16% (Grindem *et al.*, 1989; O'Connor *et al.*, 1989; Shelton *et al.*, 1989; Witt *et al.*, 1989; Yamamoto *et al.*, 1989; Friend *et al.*, 1990; Rodgers *et al.*, 1990; Braley, 1994). Japan has a very high prevalence of up to 44% (Ishida *et al.*, 1989; Furuya *et al.*, 1990). One reason for the differences in infection rates may be the different health status of the cats investigated. The prevalence in populations with a large proportion of clinical signs of chronic disease is higher than in healthy cats being screened for evidence of infection before vaccination or introduction to a household. Epidemiological investigations show that FIV transmission is influenced by behaviour (Courchamp & Pontier, 1994); cats that are free-roaming in areas of high cat denisty have an increased opportunity for exposure largely because bite wounds are known to be the most important mode of transmission (Yamamoto *et al.*, 1989).

Sera from infected cats have been identified in stored samples as far back as 1966 in Europe (Reid *et al.*, 1992), 1968 in the USA and Japan (Shelton *et al.*, 1989; Furuya *et al.*, 1990) and 1972 in Australia (Sabine *et al.*, 1988). Once introduced in a population, FIV is maintained in a stable status between numbers of susceptible and infected individuals (Courchamp *et al.*, 1995).

Mode of transmission

FIV can be isolated from blood, serum, plasma, cerebrospinal fluid and saliva of experimentally or naturally infected cats by tissue culture methods (Yamamoto *et al.*, 1988; Dow *et al.*, 1990). Because biting is more apt to occur between male cats, the infection is much more common in males than females. Cats defending their territory when allowed to roam free, and cats living in surroundings with high population density belong to high-risk groups, although use of common sleeping and eating areas by infected and non-infected cats does not lead to transmission *per se*. Cats kept strictly indoors are rarely infected, and a low prevalence in breeding cats is predominantly due to the fact that they are mostly kept under restricted living conditions (Grindem *et al.*, 1989; Hosie

et al., 1989; Ishida *et al.*, 1989; Kölbl & Schuller, 1989; Pedersen *et al.*, 1989; Shelton *et al.*, 1989; Yamamoto *et al.*, 1989; Hartmann & Hinze, 1991; Courchamp & Pontier, 1994).

Veneral transmission from infected males to non-infected females is possible. Recent studies could detect replication-competent FIV in cell-free and cell-associated forms in domestic cat semen (Jordan *et al.*, 1995). *In utero* transmission may occur *pre* and *intra partum* (Callanan *et al.*, 1991; Hopper *et al.*, 1992; Wasmoen *et al.*, 1992; O'Neil *et al.*, 1996). In experimental studies, infection has been shown to occur not only via vaginal route, but also via rectal mucous membrane (Moench *et al.*, 1993). Further investigations have demonstrated the possibility of infecting newborn kittens via milk (Sellon *et al.*, 1994; O'Neil *et al.*, 1996).

Host range

FIV appears fairly specific to the modern domestic cat (*Felis catus*). However, sera from lions, tigers, cheetahs, jaguars, bobcats, and panthers cross-react with structural antigens of FIV and have been detected by antibody ELISA (Lutz *et al.*, 1992; Olmsted *et al.*, 1992; Brown *et al.*, 1993, 1994). Although lentiviruses have been isolated from Pallas cats, Noth American Pumas, and African lions, they do not appear to cause disease in their natural host and, with the possible exception of some puma isolates, will not replicate in domestic cats (Pedersen & Torten, 1995).

There is no evidence to link FIV infection to any human disease, including acquired immunodeficiency syndrome (AIDS). FIV is antigenically and genetically distinct from HIV, and appears to be highly species specific (Pedersen *et al.*, 1987; Yamamoto *et al.*, 1988; O'Connor *et al.*, 1989; Olmsted *et al.*, 1989a,b; Talbot *et al.*, 1989; Egberink *et al.*, 1990b). Moreover, investigations have failed to identify antibodies in people that have been bitten by infected cats or who have inadvertently injected themselves with virus-containing material (Yamamoto *et al.*, 1989).

PATHOGENESIS

Cell tropism

FIV replicates in $CD4^+$ and $CD8^+$ lymphocytes (Pedersen *at al.*, 1987; Brown *et al.*, 1991; Dean *et al.*, 1996), in B lymphocytes (Dean *et al.*, 1996), in macrophages (Brunner & Pedersen, 1989; Dow *et al.*, 1990), as well as in astrocytes and microglia cells (Dow *et al.*, 1990; Koolen & Egberink, 1990; Danave *et al.*, 1994). As with HIV and simian immunodeficiency virus, some FIV strains replicate highly in lymphocytes and only minimally in macrophages, while other strains are able to replicate equally well in both cell types. Replication in these two cell types is thought to be responsible for different manifestations of disease. Virus replication of monocytes/macrophage lineage may result in disease manifestation of the central nervous system (Clements & Zink, 1996; Vahlenkamp *et al.*, 1996).

Some FIV strains *in vitro* also grow in fibroblasts like Crandell Feline Kidney (CrFK) cells (Pedersen *et al.*, 1987; Yamamoto *et al.*, 1989). For the tropism to CrFK cells mutations in the *env* gene seem to be responsible (Siebelink *et al.*, 1995; Verschoor *et al.*, 1995).

Immune response

The pathogenesis of FIV infection is not completely understood. Despite the generation of neutralizing antibodies and of a cellular immune reaction, a latent infection arises. Primary targets of infection are the lymphocytes, but already during the acute phase a marked infection of macrophages takes place which results in a drift from lymphocytotrophic to monocytotropic FIV strains (Beebe *et al.*, 1994). The quantity of inoculated virus influences the time to the appearance of viraemia and production of antibodies (Yamamoto *et al.*, 1988). The virus can be isolated from lymphocytes at the earliest between day 10 and 14 after infection. Viraemia rapidly increases until day 21 (George *et al.*, 1993; Dua *et al.*, 1994), peaks between weeks 7 and 8 and then decreases again. In the terminal stage, when CD4 cells decrease very rapidly, there is another increase in virus load. Proviral DNA can be detected by polymerase chain reaction (PCR) in peripheral blood lymphocytes after 5 days, and in various other organs after 10 days (Reubel *et al.*, 1994).

Cats react with antibody production 2 weeks after infection (Lutz *et al.*, 1988; Yamamoto *et al.*, 1988; O Connor *et al.*, 1989; Hosie & Jarret, 1990; Dawson *et al.*, 1991; Reubel *et al.*, 1994). Antibodies against envelope proteins arise first, soon followed by antibodies against core proteins (Egberink *et al.*, 1992; Rimmelzwaan *et al.*, 1994). Antigen stimulation of infected B-cells is increased compared with non-infected cells (Lehmann *et al.*, 1992). FIV-infection in cats also results in a sus-

tained polyclonal activation of B-cells with the production of antibodies to a variety of non-viral antigens (Flynn *et al.*, 1994).

Conversely, when the virus peaks, $CD4^+$ cells decrease by approximately one-third due to virus replication. However, a slow rise can be observed afterwards. During the asymptomatic phase, $CD4^+$ cells decrease only very slowly, while a very rapid decrease of the $CD4^+$ cells occurs following the terminal AIDS stage. At the same time, the number of $CD8^+$ cells increases which results in an inversion of the CD4:CD8 ratio (Diehl *et al.*, 1995; English & Tomkins, 1995; Hartmann, 1995). Decrease of $CD4^+$ cells depends on several mechanisms but is usually due to a reduced life span of the cells (Bishop *et al.*, 1993). The quantitative decrease, however, cannot just be explained by cytolysis as a result of viral infection, because the percentage of infected cells is significantly lower than the number of dying cells. Active programmed cell death, or apoptosis, is one important reason for this (Bishop *et al.*, 1993; Ameisen *et al.*, 1994; Ohno *et al.*, 1994; Holznagel *et al.*, 1995). Apart from the quantitative decrease of $CD4^+$ cells, FIV-infected cats show a dysfunction of immune cells as in HIV-infected humans (Clerici *et al.*, 1989; Weimer *et al.*, 1989; Ishida *et al.*, 1990; Torten *et al.*, 1991; Bishop, 1995).

Concurrent with the decline in $CD4^+$ cells and the inversion in the CD4:CD8 ratio, a decline in immune responsiveness can also be seen. Peripheral blood mononuclear cells of symtomatic FIV-infected cats display depressed interleukin-2 (IL-2) production in response to mitogens, accompanied by a significant increase in IL-1, IL-6, and tumour necrosis factor production. Thus, FIV produces a significant perturbation of cytokine production that may contribute to the immune dysfunction as seen in HIV-infected humans (Lawrence *et al.*, 1995). An useful overview on FIV and the feline immune system has recently been given by Willett *et al.* (1997).

Clinical staging

Attempts have been made to define the clinical course of FIV infection in different stages analogous to those of HIV infection in man. In cats, staging in only four phases makes more sense because the two different stages of persistent generalized lymphadenopathy (PGL), also termed lymphadenopathy syndrome (LAS), and the AIDS-related complex (ARC) in humans are rarely distinguished in cats (Table I).

Both, FIV and HIV infection have a well-defined first stage of disease (Yamamoto *et al.*, 1988; Barlough *et al.*, 1991; Callanan *et al.*, 1992). The primary phase of infection is characterized by varying degree of fever, diarrhoea, gingivitis, conjunctivitis, uveitis, jaundice, secondary bacterial sepsis, neutropenia (often associated with a mild to moderate leucopenia), and generalized lymphadenopathy. The fever and other clinical signs persist from a few days to several weeks before disappearing. The severity of primary disease signs varies with age. Newborn kittens develop the most florid and persistent lymphadenopathy; there is an increased severity in adolescents, while geriatric cats show minimal disease signs although they progress to the next stages much more rapidly (George & Pedersen, 1992). Mortality during

Table I
Classification of FIV infection in four stages

Stage			*Clinical signs*	*Duration*
1	Acute phase	Initial stage	Neutropenia, lymphadenopathy, fever	Weeks to months
2	Asymptomatic phase	Asympotomatic carrier AC	No clinical signs	Years
3	Phase of unspecific clinical signs	PGL/LAS+ARC	Generalized lymphadenopathy, recurrent fever, apathy, leucopenia, anaemia, anorexia, weight loss, chronic stomatitis, behavioral abnormalities	Several months to 1 year
4	Terminal AIDS-like phase	AIDS	ARC symptoms+opportunistic infections, neoplasia, neurological abnormalities	Several months

PGL, persistent generalized lymphadenopathy; LAS, lymphadenopathy syndrome; ARC, AIDS-related complex.

the initial stage is low (Yamamoto *et al.*, 1988), and in natural infection clinical signs are usually not noticed by the owners.

Following the first stage, cats enter a long period of clinically normal appearence (latent stage) although the virus can generally be isolated. The span between the primary and the third stage has not yet been precisely determined, but it can last up to 5 years or more. However, a decrease in $CD4^+$ cells and CD4:CD8 ratio, and a hypergammaglobulinaemia are often evident after 18–24 months post-infection (Ackley *et al.*, 1990; Barlough *et al.*, 1991). The proportion of cats that remain in stage 2 is unknown. There is evidence that some cats may carry FIV for life with minimal disease problems. As in man, the age of infection can also influence the latent time period. Cats infected at 10 years of age or older progress through stage 2 within 6–12 months, whereas it takes much longer in animals infected as kittens, adolescents or young adults (George & Pedersen, 1992).

About one-half of FIV-infected cats are presented to the veterinarian with signs of phase three (nonspecific signs) comparable with PGL/LAS and ARC in HIV infection. The third stage is characterized by vague signs of disease without obvious opportunistic infections. Signs of illness include recurrent fever, leucopenia, lymphadenopathy, anaemia, unthriftiness, reduced appetite, weight loss, chronic progressive oral infections, or nonspecific changes in normal behaviour. It can last between 6 months and several years (Hartmann, 1995).

Cats in stage 4 with AIDS-like disease are often suffering from opportunistic infections in multiple sites of the body. In many cases they have weight loss greater than 20%, anaemia, and leucopenia. The animals suffer from opportunistic infections, myeloproliferative disorders, tumours and neurological signs. They develop a severe immunodeficiency and are sensitive to viral, parasitic, fungal, and sometimes bacterial infections (Hartmann, 1995).

CLINICAL SIGNS

The relationship of FIV to other viral infections has frequently been studied. There are reports showing that FIV-infected cats are 1·5–4 times more likely to be infected with feline leukaemia virus (FeLV) than FIV-negative cats. Although FIV and FeLV are believed to be transmitted by dissimilar modes, the higher frequency of FeLV seropositivity in cats infected with FIV indicates the possibility that the two viruses share common routes of infection. Both are known to cause immunosuppressive disease; FIV may have rendered infected hosts more susceptible to FeLV, or *vice versa*. Seroepidemiologic investigations have shown that cats infected with both viruses tend to have more severe disease and die sooner than monoinfected animals (Ishida *et al.*, 1989; Yamamoto *et al.*, 1989; Cohen *et al.*, 1990). FeLV infection enhances FIV infection *in vitro* and *in vivo* and leads to a faster decline of the immune system and earlier signs of infection (Pedersen *et al.*, 1990).

Some authors have reported a strong correlation between feline syncytium-forming virus (FeSFV) and FIV. In a study by Yamamoto *et al.* (1989), 74% of a panel of FeSFV-infected cats were positive for FIV infection (Yamamoto *et al.*, 1989). FIV and FeSFV are usually infections of free roaming cats, and the infection rate of both viruses among confined animal groups is low. This may be attributed in particular to the importance of biting as the main mode of transmission of FIV and FeSFV, while FeLV is much more infectious by close physical contact with infectious secretions (Yamamoto *et al.*, 1989; Kölbl & Lutz, 1992; Zenger *et al.*, 1993).

Investigations in cats with chronic stomatitis showed that FIV infection positively affected the pathogenesis and clinical signs of persistent feline calicivirus infection (Knowles *et al.*, 1989; Tenorio *et al.*, 1991, Reubel *et al.*, 1994; Waters *et al.*, 1993). It is believed that there is no association between the presence of FIV and feline coronavirus antibodies (Cohen *et al.*, 1990). Nevertheless, feline infectious peritonitis has to be considered as one of the most common causes of death in FIV-infected cats and is very often found as a terminal opportunistic infection in follow-up investigations (Hartmann, 1995).

Toxoplasmosis is of high interest as an opportunistic infection in HIV-infected humans. FIV-infected cats have higher *Toxoplasma gondii* IgM antibody levels and a higher replication rate of *T. gondii* than FIV-negative cats (Witt *et al.*, 1989; Heidel *et al.*, 1990; O'Neil *et al.*, 1991; Lin *et al.*, 1992; Lappin *et al.*, 1993). Trichomoniasis in the oral cavity is found significantly more often in FIV-infected cats than in FIV-free animals (Gothe *et al.*, 1992). In FIV-infected cats with *Chlamydia psit-*

taci infection, isolation of the parasite is possible for an extended time and clinical symptoms are protracted compared with non-infected control animals (O'Dair *et al.*, 1994). In addition, fungal infections are common in FIV-infected cats with increased incidence of *Cryptococcus, Candida* and *Microsporum* species (Ferrer *et al.*, 1992; Mancianti *et al.*, 1992; Ramos-Vara *et al.*, 1994; Hartmann, 1995; Walker *et al.*, 1995).

In the primary stage, FIV-infected cats show an increase in size of peripheral and mesenteric lymph nodes, demonstrating a pronounced follicular and paracortical hyperplasia and irregular lymphoid follicles (Pedersen *et al.*, 1987; Lutz *et al.*, 1988; Yamamoto *et al.*, 1988; Dieth *et al.*, 1989; Callanan *et al.*, 1993; Sparkes *et al.*, 1993; Reubel *et al.*, 1994). In the ARC stage, a combination of follicular hyperplasia and involution, pure involution, or a combination of involution and depletion can be found, whereas in the terminal stage the nodal architecture is often disintegrated (Brown *et al.*, 1991; Rideout *et al.*, 1992; Matsumura *et al.*, 1994). In FIV-infected animals a lymph node plasmocytosis in the medulla can be seen more often than in non-infected animals, probably as a consequence of unspecific B-cell stimulation (Rideout *et al.*, 1992; Parodi *et al.*, 1994; DelFierro *et al.*, 1995). In parallel to the generalized lymphadenopathy, hyperplasia of the spleen and lymphatic tissues of the intestine may appear. In some cases, lymphoid follicles or a concentration of lymphoid cells in other organs such as bone marrow, thymus, adrenal glands, thyroid glands, kidneys, and eyes have been described (Shelton *et al.*, 1989; Reinacher & Holznagel, 1991; Callanan *et al.*, 1992).

Gastrointestinal lesions are most frequently observed with inflammation in the oral cavity ranging from a mild stomatitis or periodontitis to erosive, ulceroproliferative lesions which may have a hyperplastic appearance (Lutz *et al.*, 1988; Hopper *et al.*, 1989; Ishida *et al.*, 1989; Knowles *et al.*, 1989; Pedersen *et al.*, 1989; Yamamoto *et al.*, 1989; Zetner *et al.*, 1989; Hartmann & Hinze, 1991; Tenorio *et al.*, 1991; Sparkes *et al.*, 1993; Hartmann, 1995). The worst cases of stomatitis are often followed by anorexia leading to emaciation (Hopper *et al.*, 1989). Further diseases of the gastrointestinal tract include chronic enteritis, gastritis and rarely, disorders of the pancreas and liver (Pedersen *et al.*, 1987; Hopper *et al.*, 1989; Yamamoto *et al.*, 1989; Hartmann & Hinze, 1991). Histopathological findings characteristically show chronic inflammatory changes of the intestines, and a severe and diffuse villous atrophy that is particularly evident in the lower half of the small bowel. Lymphoid tissue within the intestinal wall is often found to be hyperplastic (Dieth *et al.*, 1989; Brown *et al.*, 1991).

Diseases of the respiratory system predominantly affect the upper respiratory tract (Hopper *et al.*, 1989; Hosie *et al.*, 1989; Pedersen *et al.*, 1989; Yamamoto *et al.*, 1989; Hartmann & Hinze, 1991; Sparkes *et al.*, 1993). These findings are also corroborated by histopathological investigations (Reinacher, 1990; Brown *et al.*, 1991, Reinacher & Holznagel, 1991).

Changes in the kidneys of FIV-infected cats can include glomerulonephritis (Reinacher & Frese, 1991) leading to azotaemia and proteinuria (Poli *et al.*, 1993; Thomas *et al.*, 1993), and the increased prevalence of atrophic kidneys is statistically significant (Thomas *et al.*, 1993). Histological changes include mesangial dilatation, glomerulosclerosis, and tubulointerstitial lesions (Poli *et al.*, 1993). In the lower urinary tract, bacterial as well as non-bacterial cystitis can occur (Hopper *et al.*, 1989; Yamamoto *et al.*, 1989, Pedersen & Barlough, 1991).

Skin changes are generally of chronic nature. Abscesses, especially following biting, pustular dermatitis, facial dermatitis, chronic miliary dermatitis, generalized *Demodex* and *Notoedres* infestation, or atypic dermal mycobacteriosis have all been described in the literature (Chalmers *et al.*, 1989; Medleau, 1990; Hartmann & Hinze, 1991; Pedersen & Barlough, 1991).

Rarely, symptoms of the central nervous system are found. About 5% of clinically diseased FIV-infected cats will have neurological abnormalities as a predominant clinical feature of their disease (Shelton *et al.*, 1989; Swinney *et al.*, 1989, Zenger, 1990). These may result from a direct effect of the virus on brain cells (Dow *et al.*, 1990) or, uncommonly, as a manifestation of some opportunistic infections such as toxoplasmosis (Heidel *et al.*, 1990). Neuronal apoptosis has also been discussed (Ameisen, 1994). Neurological aberrations tend to be more behavioural than motor. Dementia, twitching movements of the face and tongue, psychotic behavior, loss of bladder and rectal control, and compulsive roaming have all been recognized in FIV-infected cats. Convulsions, nystagmus, ataxia, and intention tremor have also been described (Harbour *et al.*, 1988; Hopper *et al.*, 1989; Yamamoto *et al.*, 1989; Podell *et al.*, 1993). In

addition, reduced auditory evoked potentials and abnormal sleeping patterns can occur. Magnetic resonance studies have revealed cortical atrophy, moderate ventricular increase, and slight lightening in the white substance in some cases (Wheeler *et al.*, 1991; Podell *et al.*, 1993). Histopathologically perivascular lymphocytic infiltrations, focal meningitis, encephalomeningitis, fibrosis of the plexus chorioideus, demyelinization, diffuse glioses, glial nodules, and satellites have been found (Dow *et al.*, 1990; Hurtrel *et al.*, 1992; Podell *et al.*, 1993; Beebe *et al.*, 1994; Phillips *et al.*, 1994). Although only about 5% of FIV-infected cats exhibit abnormal neurologic signs, a much larger proportion of naturally and experimentally infected cats exhibit microscopic lesions in their central nervous system (Dow *et al.*, 1990). Indeed, Wheeler *et al.* (1991) found that many naturally FIV-infected cats without outward neurological changes had abnormal slow motor and sensory nerve conduction velocities. They also found evidence of demyelinization and selective nerve dropout in various locations (Wheeler *et al.*, 1991).

Inflammatory disease of the eye, in particular of the anterior uveal tract, has been seen in several FIV-infected cats (English *et al.*, 1990; Gruffydd-Jones *et al.*, 1988). Chorioretinitis is found significantly more often than in non-infected animals (Heider, 1994). Some eye lesions are caused by other agents, in particular by *T. gondii* (Lappin *et al.*, 1993). Glaucoma with or without concurrent uveitis are other conditions that have been associated with FIV infection (English *et al.*, 1990). There are also descriptions of cotton-wool spot like changes similar to those characteristic for HIV infection (Geier *et al.*, 1994; Hartmann, 1995).

Although no haematological abnormalities are pathognomonic for FIV infection, a number of changes in blood parameters have been observed in FIV-infected animals. This is largely due to FIV replication in mononuclear cells leading to immunosuppression and changes in the haematopoetic system (Hopper *et al.*, 1989; Robinson *et al.*, 1990; George & Pedersen, 1991). In the primary stage, a leucopenia, mainly due to an absolute neutropenia is commonly seen (Yamamoto *et al.*, 1988). In later stages, in naturally infected animals, the most common findings are leucopenia and anaemia (Ishida *et al.*, 1989; Hartmann & Hinze, 1991; Callanan, 1995). There might also be a generalized cytopenia with neutropenia, anaemia, lymphopenia, and thrombocytopenia (Hopper *et al.*, 1989; Shelton *et al.*, 1989, 1991; Thomas *et al.*, 1993; Hart & Nolte, 1994). Anaemias are usually non-responsive in nature. Maturation arrests in red blood cells are common. Examination of the bone marrow often shows either hyperplasia (immune-mediated anaemias) or myeloid dysplasia (myeloproliferative disorders). There are also anemias described in common with haemobartonellosis (Hopper *et al.*, 1989). In some FIV-infected cats, prolonged clotting times can occur (Hart & Nolte, 1994). Alterations of clinical chemistry parameters include only an unspecific polyclonal hypergammaglobulinaemia (Ishida *et al.*, 1989; Yamamoto *et al.*, 1989, Thomas *et al.*, 1993; Grant, 1995).

There is mounting evidence that FIV-infected cats have a higher incidence of certain types of tumours. FIV-associated tumours appear usually as lymphoid tumours, less frequently as myeloid tumours or miscellaneous solid carcinomas and sarcomas (Hopper *et al.*, 1989; Ishida *et al.*, 1989; Shelton *et al.*, 1989, 1990; Yamamoto *et al.*, 1989; Hutson *et al.*, 1991; Burraco *et al.*, 1992). It is not known how FIV is associated with these cancers. Examinations of tumours in FIV-infected cats with molecular probes to screen for integrated viral sequences have not detected integrated FIV genome in any of the tumours suggesting that the role of FIV in lymphomagenesis is generally indirect (Terry *et al.*, 1995). There are however, several theories about the association of tumours with FIV infection. FIV might increase cancer incidence by decreasing tumour immunosurveillance mechanisms, it might promote tumour development through immunostimulatory effects, it might impair immunological control of FeLV infection and hence accelerate the overgrowth of transformed lymphoid cells, or it might allow other cancer-causing agents to be activated.

DIAGNOSIS

Clinical symptoms *per se* are not sufficient for a reliable diagnosis of FIV infection. Classical virus detection by blood cell culture and virus isolation from plasma or peripheral blood lymphocytes is possible over the whole infection period, but not practicable for routine diagnosis (Jarrett *et al.*, 1991; Pedersen & Barlough; 1991). Currently, FIV infection is diagnosed by antibody detection in the blood. As cats do not recover from FIV infection, a direct correlation between the presence of antibodies and virus infection exists (Yamamoto *et*

al., 1989). Antibodies can be detected by an indirect fluorescent antibody (IFA) assay using FIV-infected T-lymphocyte-enriched peripheral blood mononuclear or CrFK cells as substrate, by enzyme-linked immunosorbent assay (ELISA) using FIV proteins or peptides produced by recombinant DNA technology (Reid *et al.*, 1991), or by ELISA or Western blotting using gradient-purified tissue culture-grown virus as antigen source (Pedersen *et al.*, 1987; O'Connor *et al.*, 1989; Yamamoto *et al.*, 1989). Antibodies usually appear within 2–4 weeks of experimental infection, and are usually detectable for the rest of the life of the animal (Yamamoto *et al.*, 1988; O'Connor *et al.*, 1989). However, a small portion of experimentally infected cats may not present antibodies for up to 1 year following infection (Yamamoto *et al.*, 1988). Furthermore, in the final stage, antibody levels can fall below detection level (Pedersen *et al.*, 1989). A small proportion of cats never possess detectable levels of antibodies in their blood, yet have recoverable virus in their peripheral blood lymphocytes (Harbour *et al.*, 1988; Hopper *et al.*, 1989; Dandecar *et al.*, 1992).

Normally, ELISA are used as screening tests in veterinary practice (Reid *et al.*, 1992) They are commercially available and usually search for antibodies against the core protein p24. Those tests however, might be particularly troublesome in some areas and in cat populations with a low infection risk as in Germany. In such conditions, the incidence of false-positive serological reactions may greatly exceed the true incidence of the infection, and all positive ELISA results need to be confirmed by more specific tests such as Western blotting (Hartmann *et al.*, 1994b) which detects multiple antibody specificities in one reaction against various viral proteins (Kawaguchi *et al.*, 1990; Egberink *et al.*, 1991b; Hardy & Zuckermann, 1991). Unfortunately, it is not convenient for veterinary practice. Several new one-step diagnostic test kits for antibody detection in veterinary practice have just been developed or will be available in the near future. Comparative studies to determine sensitivity and specificity are currently underway.

PREVENTION

FIV infection can be best prevented by keeping cats out of environments that encourage 'high-risk' behaviour. Cats should be neutered, kept indoors whenever possible, and not be exposed to new homeless, feral, abandoned, or stray cats, unless those animals are tested first.

Table II
Treatment studies against FIV infection in cell culture (*in vitro*) and FIV-infected cats (*in vivo*) with antiviral compounds derived from HIV research

Compound	*Abbreviation*	In vitro *investigations*	In vivo *investigations*
3'-azido-3'-deoxythymidine	AZT	Egberink *et al.*, 1990a; Hartmann *et al.*, 1994a; Smyth *et al.*, 1994b; Smith *et al.*, 1995	Hartmann *et al.*, 1992, 1995a,b; Hart & Nolte, 1993; Hayes *et al.*, 1993; Meers *et al.*, 1993; Smyth *et al.*, 1994a
9-(2-phosphono-methoxyethyl)-adenine	PMEA	Egberink *et al.*, 1990a; Hartmann *et al.*, 1994a; Smith *et al.*, 1995	Egberink *et al.*, 1990a, 1991a; Hartmann *et al.*, 1992; Philpott *et al.*, 1992; Vahlenkamp *et al.*, 1995
9-(2-phosphono-methoxypropyl)-2,6-diaminopurin	PMPDAP	Vahlenkamp *et al.*, 1995	Vahlenkamp *et al.*, 1995; Wilhelm, 1996
9-(3-fluoro-2-phosphono-methoxypropyl)-adenine	FPMPA	Hartmann *et al.*, 1994a	Hartmann, 1995; Kuffer, 1996
9-[(2R,5R-dihydro-5-phosphono-methoxy)-2-furanyl]adenine	D4API	Hartmann *et al.*, 1997	Hartmann *et al.*, 1997
Dideoxycytidine-5'-triphosphate	ddCTP	Fraternale *et al.*, 1994; Magnani *et al.*, 1994	Magnani *et al.*, 1994

Research on FIV vaccines is currently underway. It is difficult to generate an effective vaccine because of the nature of the retrovirus–host interaction, as well as the relatively poor immunogenicity of the viral antigens that induce vaccinal immunity. Furthermore, the mechanisms leading to protective immunity against retroviral infections are still poorly understood. A useful overview on the development of a vaccine against FIV has been given by Hosie (1995).

TREATMENT

Besides symptomatic treatment of opportunistic organisms, antiviral chemotherapy derived from HIV research can be used in FIV-infected cats as most enzymes of FIV and HIV have similar sensitivities to various inhibitors (North *et al.*, 1990; Tanabe-Tochkura *et al.*, 1992; Gustchina, 1995). In cell culture, many compounds have been shown to be active against FIV (Table II). Several treatment studies have been reported in experimentally FIV-infected cats (Egberink *et al.*, 1990a; Philpott *et al.*, 1992; Hayes *et al.*, 1993; Meers *et al.*, 1993; Magnani *et al.*, 1994; Smyth *et al.*, 1994a; Hartmann, 1995; Vahlenkamp *et al.*, 1995), but not many studies exist in naturally infected field cats (Hartmann *et al.* 1992, 1995a,b; Hart & Nolte, 1993).

The only drug routinely available for treatment in veterinary practice shown to be antivirally active in naturally FIV-infected cats which is commercially available at the moment is AZT (zidovudin 3'-azido-2',3'-dideoxythymidine, Retrovir, Glaxo-Wellcome). AZT inhibits virus replication *in vitro* and *in vivo* (Hartmann *et al.*, 1992; 1995a,b). It improves the immunological and clinical status of FIV-infected cats, increases quality of life and prolongs life expectation. It should be used at a dosage of 5 mg kg^{-1} body weight twice a day orally or by subcutaneous injection. For subcutaneous injection the lyophilized product should be diluted in isotonic NaCl solution to prevent local irritation. For oral application, syrup or gelatine capsules (dosage/weight individually for every cat) can be given. During treatment, regular blood cell counts are necessary because anaemia is a common side effect (Hartmann *et al.*, 1992; 1995a,b). However, as shown in long-term studies, AZT is well tolerated and there is only mild decrease of haemoglobin values (Hart & Nolte, 1993; Hartmann *et al.*, 1995a,b). Unfortunately, as in HIV, AZT-resistant mutants of FIV can arise (Remington *et al.*, 1990). Furthermore, other nucleoside analogues like acyclic nucleoside phosphonates (e.g., PMEA and derivatives) possess better antiviral potency in cell cultures and in naturally infected animals (Hartmann *et al.*, 1992, 1994a) but are currently not commercially available. Thus, AZT has to be considered as the drug of choice for causative treatment of FIV-infected cats at this time.

ACKNOWLEDGEMENTS

We thank the Human Capital and Mobility Programme of the European Community for their support of many investigations.

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(Accepted for publication 17 July 1997)