GUIDELINE for Feline immunodeficiency virus

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Synopsis

Feline immunodeficiency virus (FIV) is a retrovirus of the genus Lentivirus that is closely related to HIV; however, humans are not susceptible to the cat virus, which occurs in 5 subtypes (clades) worldwide. Seroprevalence is highly variable geographically, with estimates of 1 to 14% in cats with no clinical signs and up to 44% in sick cats. Sick adult cats, male cats and entire cats are most likely to be infected, mostly through the inoculation of saliva during fighting. Most clinical signs are not caused by the virus, rather by secondary infections, a consequence of immunodeficiency and/or immune stimulation, which most frequently appears in the form of chronic gingivostomatitis, chronic rhinitis, lymphadenopathy, immune-mediated glomerulonephritis and weight loss. Routinely, FIV infection is diagnosed by detecting antibodies using ELISA and immunochromatography methods. Western blot is used to confirm questionable results.

Healthy seropositive cats should never be euthanized – they may live as long as uninfected ones. ABCD does not recommend the use of the vaccine available outside Europe, given the problems associated with serological diagnosis of infections and lack of evidence of efficacy against European isolates.

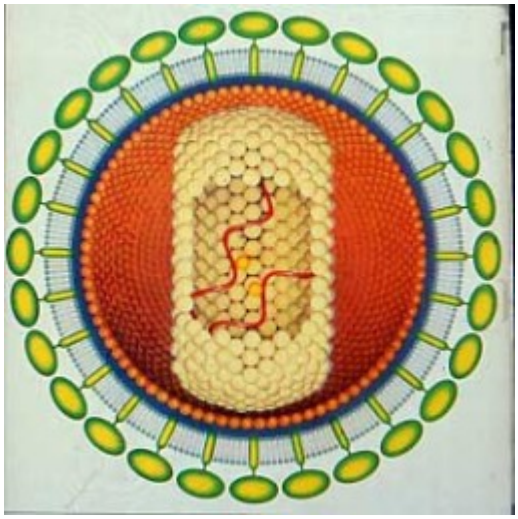

Fig. 1. Cartoon of a lentivirus particle; for a structural comparison, see the FeLV chapter. ©Scientific American

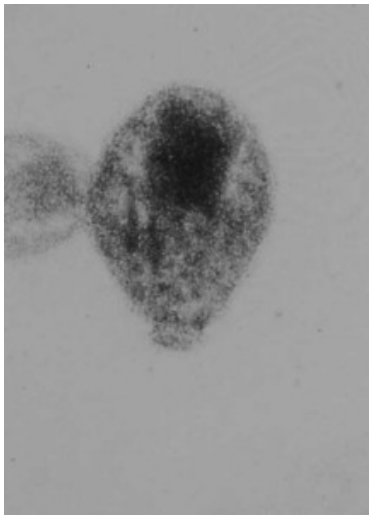

Fig. 2. Thin section electron micrograph of a lentivirus particle, showing the characteristic cone-shaped uncleocapsid. ©Marian C. Horzinek

Virus

Feline immunodeficiency virus (FIV) is a retrovirus of the genus *Lentivirus* that is closely related to

HIV, sharing a similar structure, life cycle and pathogenesis (Miller et al., 2000).
However, it is important to emphasise that human beings are not susceptible to FIV infection. It has become clear that FIVs are a large and ancient group of viruses; species-specific strains have been isolated from a variety of non-domestic *Felidae*, including the puma, lion, leopard, and pallas cat (Olmsted et al., 1992, Brown et al., 1994, Carpenter et al., 1996, Barr et al., 1997).
Lentiviruses such as FIV are complex retroviruses, containing accessory genes in addition to *gag*, *pol* and *env*. The FIV *gag* gene encodes among others the capsid protein p24 which is important for diagnosis. The *pol* gene encodes protease, integrase and reverse transcriptase proteins as well as additional enzymes that are important to the virulence of FIV. Both *gag* and *pol* are relatively conserved between strains. The *env* gene encodes the viral glycoprotein (gp120) and the transmembrane protein (gp41), the major determinants of viral diversity amongst isolates (Olmsted et al., 1989).

Fig. 3. Worldwide distribution of FIV clades. Courtesy of Margaret Hosie, Glasgow

Five genetically distinct subtypes or clades (designated A to E) have been defined, with considerable sequence diversity (up to 26%) amongst regions of *env* (Sodora et al., 1994, Kakinuma et al., 1995, Pecoraro et al., 1996). The majority of viruses identified so far belong to either subtype A or B. Although multiple subtypes have been documented in cats from the same continent, geographic clustering of subtypes is evident (Fig. 3), which is important for PCR diagnosis. In the UK, only subtype A viruses are found. In other countries subtype A viruses predominate, but other clades are present (e.g. Switzerland, Australia, the western United States, northern Japan, Germany and South Africa) (Sodora et al., 1994, Kakinuma et al., 1995, Bachmann et al., 1997, Kann et al., 2006). Subtype B

viruses are also distributed worldwide but have been more consistently identified in eastern Japan, Italy, Portugal, and eastern United States. In contrast, subtype C viruses are less common. All of the reported subtype D viruses have arisen from Japan (Kakinuma et al., 1995) and two strains from Argentina have been assigned to subtype E (Pecoraro et al., 1996).

The virus survives only minutes outside the host and is susceptible to all disinfectants including common soap.

Epidemiology

Since FIV was first isolated in 1986 (Pedersen et al., 1987), serological studies have demonstrated that FIV is endemic in domestic cat populations worldwide; the seroprevalence of FIV is highly variable between regions, with estimates of 1 to 14% in cats with no clinical signs and up to 44% in sick cats (Hartmann, 1998).

Sick adult cats, male cats and entire cats are most likely to be infected (Hosie et al., 1989). The major route of natural transmission is believed to be via the inoculation of saliva during fighting (Yamamoto et al., 1989). Vertical transmission and transmission between cats in stable households is relatively uncommon. Indeed, no transmission of FIV was observed in a study of cats cohabiting in a mixed household over a period of months to years, despite mutual grooming, mild aggression, shared food bowls, litter boxes and bedding (Litster, 2014). Most natural FIV infections are acquired by biting, presumably through the inoculation of virus, or virus-infected cells, from the saliva of persistently infected cats. Transmission from mother to kittens may occur but only a proportion of the offspring become persistently infected. The proportion of kittens infected depends on the viral load of the queen during pregnancy and birth. E.g. if the queen is acutely infected up to 70% of the kittens may be infected, but if the queen is clinically normal but chronically infected hardly any kittens will be infected (O'Neil et al., 1995a, 1995b, 1996). Although neither oronasal nor venereal spread has been documented in nature, cats can be infected by experimental inoculation of virus into the nose, mouth, vagina and rectum (Moench et al., 1993) and virus can be recovered from semen following natural or experimental infection (Jordan et al., 1998). Queens however may still be infected at mating if bitten by an infected tomcat.

FIV infection was found to be prevalent in a survey of four large-scale hoarding situations; this high prevalence was probably related to the cats living in close confinement, under stressful conditions in which cats exhibited aggressive behaviour (Polak et al., 2014). Therefore, it is recommended that cats should be tested for FIV infection at the time of seizure during hoarding investigations as the results will influence housing decisions, medical care and adoption options.

FIV infection is also common in rescue shelters and it is recommended that all cats in rescue centres should be spayed or neutered and kept indoors, in order to reduce the risk of territorial aggression, which can result in penetrating bite wounds and consequently FIV transmission. This recommendation is supported by studies linking cat bite wounds and abscesses with FIV infection (Goldkamp et al., 2008; Chang-Fung-Martel et al., 2013). A survey of cats in a rescue shelter in which FIV-infected cats were housed together with uninfected cats found no evidence of FIV transmission, despite the cats having unrestricted access and sharing food and water bowls, litter trays and bedding for several years (Litster, 2014). However, it is possibly significant that cats were spayed/neutered before entering this shelter and the median age of the uninfected cats was 4 months; kittens are a low risk group for FIV infection (Levy et al., 2006) because territorial aggression has not yet developed. Similarly, neutered cats are less likely to display territorial aggression than intact cats and therefore FIV transmission might be more likely to occur in rescue centres housing older cats, especially if those cats exhibit aggressive behaviour.

Pathogenesis

The major targets for FIV infection are activated CD4+ T-lymphocytes. These cells typically function as T-helper cells which have a central role in immune function, facilitating the development of humoral and cell-mediated immunity. The FIV envelope glycoprotein gp120 binds to a primary receptor on the cell surface, CD134 (Shimojima et al., 2004; Willett et al., 2006). A conformational change occurs in gp120 that enables a second interaction with the co-receptor, CXCR4, triggering membrane fusion and viral entry. The viral enzyme reverse transcriptase that mediates copying of its RNA genome into a DNA copy (or provirus) is error prone and lacks a proofreading function; thus FIV may mutate rapidly and exist as multiple strains. This genetic diversity results in variants that may evade immune detection and is an important consideration in the development of both molecular diagnostic techniques and vaccines.

Latent infection arises when a cell carries an integrated copy of provirus but does not produce new virus particles unless it becomes activated. Latently infected cells represent a "reservoir" of infection that is not susceptible to neutralising antibodies, posing an

obstacle for effective vaccination.

In the first few days following experimental inoculation, FIV grows in dendritic cells, macrophages and CD4+ T lymphocytes, and may be detected in the plasma within two weeks. The level of virus in the plasma and proviral DNA in the blood mononuclear cells increase, reaching a peak 8 to 12 weeks post infection. During this period, mild to moderate clinical signs such as anorexia, depression and pyrexia may be observed. These conditions generally subside rapidly; in contrast signs such as generalised lymphadenopathy, due to increased numbers and size of active germinal centres in the lymph nodes, may persist for weeks or months. The decrease in plasma viral load marks the beginning of the so-called 'asymptomatic' phase that can last for many years, or may be lifelong. It is assumed that viral replication is controlled by the immune response during this phase while the infected cat remains relatively free of clinical signs.

The final outcome of FIV infection is variable. During the asymptomatic phase the plasma virus load is stable but there is a progressive decline in CD4+ T lymphocyte numbers which results in a decreased CD4:CD8 T lymphocyte ratio (Torten et al., 1991). In a proportion of infected cats this leads to a functional immunodeficiency, clinical signs of AIDS and death.

Immunity

Passive immunity

In the face of natural infection, the efficacy of passive immunity acquired via colostrum from FIV-infected or vaccinated queens is not known. Experimentally, it has been demonstrated that susceptible kittens can be protected from FIV infection following passive transfer of antibody, indicating that antibodies may be protective (Hohdatsu et al., 1993; Pu et al., 1995) in response to challenge with laboratory-adapted isolates of FIV. However, passive transfer of antibody may not protect kittens against infection with virulent field isolates and indeed there is a report of enhanced infection in experimental cats following the passive transfer of antibodies from cats immunised with an experimental vaccine, indicating that a fine balance may exist between neutralising and enhancing antibodies (Siebelink et al., 1995).

Active immune response

Cats infected with FIV are persistently infected in spite of mounting antibody and cell- mediated immune responses. CD8+ FIV-specific cytotoxic T cells (CTL) can be detected in the blood within one week of infection (Beatty et al., 1996). Coincident with the peak in virus load, anti-FIV antibodies, including virus-neutralizing antibodies, appear in the plasma (Fevereiro et al., 1991). In general, anti-FIV antibodies are detectable from 2-4 weeks post infection, although seroconversion may be delayed in cats exposed to low doses of virus (Hosie and Jarrett, 1990). In experimentally infected cats, it was shown that antibodies recognising e*nv* appeared earlier than antibodies against the *gag* protein p24 (Rimmelzwaan et al., 1994). A population of CD8+ T cells termed CD8low (Willett et al., 1993) has been observed in early FIV infection with some isolates; these cells act as a marker of immune activation by more virulent strains of FIV and may contribute functionally to the noncytolytic activity against FIV mediated by CD8+ T cells (Flynn et al., 2002).

Clinical signs

Most clinical signs that FIV-infected cats present with are not directly caused by the FIV itself; so it is vital to check for the underlying cause of the presenting clinical signs. In many cases, the clinical signs will be caused by a secondary infection that should be identified and treated (see below). FIV itself is responsible for immunodeficiency (making the cat more susceptible to secondary infections and neoplasia) or immune stimulation (resulting in immune-mediated disease). In rare cases, the virus can cause neurological disease.

In the first weeks to months post FIV infection, transient clinical signs lasting a few days to a few weeks may be seen during the primary phase of FIV infection. These may include mild pyrexia, lethargy and peripheral lymphadenopathy (del Fierro et al., 1995). Haematology may show a neutropenia (Pedersen et al., 1989).

Infected cats then generally remain free of clinical signs for an extended period of time before problems associated with immunodeficiency develop (Ishida et al., 1992). This asymptomatic period will generally last for years in most cases (Addie et al., 2000), but some cats will never develop FIV-related clinical signs in their lives. Clinical disease is therefore not seen until later in life – generally 4-6 years of age or older.

Immunodeficiency and/or immunostimulation most frequently appears in the form of chronic gingivostomatitis, chronic rhinitis,

lymphadenopathy, immune-mediated glomerulonephritis and weight loss.
Many concurrent viral (Brown et al., 1989), bacterial (Hughes et al., 1999), fungal (Schubach et al., 2003) and protozoal (Pennisi, 2002) infections have been reported in FIV-infected cats. Unusual clinical presentations, such as unusual or severe parasitic skin disease (e.g. demodecosis, pediculosis), or tumours should also alert the clinical to the possibility of FIV infection. B cell lymphosarcomas (Callanan et al., 1996), myeloproliferative disease and squamous cell carcinoma (Hutson et al., 1991) have been reported in association with FIV infection.

Because it impairs cats' life quality, feline chronic gingivostomatitis is one the most common presenting signs of FIV-infected cats (Tenorio et al., 1991).
As confirmed by experimental infections with neurovirulent strains, CNS involvement (Ryan et al., 2005) and peripheral neuropathy (Kennedy et al., 2004) are early subclinical events, often associated only with altered forebrain or peripheral nerve electrical activity. Behavioural changes, seizures, disrupted sleep patterns, impaired learning and paresis have also been reported (Phillips et al., 1996). Reproductive failure is described in infected cats and associated with PCR-positive placental and foetal tissues (Weaver et al., 2005). Renal involvement due to glomerular and tubulo-interstitial lesions associated with severe proteinuria is a frequent occurrence in FIV-infected cats (Poli et al., 1993). A direct role of FIV in the induction of the renal damage is possible (Poli et al., 1995a) together with that of renal immune deposits (Poli et al., 1995b). Polyclonal B cell activation actually sustains hyperglobulinaemia and a high level of circulating immune complexes (Matsumoto et al., 1997) and autoantibodies (Pennisi et al., 1994, Masucci et al., 2006).

Diagnosis

Virus isolation

A highly reliable method of diagnosis is virus isolation. Peripheral blood lymphocytes are prepared from fresh samples of heparinised blood and are co-cultivated with primary feline T cells for 2-3 weeks and the presence of virus in cultures is confirmed by measuring the levels of viral core proteins in the culture fluids. The procedure is laborious and is not used routinely.

Polymerase chain reaction (PCR)

Polymerase chain reaction (PCR)-based assays that detect proviral DNA, are available. However, it has been shown that such PCR tests are variable in performance and may in some cases be inferior to serological tests (Bienzle et al., 2004, Levy et al., 2004, MacDonald et al., 2004; EBM grade I), with sensitivities and specificities ranging from 40 to 100%; PCR assays currently available detect clade A viruses well, but the other strains more variably. Strain variation may also explain discrepant results when identical samples are sent to different labs (Crawford et al., 2005, Crawford and Levy, 2007). Discrepant results may also occur when serology and PCR are compared (seropositive, PCR negative), and may be explained by the presence of an FIV subtype not recognised by the PCR, rather than by the absence of FIV infection. This aspect is important when a cat may have been vaccinated against FIV. However, discrepant results (seronegative, PCR positive) may also be found: cats living in close contact with FIV-infected seropositive cats can become provirus positive without developing detectable levels of serum antibodies or disease (Dandekar et al., 1992). These cats are infected and in most cases will seroconvert weeks to months later.

Serology

Point of care (POC) FIV test kits detect antibodies recognizing viral structural proteins (such as the capsid protein p24 and a gp41 peptide) and may take the form of ELISA or immunochromatography tests. Western blotting is considered the "gold standard" for FIV

serology and is used to confirm questionable results. A negative FIV POC test result is reliable, although cats should be retested 2 months later if there is any possibility that infection could have occurred recently.

In-house tests based on ELISA detect anti-FIV antibodies and are based on p24 and the transmembrane antigen (communication from Idexx, March 2008). In contrast, immunochromatography tests only detect antibodies to short peptides corresponding to the transmembrane protein. In Western blots purified FIV is separated by gel electrophoresis into its constituent proteins. This allows the detection of antibodies to each individual FIV protein (Lutz et al., 1988a).

Both ELISA and immunochromatography tests are generally appropriate in most situations, but do have their limitations because the diagnostic specificity of the commonly used test is below 100% which is especially important in low prevalence populations and when healthy cats test positive: for example, an FIV prevalence of 1% results in one positive test per 100 cats and a diagnostic specificity of 99% also results in one false positive in the same 100 cats. This gives two positive results in 100 cats only one of which is correct (positive predictive value equal to only 50%). Any positive result in a low prevalence population (e.g. young, indoor, pure bred cats) must therefore be confirmed e.g. by Western blot. A positive result in a cat from a high-risk group (e.g. a free roaming, aged, entire male) is likely to be a true positive because the frequency of true positives will exceed the frequency of false positives in this population. In contrast, negative results in low prevalence populations are generally very accurate, with the following exceptions. False negative results may be obtained early in infection, when cats become provirus positive but remain seronegative for several weeks to months. In addition, false negative results may be also obtained in the terminal stages of disease due to immunodeficiency and when high viral titres may lead to sequestration of anti-FIV antibodies in virus-antibody complexes.

Kittens born to FIV-infected queens may test seropositive as a result of passively acquired maternal antibodies (MDA). In such cases, kittens should be retested after approximately 16 weeks of age, by which time in most cases levels of MDA will have declined to undetectable levels so that a positive result is indicative of FIV infection in the kitten. However in rare cases antibodies may persist up to six months (Levy et al., 2003). Therefore, a kitten testing seropositive at 16 weeks-of-age should be retested two months later. If it is still positive at six months it is infected. If an earlier result is required, PCR may be employed to detect virus negative kittens: in such cases, it is important that the queen is tested in parallel to ensure that the PCR can detect the infecting strain.

If a positive FIV antibody result is obtained using a POC test in a cat that might have been vaccinated recently, confirmation of infection using FIV PCR testing or virus isolation is recommended. Although there is no FIV vaccine licensed for use in Europe, and the vaccine is no longer available in US, a study conducted in Australia demonstrated that antibodies detected by POC tests can persist for up to 6 months post vaccination (Westman et al., 2016a). However, POC FIV antibody test kits accurately identified natural FIV infection in client-owned Australian cats when saliva was tested, irrespective of FIV vaccination history (Westman et al., 2017).

In research settings, it is possible to stage the level of immune dysfunction by determining the number of CD4+ and CD8+ lymphocytes (Litster et al., 2014). However, the complexity of these assays and the fact that in clinical situations pre-infection values are not available, means that such tests are often not clinically useful.

Disease management

Prognosis for FIV-infected cats

ABCD recommends that cats should never be euthanised just because of an FIV positive test result. It is generally accepted that FIV infection can induce clinical signs of immunodeficiency, leading to opportunistic infections or lymphomas, and clinical signs consistent with immunodeficiency in natural infection have been documented (Barrs et al., 2000). However, in some cats the clinical signs are mild, which likely reflects heterogeneity amongst both circulating field isolates as well as host factors, and it has been reported that many FIV-infected cats have an apparently normal life expectancy (Addie et al., 2000; Ravi et al., 2010; Liem et al., 2013). However, FIV-positive cats have a higher chance of developing clinical signs, mainly due to secondary infection, immune-mediated disease or neoplasia (Lutz et al., 1988b; Hosie et al., 1989; Lutz et al., 1990).

Therefore, surrogate markers are required to provide an objective assessment of FIV progression in individual cats. Recently it was shown that viruses dominating in early infection display a distinct receptor usage phenotype and that the emergence of viruses with an altered receptor usage phenotype coincides with the onset of immunodeficiency (Bęckzkowski et al., 2014). Accordingly, viral phenotyping may assist in the clinical staging of individual cats diagnosed with FIV infection.

The duration of asymptomatic stage varies according to the infecting variant (Pedersen et al., 2001). Based on experimental studies, cats infected at a younger age are more likely to progress to an immunodeficiency state (George et al., 1993; Podell at al., 1997; EBM grade III).

General management

To minimise a cat's risk of FIV infection, owners should consider limiting outdoor access or keeping their cat(s) exclusively indoors. Careful management is required when cats are first introduced to one another, as the potential for agonistic interactions that could result in FIV transmission is increased. Because of this, it is important to determine FIV status before cats are introduced to one another and then to observe interactions until the likelihood of aggression resulting in penetrating bite wounds is considered negligible. If there is a reasonable suspicion that such interactions will occur when cats are left unsupervised, FIV-positive and FIV-negative cats should be segregated.

Keeping FIV-infected cats in overcrowded conditions can have a significant impact on the risk of disease progression, particularly in cats which already have their immune systems compromised by FIV infection. In contrast, FIV-positive cats remained in relatively good health when living in stable, single cat households (Bęczkowski et al., 2015).

One of the most important preventative health measures is to protect the FIV-infected cat from other infections. In FIV infected cats, secondary infections may not only cause clinical signs but may also lead to progression of the FIV infection itself. Confining the cat indoors will help to avoid the risk of acquiring other infections through contact with neighbouring cats – as well as avoiding potential transmission of FIV. In some multicat households in which other infectious disease problems are endemic, consideration should be given to isolating FIV infected cats.

Asymptomatic FIV infected cats should be neutered. This will help to reduce aggression in male cats and the risk of transmission of infection. It will also help to reduce wandering and contact with neighbouring cats. FIV-infected cats should receive veterinary health checks at least every six months which should include monitoring of their weight. Periodic routine laboratory testing (haematology, biochemistry, urinalysis) should be considered. CD4 and CD8 monitoring to stage FIV infected cats is controversial and is neither generally available nor realistic in most practice situations.

Surgery is generally well tolerated by asymptomatic FIV-infected cats, but perioperative antibiotic administration should be used in all surgeries and dental procedures. FIV-infected cats can be housed in the same ward as other hospitalised patients; they should, however, be housed in individual cages. It should be considered that they may be immune-deficient and should be kept away from cats with other infectious diseases. Under no circumstances should they be placed in a "contagious ward" with cats suffering from infections such as viral respiratory disease.

Vaccination of FIV-infected cats

Whether or not FIV-infected cats should receive routine vaccination is a controversial subject. Experimental studies have shown that asymptomatic infected FIV-cats in early stages of infection develop a strong immune response following vaccination indicating that efficacy of vaccines is as good as would be expected in non-infected cats. However, it is not known if cats who have progressed to later stages of infection with immunodeficiency develop an adequate response to vaccination. On the other hand, safety concerns have been raised about vaccination in FIV-infected cats. First, immune stimulation related to the vaccine may lead to progression of FIV infection by altering the balance between immune system and virus. Stimulation of FIV- infected lymphocytes is also known to promote virus production *in vitro*. *In vivo*, vaccination of chronically infected FIV-infected cats with a synthetic peptide was associated with a decrease in the CD4/CD8 ratio. The potential benefits and risks of vaccinating FIV-infected cats should be weighed up in individual cats. In elderly indoor cats which have been vaccinated previously, the risk of acquiring infection is very low so booster vaccination is (probably) best avoided. In outdoor cats with risk of exposure to other infections vaccination is strongly advised. Although there is no scientific evidence that FIV-infected cats are at increased risk from modified life virus vaccines, inactivated vaccines are recommended whenever available as in immune-suppressed cats MLV vaccines may retain some pathogenic potential and cause clinical disease.

Supportive Treatment

Appropriate supportive treatment of FIV-infected cats relevant to presenting clinical signs should be instituted as early as possible. If FIV-infected cats are sick, prompt and accurate identification of the secondary illness is essential to allow early therapeutic intervention and a successful outcome of treatment. Therefore, more intensive diagnostic testing should proceed earlier in the course of illness than might be recommended for uninfected cats. Many cats with FIV infection respond as well as uninfected cats to appropriate medications although a longer or more aggressive course of therapy (e.g., antibiotics) may be needed.

Some clinicians report clinical benefits using corticosteroids and other immune suppressive drugs in FIV-infected cats with chronic stomatitis, but their use is controversial because of potential side effects. Griseofulvin has been shown to cause bone marrow suppression in FIV-infected cats and should not be used (Shelton et al., 1990). Filgastrim, granulocyte colony-stimulation factor, G-CSF, a cytokine that is on the market as recombinant human product (rHuG-CSF), have been used in FIV-infected cats with profound neutropenia but can increase neutrophil counts in cats with FIV infection (Phillips et al., 2005), but can also lead to a significant increase in virus load in peripheral blood mononuclear cells during treatment by enhancing infection of lymphocytes or increased expression of FIV by infected lymphocytes (Aral et al., 2000; EBM grade III).

Erythropoietin, EPO, is on the market as recombinant human product (rHuEPO) and is effectively used in cats with non-regenerative anaemia due to endogenous erythropoietin deficiency in chronic renal failure. FIV-infected cats treated with human erythropoietin (100 IU/kg SQ q48h) showed a gradual increase in red and white blood cell counts (Aral et al., 2000; EBM grade IV). No increase in virus loads was observed, and thus, human erythropoietin can be used safely in FIV-infected cats.

Insulin-like growth factor-1, IGF-1, is on the market as recombinant human product (rHuIGF-1) and, besides other actions, has the ability to induce thymic growth and to stimulate T-cell function. Treatment with human insulin-like growth factor-1 resulted in a significant increase in thymus size and thymic cortical regeneration replenishing the peripheral T cell pool in experimentally FIV-infected cats (Woo et al., 1999; EBM grade III). It could be considered in young FIV-infected cats as supportive

treatment, but there are no field studies so far to show its effect in naturally FIV-infected cats.

Antiviral therapy

Most antiviral drugs used in cats are licensed for humans and are specifically intended for treatment of HIV infection. Some of those can be used to treat FIV infection. However, many of the available drugs are toxic to cats or ineffective.

AZT (3'-azido-2',3'-dideoxythymidine) is a nucleoside analogue (thymidine derivative) that blocks the reverse transcriptase of retroviruses. It has been shown that AZT inhibits FIV virus replication *in vitro* and *in vivo*; it can reduce plasma virus load, improve the immunological and clinical status of FIV-infected cats, and increases quality of life. In a placebo-controlled trial, AZT improved stomatitis in naturally infected cats (Hartmann et al., 1995; EBM grade I). Dosage is 5-10 mg/kg q12h PO or SQ. The higher dose should be used carefully as side effects can develop. For SQ injection, the lyophilised product should be diluted in isotonic NaCl solution to prevent local irritation. For PO application, syrup or gelatine capsules (dosage/weight individually for every cat) can be given. During treatment, a CBC should be performed regularly (weekly for the first month) because non-regenerative anaemia is a common side effect especially if the higher dosage is used. If values are stable after the first month, a monthly check is sufficient. Cats with bone marrow suppression should not be treated. Studies in which FIV-infected cats were treated for two years showed that AZT is well tolerated. Some cats may develop a mild decrease of haematocrit initially in the first three weeks that resolves even if treatment is continued. If haematocrit drops below 20 %, discontinuation is recommended and anaemia usually resolves within a few days. Unfortunately, as in HIV, AZT-resistant mutants of FIV can arise as early as six months after initiation of treatment.

AMD3100, 1,1'-(1,4-phenylenebis(methylene))bis-1,4,8,11-tetraazacyclotetradecane octahydrochloride, JM3100, SID791, belongs to the new class of bicyclams that act as selective antagonists of the chemokine receptor CXCR4. CXCR4 is the main co-receptor for T-cell-line-adapted HIV strains, and blocking the CXCR4 receptor leads to inhibition of virus entry. FIV also uses CXCR4 for virus entry (Willett et al., 1997, Richardson et al., 1999, Egberink et al., 1999, Frey et al., 2001), and a high degree of homology exists between the human and feline CXCR4. AMD3100 is not licensed as antiviral compound but as a stem cell activator for patients that undergo bone marrow transplantation. It is effective against FIV *in vitro*, and in a placebo-controlled double-blind study in which 40 naturally FIV-infected cats were treated with AMD 3100 (0.5 mg/kg q12h SQ for 6 weeks), it caused a statistically significant improvement in clinical signs and decreased the proviral load in FIV-infected cats. Cats receiving AMD3100 did not show side effects (Hartmann et al., 2002; EBM grade I).

Feline interferon-ω was recently licensed for use in veterinary medicine in some European countries and Japan. Interferons are species-specific; therefore, feline interferon-ω can be used life-long without stimulating antibody development. No side effects have been reported in cats. Feline interferon-ω is active against FIV *in vitro* but so far, only one study has been performed in field cats that did not show significant changes in survival rate when compared to a placebo group (de Mari et al., 2004; EBM

grade I).
Human interferon-α has immune-modulatory effects, but also acts as a true antiviral compound by inducing a general antiviral state of cells that protects them against virus replication (Tompkins 1999). Two common treatment regimens exist for use of human interferon-α in cats, SQ injection of high-dose (104-106 IU/kg q24h) or PO application of low-dose (1 to 50 IU/kg q24h). When given SQ in high dosage, interferon-α leads to detectable serum levels. However, it becomes ineffective after three to seven weeks due to development of neutralizing antibodies (Zeidner et al., 1990). A placebo controlled clinical study using dose human interferon-a PO (10 IU/kg daily) prolonged CD4+ T cell survival (Pedretti et al., 2006; EBM grade III).

Immune modulators

Immune modulators or interferon inducers are widely used medications in FIV-infected cats. It has been suggested that these agents may benefit infected animals by restoring compromised immune function, thereby allowing the patient to control viral burden and recover from the disease. There is no conclusive evidence from controlled studies that immune modulators or alternative drugs have any beneficial effects on the health or survival of asymptomatic or symptomatic FIV-infected cats. A non-specific stimulation of the immune system might even be contraindicated in FIV infection as it can lead to an increase in virus replication caused by activation of latently infected lymphocytes and macrophages, and therefore can effect a progression of disease. Hence, unspecific immune modulators with unknown effects should not be used in FIV-infected cats.

Vaccination

At present there is no FIV vaccine available commercially in Europe. Experimentally, vaccine-induced protection against FIV infection has been achieved in cats using several immunogens, including inactivated virus or inactivated infected cell vaccines, canarypox-based vaccines in combination with inactivated cells and DNA vaccines (Hosie and Beatty, 2007). Of these vaccines, the most successful to date have been whole inactivated virus vaccines (WIV) preparations; one such vaccine was made available commercially to veterinarians in the USA in 2002 and in Australia and New Zealand in 2004. However, the vaccine is no longer available in USA.

However, the efficacy of the vaccine has not been tested against a range of European field isolates. In one experimental study, vaccination was shown not to protect cats against a virulent UK primary isolate of FIV (Dunham et al., 2006; EBM grade III) and it is likely that imported vaccinated cats might not be protected against natural challenge with European FIV isolates. Furthermore, a recent Australian study raised doubts concerning the efficacy of Fel-O-Vax FIV under field conditions, with a vaccine protective rate of only 56% (Westman et al., 2016b). Vaccination did not significantly reduce the risk of client-owned cats becoming infected with FIV.

ABCD does not recommend the use of the whole inactivated virus vaccine available outside Europe, given the problems associated with serological diagnosis of infections and lack of evidence of efficacy against naturally occurring field isolates.

Control in specific situations

Multi-cat households

A number of factors can influence the risk of transmission of FIV between cats within a household, for example the strain of virus and/or the saliva virus load. In most situations, the risk of transmission is

low in households with socially well-adapted structures. If a cat is diagnosed with a FIV infection d, all cats in that household should be tested to determine their status. FIV is mainly transmitted through biting and fighting, and if no fights occur due to the stability of social structures, FIV will probably not be transmitted. In follow-up studies of households with FIV-infected cats, few additional cats became FIV-positive over time; some households exist in which no transmission has occurred over many years. It is advisable that all cats in these households be neutered, and it is crucial not to introduce new cats, as this might lead to fights and hence transmission may occur, even between cats that have lived peacefully together for a long time.
However, if other infectious diseases are present they may be spread between cats and the risk of transmission may be higher. Therefore in that situation consideration should be given to isolating infected individuals to avoid spread of infection

Shelters

FIV is an important consideration in rescue shelters. A high prevalence of infection is found in this population of cats, particularly those with a feral background and if male and entire. The prevalence of infection may not be significantly higher in pre-owned cats that have recently been relinquished compared to the local household pet cat population, but may be higher if it is a stray cat.

ABCD panel recommends all cats should be tested, but as an absolute minimum all sick cats should be tested for FIV and euthanasia should be considered for positive cats in which the clinical problems significantly affecting their quality of life are suspected to be related to an advanced stage of FIV infection.

Serological tests cannot be used to reliably identify infected kittens under 6 months of age. A positive result does not confirm that the kitten is infected (see diagnosis section) and we strongly emphasise that this is not an indication for euthanasia. In this situation, PCR may be considered, although it has potential limitations.

ABCD recommends that rescue shelters should house cats individually (unless from the same household) to avoid the possibility of cross infection, but as an absolute minimum FIV positive cats should be segregated from FIV negative cats.

Some shelters will home FIV positive healthy cats to selected adopters (in situations where risk of infection to other cats is minimal) but this requires careful counselling.

Breeding catteries

FIV is rare in breeding catteries because usually the cats are kept indoors and are tested annually. New cats should be FIV tested before being introduced and cat breeders, either using a stud belonging to another person or allowing a queen to visit their stud, should require proof of FIV negative status. Cats which have escaped and returned should be quarantined for 3 months, then FIV tested and only returned to their group if found to test negative.

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