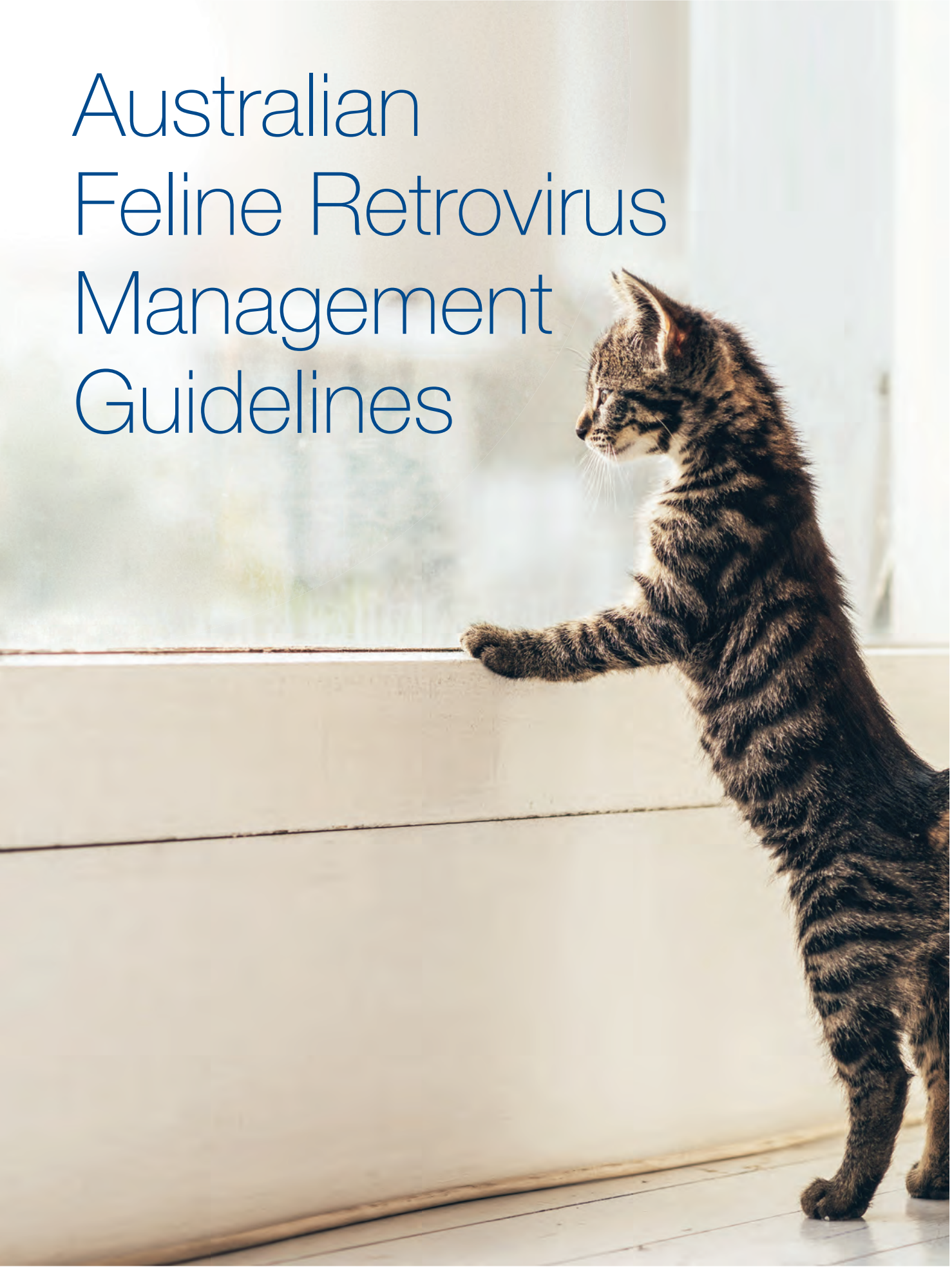
Australian Feline Retrovirus Management Guidelines



Part 1: Feline Immunodeficiency Virus (FIV)

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Contents

Australian Feline Retrovirus Advisory Panel members

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Panel Chairperson – Dr Mark Westman

BVSc (Hons) PhD MANZCVS (Animal Welfare) GradCertEdStud (Higher Ed)

Mark has a history working in shelter medicine with many animal charities and rescue organisations. After working as a clinical veterinarian for 10 years, he completed a PhD in feline retroviruses at The University of Sydney and postdoctoral research at the Centre For Virus Research, University of Glasgow. Mark maintains an active research interest in small animal infectious diseases and was a member of the 2020 AAFP/AAHA feline vaccination guidelines panel. He also co-founded Pets in the Park, Australia's largest charity dedicated to providing veterinary care to pets owned by the homeless.

Dr Sally Coggins

BVSc (Hons I) MANZCVS (Feline Medicine)

Soon after graduating, Sally completed the Feline Medicine course with the Centre for Veterinary Education (CVE) and then spent a decade at The Cat Clinic in Prahran (Melbourne) where she became a partner and director. After becoming a member of the Feline Medicine chapter, Sally served as an examiner for the ANZCVS from 2016-2018. Sally is currently conducting a PhD in therapeutic options for feline infectious peritonitis, works as a feline-only clinician at Gordon Veterinary Hospital in NSW and is a tutor both for DVM students at The University of Sydney and for CVE's Feline Medicine course.

Dr Moira van Dorsselaer

BVSc

Moira is the principal vet and owner of The Cat Clinic Hobart. She graduated from the University of Queensland before moving to Hobart, spending the first 12 years of her career as a small animal veterinarian seeing both cats and dogs. Recognising the need for a feline only practice, Moira set up The Cat Clinic Hobart in 2013. The practice has since grown in size and successfully achieved ISFM gold standard accreditation. Moira is passionate about providing excellent care for the cats of Hobart, and enjoys dentistry, sonography, and surgery.

Professor Richard Malik

DVSc DipVetAn MVetClinStud PhD FACVSc FASM

Richard Malik is a respected and well known feline clinician. As well as being a registered small animal medicine specialist, Richard has a PhD in neuropharmacology and maintains a steady research output, mainly as a result of young productive PhD and honours students. He is passionate about all aspects of feline medicine and has a special focus on treating common diseases using new therapeutic regimens. Currently Richard works as a consultant for CVE and practices at several veterinary hospitals in NSW. He lives on a farm in the Southern Highlands of NSW and helps run a brumby sanctuary.

Professor Jacqueline Norris

BVSc MVSt PhD FASM MASID GradCertEdStud (Higher Ed). RCVS (Veterinary Microbiology)

Jacqui Norris is a Professor of Veterinary Microbiology and Infectious Diseases at The University of Sydney and is a specialist in veterinary microbiology through the UK's RCVS. She is passionate about practical research projects and education programs for veterinary professionals, animal breeders and animal owners. Jacqui is the one of the founding members of the antimicrobial resistance (AMR) Vet Collective (www.amrvetcollective.com). She continues active research in a number of fields including companion animal viral diseases, multidrug resistant bacterial infections, AMR stewardship and chronic kidney diseases in all felids.

Associate Professor Richard Squires

BVSc (Hons) PhD DVR DipACVIM DipECVIM-CA, GCertEd

Richard Squires is a Diplomate of both the American and European Colleges of Veterinary Internal Medicine and holds the Royal College of Veterinary Surgeons' Diploma of Radiology. Richard currently leads the veterinary clinical sciences team at James Cook University in Townsville. Much of Richard's research has been on canine and feline infectious diseases. He was a member of the World Small Animal Veterinary Association's (WSAVA) Scientific Advisory Committee from 2008 – 2019, has been a member of the WSAVA Vaccination Guidelines Group since 2010 and recently became chair of that committee.

Associate Professor Mary Thompson

BVSc (Hons) PhD DACVIM MANZCVS FHEA

Mary is an Associate Professor in Small Animal Medicine at The University of Sydney. Mary has spent the last 16 years working in clinical academic roles at The University of Queensland, where she completed her PhD, and more recently (2015-2020) at Murdoch University. Her major areas of clinical and research interest are bacterial urinary tract infection/colonisation and infectious disease of cats and dogs and she greatly enjoys working with veterinary students in the final years of their studies.

Introduction

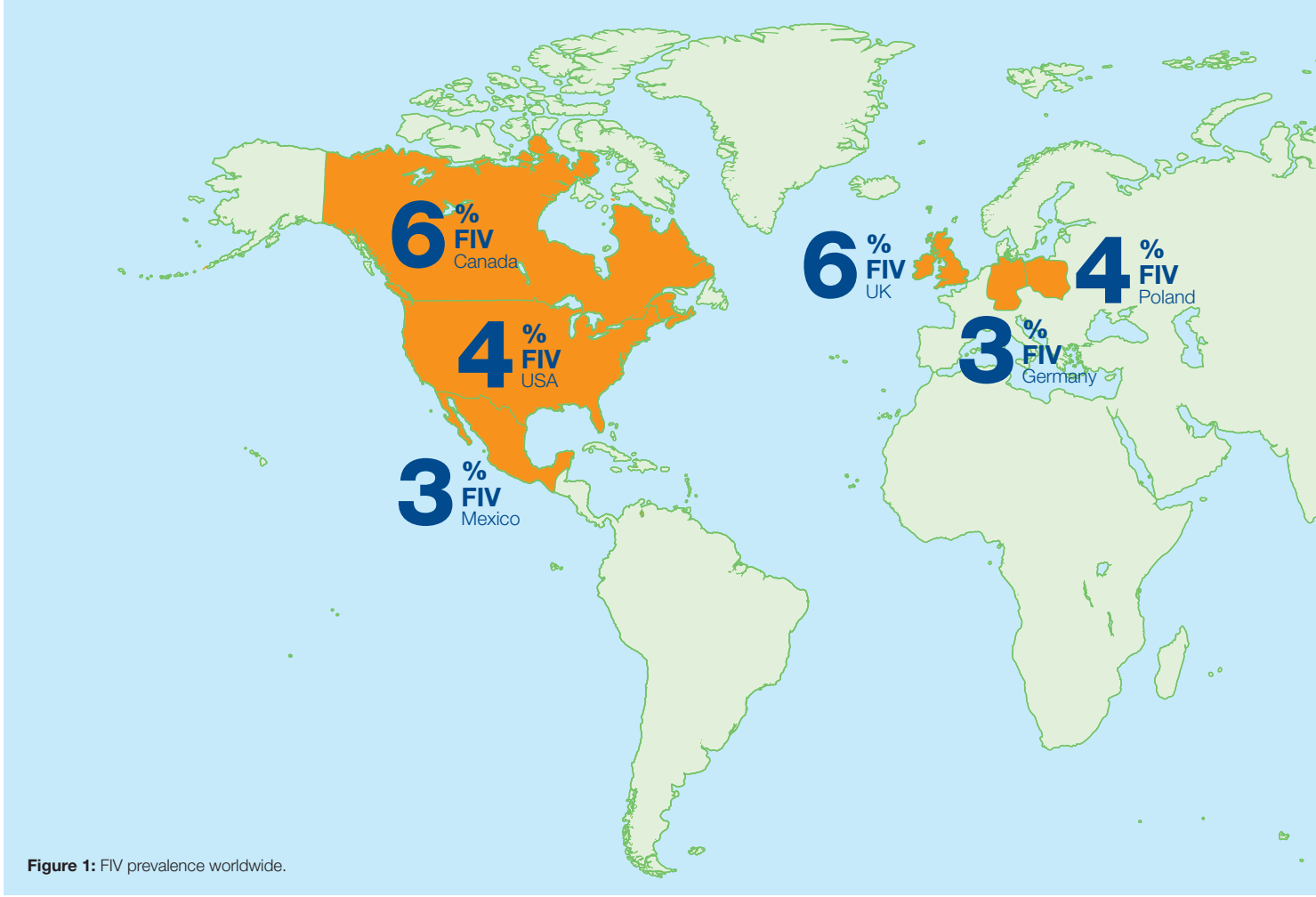


Figure 1: FIV prevalence worldwide.

Introduction

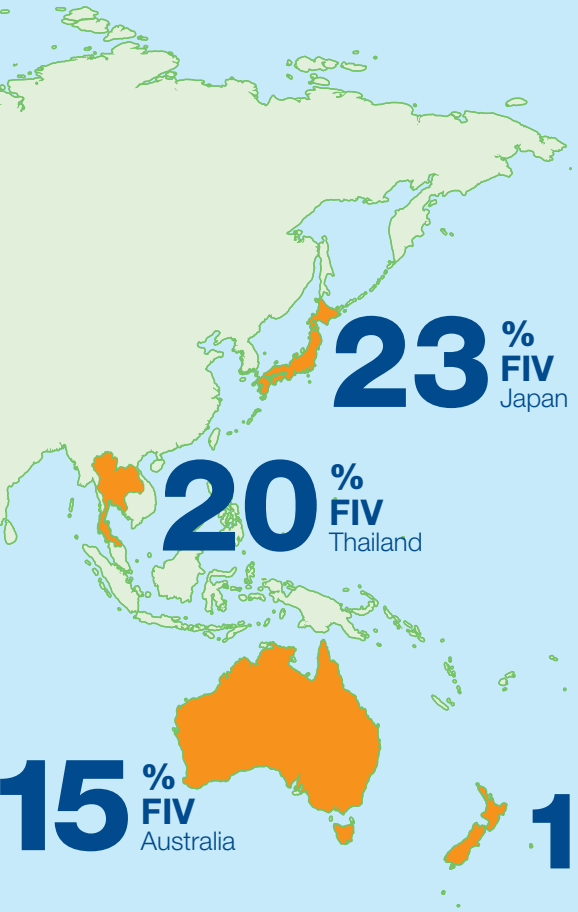
Feline immunodeficiency virus (FIV) is a lentivirus with many similarities to human immunodeficiency virus (HIV). A critical difference between FIV-associated disease in cats versus HIV-associated disease in humans stems from the length of time that cats have lived with FIV. While humans are believed to have first been infected with HIV a little over 100 years ago, cats and FIV have co-evolved for 10-20,000 years, such that viral virulence has been reduced substantially over time[1].

Seven subtypes (or clades) of FIV (A, B, C, D, E, F and U-NZenv) have been identified based on nucleotide sequence differences[2-7]. These differences may impact disease associations, virulence and protection offered by vaccination.

FIV transmission primarily occurs via bite wounds that introduce saliva containing virus and FIV-infected white blood cells[9]. Therefore, male cats, especially sexually intact male cats, have the highest FIV infection prevalence [10, 11]. Indeed, the overall prevalence of FIV in a given environment depends on the density of free-roaming tom cats. Infection can also occur iatrogenically through inoculation with infected blood or saliva, such as via blood transfusions, inadequate sterilisation of dental and surgical equipment, and by breaches in aseptic technique when using multi-dose vials. Kittens can also acquire FIV from their mothers, although anecdotally, this seems a less important route in Australia.

Australia, like Japan and Thailand, has a high prevalence of FIV compared to most countries, possibly because many owners permit cats to live outdoors and populations of feral cats persist in many locations[10-14]. One survey revealed that 83% of cats in Australia and New Zealand currently have, or have had, some level of access to the outdoors[15]. As a generalisation, in Australia, FIV is uncommon in well-run catteries, although endemic FIV can emerge in poorly run catteries or shelters.

In the first weeks following experimental inoculation, FIV infection is associated with transient fever, lymphadenomegaly and lymphopenia, known as the primary phase of FIV infection. During this acute phase, FIV can easily be detected in blood with PCR testing. A sharp decline in lymphocyte populations, particularly CD4+ T lymphocytes, also occurs.



The prevalence of FIV in Australian cats is one of the highest in the world.

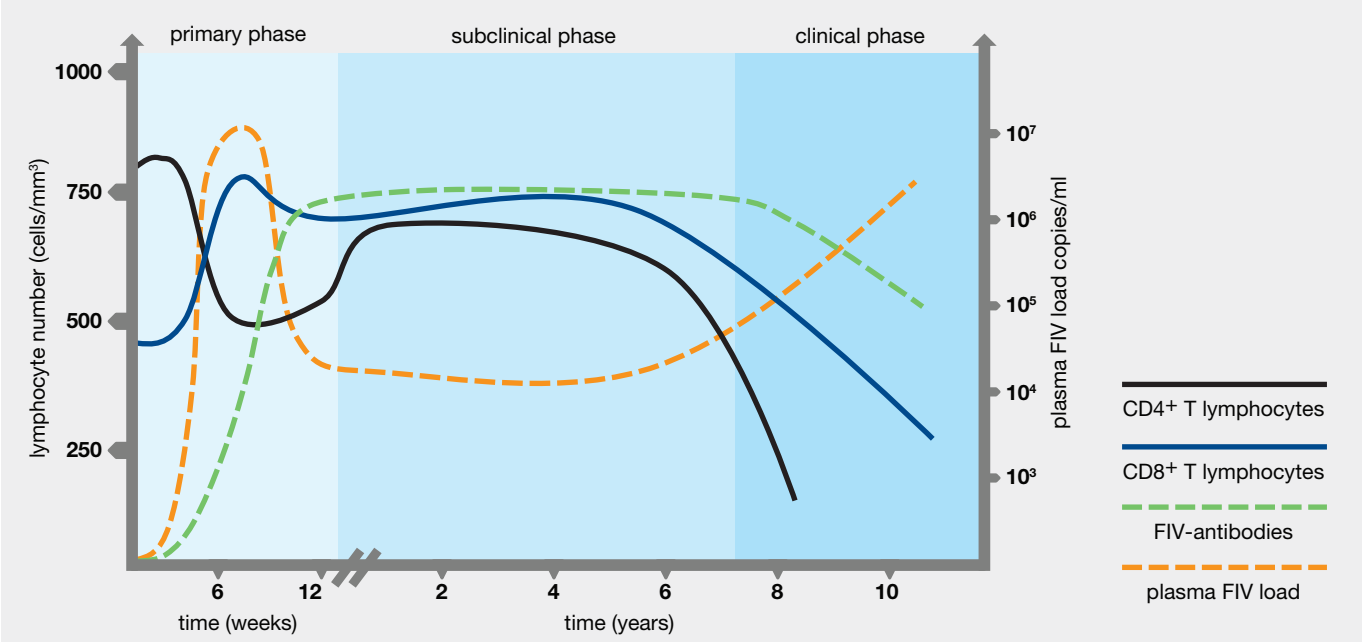


Figure 2: Changes in the levels of FIV antibody, virus and CD4+/CD8+ T lymphocyte counts, during the different phases of FIV infection in cats. The x-axis shows the timescale in weeks for the primary phase, and in years for the subclinical and clinical phases. The left y-axis shows CD4+ and CD8+ T lymphocyte numbers (cells/mm³). The right y-axis shows the plasma viral load. Figure kindly supplied by Dr Navapon Techakriengkrai, Department of Veterinary Microbiology, Faculty of Veterinary Science, Chulalongkorn University, Thailand.

Following the primary phase of FIV disease, cats enter a long subclinical phase that can last for many years. The beginning of the subclinical phase sees the production of FIV antibodies and suppression of circulating virus, resulting in a vastly reduced viral load, or even an undetectably low viral load in some cases (PCR false-negative; see later). CD8+ T lymphocyte levels also increase, which, combined with the dropping CD4+ T lymphocytes, produces an inversion of the CD4+:CD8+ ratio early in the subclinical phase. This inversion of the CD4+:CD8+ ratio persists for life, and can sometimes be useful in staging FIV disease.

It is important to stress to owners that FIV is not a death sentence and does not constitute grounds for euthanasia.

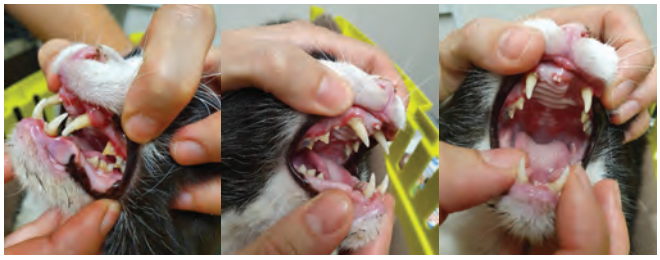


Figure 3: Gingivostomatitis is a common finding in FIV-infected cats. Images kindly provided by Dr Tessa Clark.

Over time, the general trend with FIV infection is that both CD4+ (helper) and CD8+ (cytotoxic) lymphocyte numbers gradually decline (Figure 2), causing progressive dysfunction of the immune system until cats enter the clinical phase of FIV infection. During this third phase, FIV-infected cats are predisposed to chronic and recurrent infections of various types. Gingivostomatitis is often present and is classically more severe and refractory to treatment than in FIV-negative cats.

Top tip

We can monitor CD4+ and CD8+ lymphocytes in Australia: At the time of writing quantification of lymphocyte subsets by flow cytometry is available only from Vetnostics and partner laboratories (QML, ASAP). Testing to determine CD4+ and CD8+ numbers, the CD4+:CD8+ ratio and a panleukocyte marker for gating purposes currently costs $90.00 excluding GST (George Reppas, Vetnostics, *per comm* 26/2/2021).

In people with HIV infection, the marked decline in CD4+ cell numbers results in profound immunodeficiency and the development of opportunistic infections, often sequentially. Although chronic inflammatory conditions and secondary infections can occur in cats with low CD4+ cell counts, the classic opportunistic infections seen in HIV patients (cryptococcosis, *Pneumocystis* pneumonia and *Mycobacterium avium* complex infections) are rarely diagnosed in FIV-positive cats. Many cats appear to be able to cope with CD4+ cytopenia and remain free of serious infections. Instead, the most important long-term impact of FIV infection is the development of neoplasia, typically B cell lymphoblastic lymphoma in the intestine, abdominal lymph nodes or kidneys, although lymphomagenesis usually does not occur until many years after the primary phase of FIV infection. Leukaemia/lymphoma is about 6-times more likely in FIV-infected cats than in FIV-negative cats.

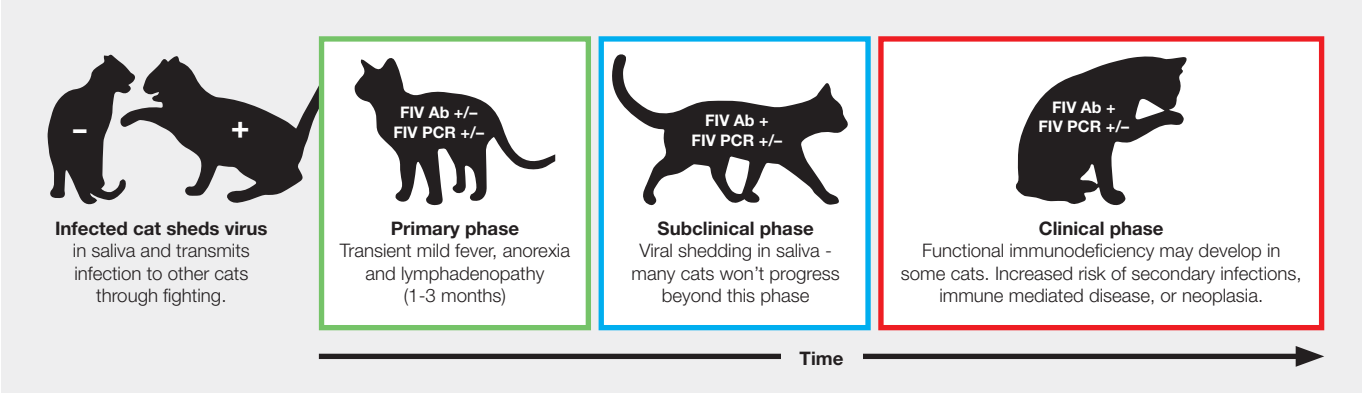


Figure 4: The three phases of FIV infection in cats[16]. Adapted from 2020 AAFP Feline Retrovirus Testing and Management Guidelines.

Cellular immunity (mediated by T lymphocytes) is more profoundly affected by longstanding FIV infection than humoral immunity (antibody-mediated, produced by B lymphocytes). Hyperglobulinaemia, reflecting nonspecific stimulation of humoral immunity, occurs in some cats. Survival time of FIV-infected cats is highly variable and in some studies of naturally infected cats it has been similar to that of FIV-uninfected cats. FIV subtype, co-infections, feline genomics and stress likely impact on disease development, but our current understanding is that FIV infection in some cats can have devastating health impacts. Other FIV-infected cats can live a relatively normal life for a protracted period, with a near-normal lifespan. This is a confusing concept to convey to colleagues and owners[12].

One study in the USA found that many FIV-infected cats housed in a high-stress, large multi-cat household died of diseases consistent with severe immunodeficiency, most commonly lymphoma.

Conversely, in the same study, FIV-infected cats housed in small, low-stress groups mostly remained healthy for the duration of the 22-month study[8].

These results emphasised the importance of management and housing conditions on the outcomes of FIV infection. FIV infection is not a death sentence and does not constitute grounds for euthanasia.

Studies on the impact of FIV disease rarely document the date of initial infection, nor the subtype involved, so unravelling the actual impact of FIV from retrospective data sets is problematic. Therefore, it is often not clear if cats with FIV infection have had the infection for a short time, a moderate period, or for many years – and grouping such cats into the single category of 'FIV-infected' and drawing broad conclusions is misleading. Further problems facing veterinarians are that prospective studies of natural FIV infection are exceedingly rare, and experimental FIV infection studies in laboratory cats usually only last for 6-7 years, and therefore are not a true reflection of what happens in nature.

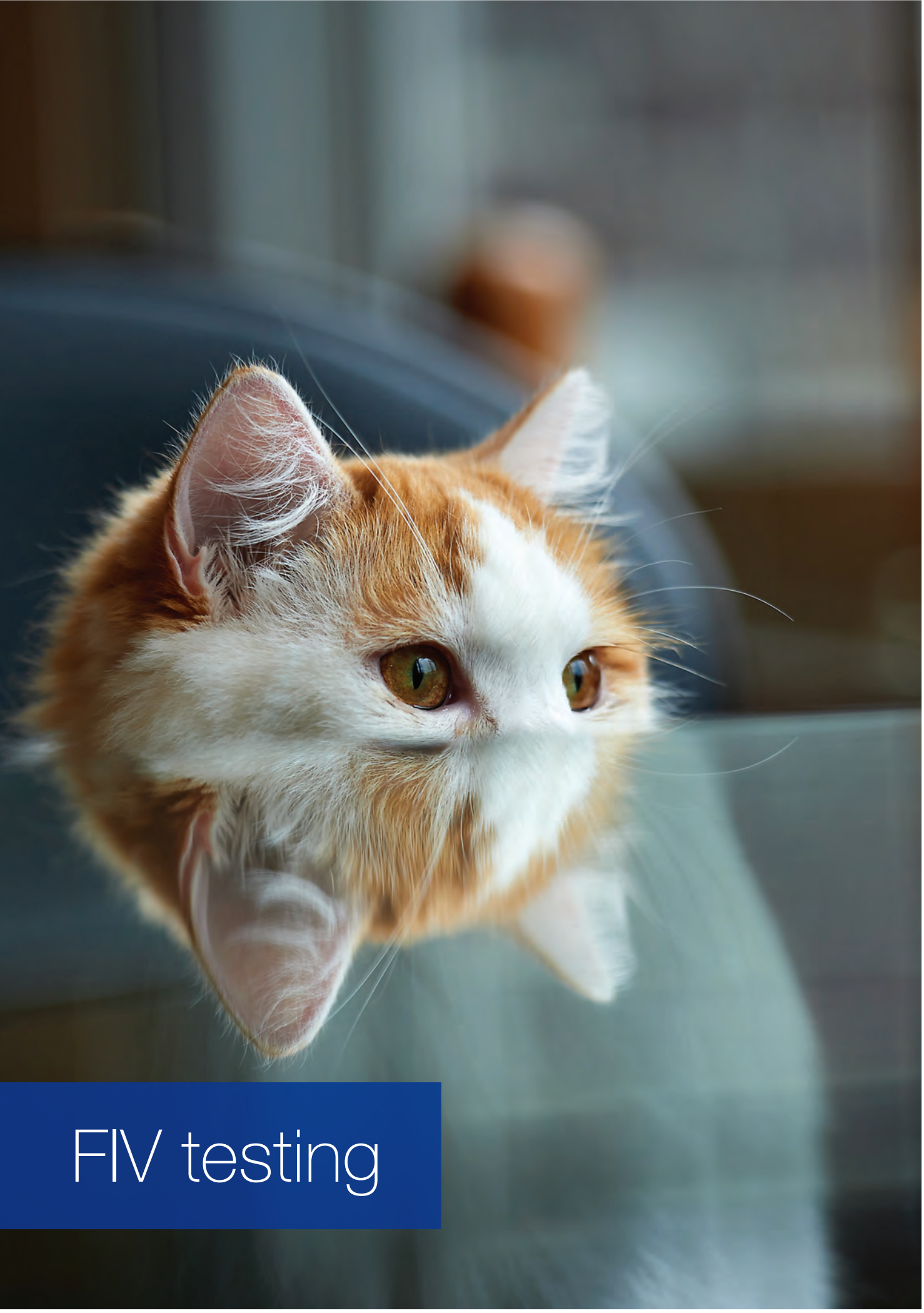
Executive summary

Despite the passage of over 30 years since its discovery, the importance of FIV infection on health and longevity is hotly debated amongst feline experts.

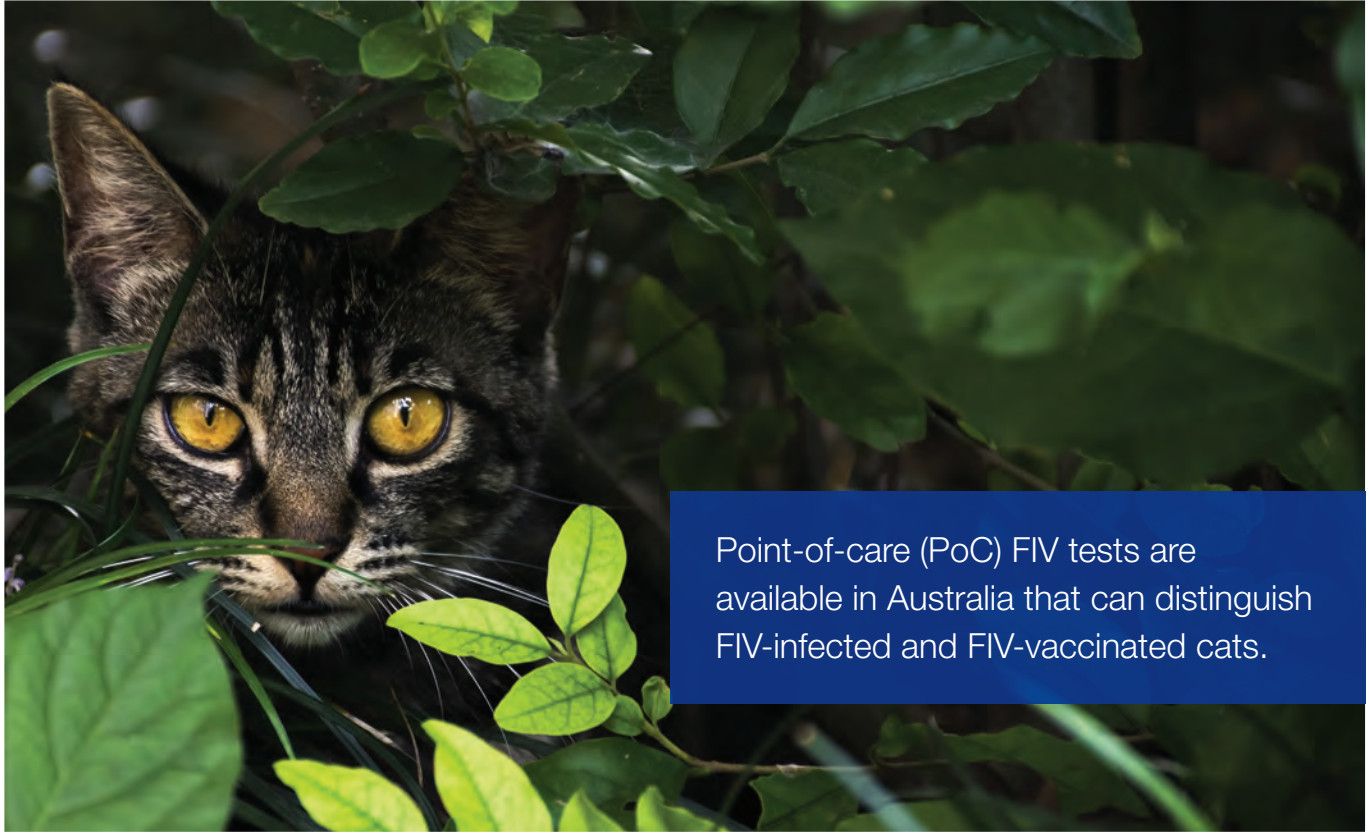
Even in the absence of good quality information, Australian veterinarians should aim to minimise the exposure of cats to FIV.

The most reliable way to achieve this is to recommend that all cats are kept exclusively indoors, or with secure outdoor access (e.g. cat enclosures, secure gardens – see later), with FIV testing of any in-contact cats.

Australia is one of the few countries where a polyvalent FIV vaccine is available to prevent infection, offering a further avenue for disease prevention.



FIV testing



Point-of-care (PoC) FIV tests are available in Australia that can distinguish FIV-infected and FIV-vaccinated cats.

PoC FIV tests using whole blood

Determining an individual cat's FIV status is useful in assisting with patient management and in managing the risk of FIV transmission to uninfected cats.

The Panel recommends minimising stress associated with FIV testing, and consequently the use of saliva or ear/pad prick bleeding are discussed below as alternatives to jugular, saphenous or cephalic venepuncture, even though such testing is not recommended by the test kit manufacturers (figures 7-9).

No FIV test is perfect (i.e. 100% specific and 100% sensitive), therefore follow-up ('confirmatory') FIV testing is recommended for all FIV-positive test results, since a diagnosis of FIV infection may result in management changes and/or euthanasia in a shelter setting.

Choice of FIV antibody test kit (blood): A variety of FIV antibody test kits are available commercially in Australia. The Panel recommends that Australian clinicians use test kits that have been independently validated under Australian conditions, and to exercise caution when using kits that have not been rigorously tested by independent researchers.

Figure 5: Anigen Rapid™ (top) and Witness™ (bottom left) PoC kits have an advantage over SNAP Combo™ kits (bottom right) in testing FIV-vaccinated cats or when vaccination status is unknown.

Top tip

Blood collection for FIV testing: The Panel recommends low-stress handling (e.g. towel wraps for gentle restraint) and the use of EMLA™ cream on clipped skin 30 minutes before sampling. If necessary, use sedation.

In FIV-unvaccinated cats, three FIV test kits currently available in Australia have shown good sensitivity (Se) and specificity (Sp) under Australian conditions in an independent study: Anigen Rapid™ (Se 100%, Sp 100%), Witness™ (Se 100%, Sp 100%) and SNAP Combo™ (Se 100%, Sp 97%)[17].

In FIV-vaccinated cats, or when the FIV vaccination status of cats is unknown, the choice of FIV antibody test kit is more limited. To date, only two test kits, Anigen Rapid™ and Witness™, have demonstrated the ability to distinguish antibodies produced in FIV-vaccinated cats (cats test negative, unless FIV-infected) and FIV-infected cats (cats test positive). In a cohort of FIV-vaccinated cats in Australia, the Se/Sp of each kit was 100%/95% (Witness™), and 100%/100% (Anigen Rapid™)[17]. SNAP Combo™ cannot differentiate FIV-vaccinated and FIV-infected cats, with both groups testing FIV-positive with this kit[17-19]. At the time of writing, IDEXX Laboratories (manufacturer of the SNAP Combo™ kit) offers free PCR confirmation of positive FIV SNAP Combo™ test results. Therefore, Anigen Rapid™ and Witness™ kits have an advantage if an immediate PoC result is required for FIV testing of cats with a history of FIV vaccination or an unknown vaccine history. Testing a cat with an unknown vaccine history using a SNAP Combo™ kit, followed by confirmatory FIV PCR testing at the laboratory if positive, is similarly accurate to using an Anigen Rapid™ or Witness™ kit, although PCR results may take several days, and it is important to remember that some FIV-infected cats may test PCR negative during the subclinical phase of infection (see page 14 for discussion on PCR testing).

Anigen Rapid™ and Witness™ FIV kits are reliable to use in cats that have recently been given an annual FIV vaccination. However, both kits should be used with caution in kittens and cats that have recently (< 6 months) been given a primary course of three FIV vaccines, with a false-positive rate of up to 67% reported two weeks after the second primary FIV vaccine dose[18]. If FIV testing is required during this period, confirmatory FIV PCR testing is recommended in cats that test positive with an Anigen Rapid™ and Witness™ kit. SNAP Combo™ kits should never be used in any FIV-vaccinated cats, irrespective of how recently a primary or annual FIV vaccination has been administered.

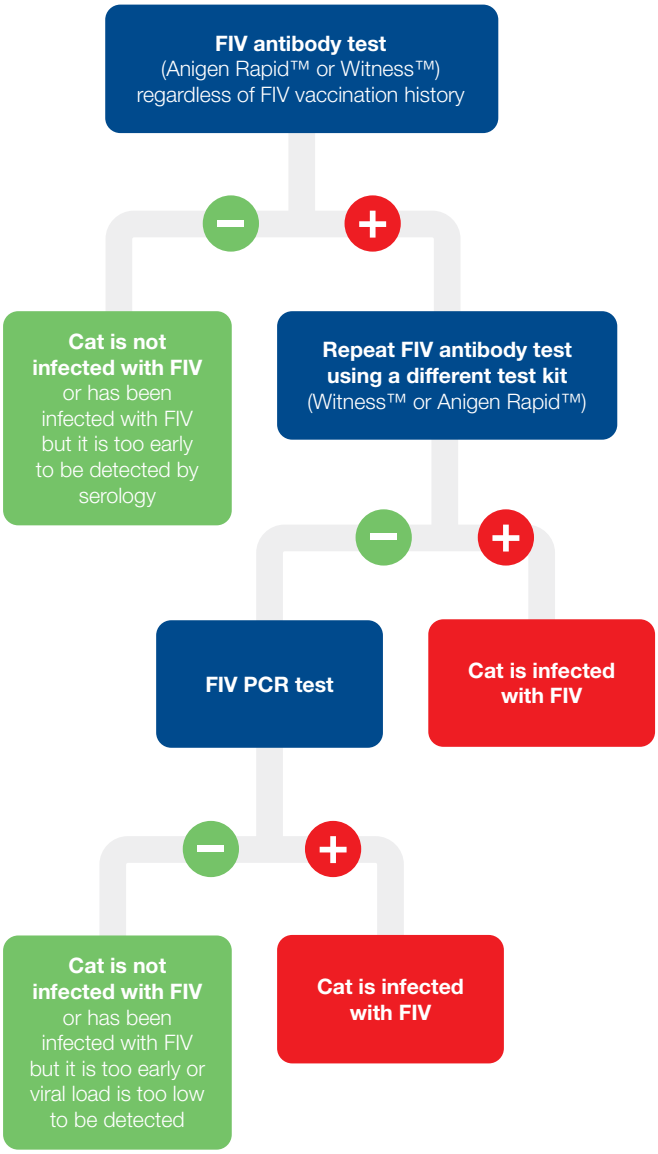


Figure 6: Suggested decision algorithm for diagnosis of FIV infection, using blood as the diagnostic specimen. Taken from Westman et al. (2015)[17].

Figure 7: Foot pad bleeding for FIV testing.

The patient is held gently in whatever way is most comfortable for the cat. Both metacarpal (A-C) and metatarsal foot pads (D) can be used, depending on which is less stressful for the patient. A lancet device is used to obtain a capillary blood sample by puncturing the skin of the foot pad. Most lancet devices allow for selection of the depth of penetration, and in the case of foot pad collection a slightly deeper penetration is usually required. After lancing, the foot pad is squeezed gently to produce a drop of blood that is placed directly onto the PoC test strip. The test is then performed as per the manufacturer's instructions, using the recommended amount of buffer. This method of capillary blood sampling is well tolerated when the patient is gently restrained in a position that they prefer. Distracting the cat during sample collection with patting or treats is usually all that is required, with most cats barely aware of the sample being taken.

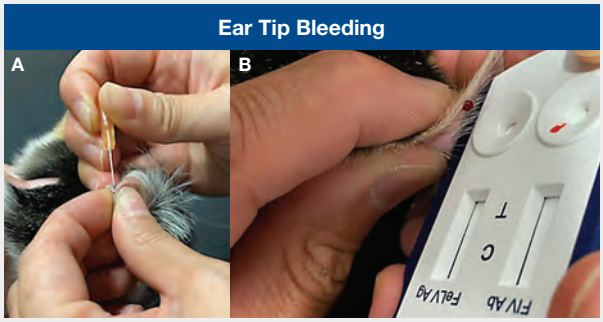


Figure 8: Ear tip bleeding for FIV testing.

A procedure for ear tip bleeding for FIV testing has been adapted from ear prick sampling for blood glucose testing. Ideally, a vein on the dorsal (outside) surface of the pinna is used for sampling; alternatively, if a vein is unable to be visualised (e.g. dark-coloured cats), the medial (inside) surface of the pinna can be used (A). The pinna should be massaged prior to sampling to encourage blood flow to the tip of the pinna. The skin is pricked with a 25g needle, and a drop of blood squeezed directly onto the test kit strip (B). Gentle compression of the puncture site afterwards will result in the bleeding stopping. Fractious cats can be gently restrained using a towel wrap while sampling is performed. Images kindly provided by Dr Jeffrey So.

PoC FIV tests using saliva

Although testing of whole blood, serum or plasma remains the gold standard for FIV diagnosis, the Panel that believes saliva testing for FIV antibodies using Anigen Rapid™ kits offers a welfare-friendly alternative to blood testing.

Saliva testing in a clinic or shelter setting is often easier to perform than blood testing, and is also less stressful for the cat, its owner and staff member(s) performing the test. In particular, testing with saliva is beneficial in kittens and in shelters where staff need not be trained in venepuncture. Conversely, some cats actually tolerate blood sampling better than saliva sampling, due to the unusual sensation of a dry cotton tip on the gums, and in these instances blood sampling should be pursued (e.g. blood collection from the ear tip or foot pad).

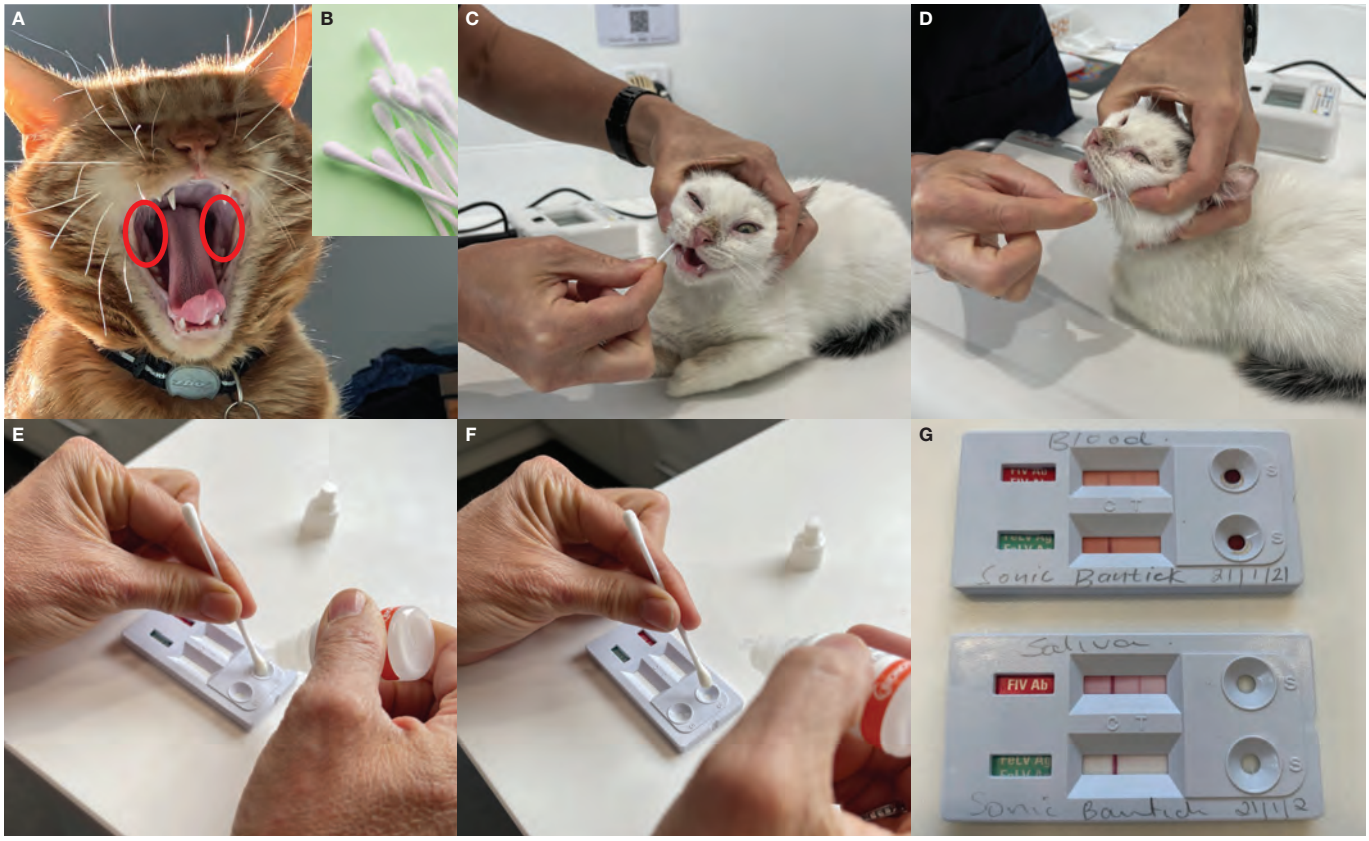
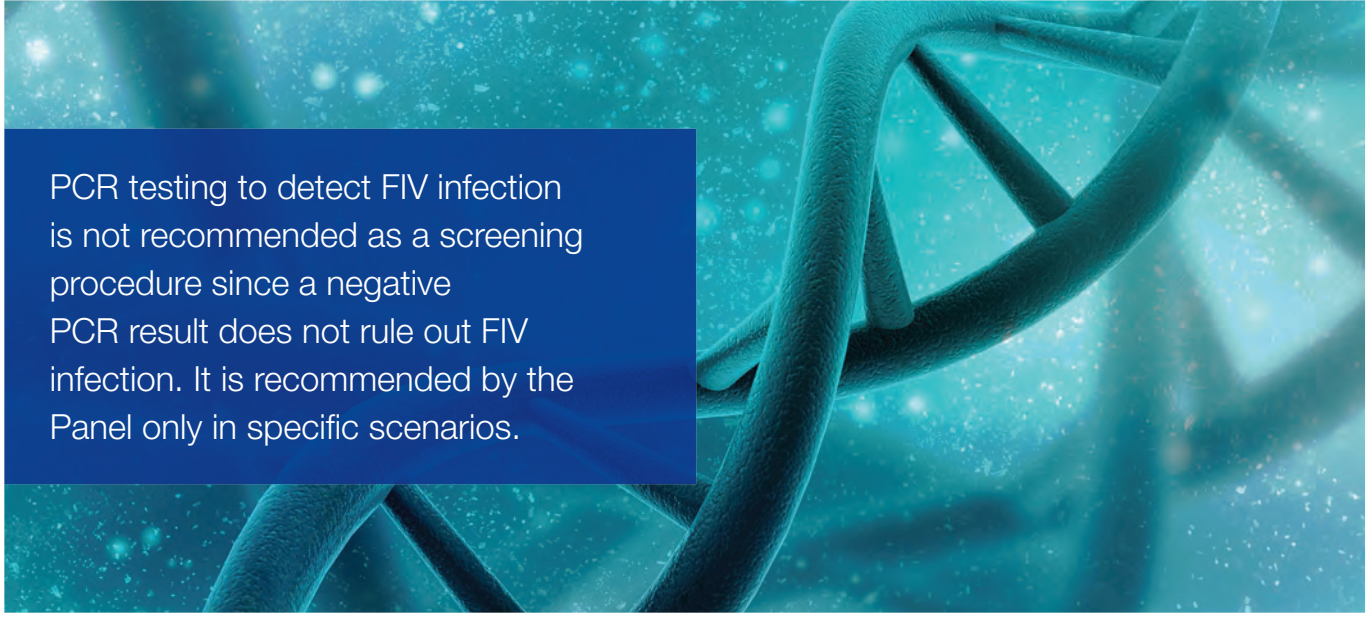


Figure 9: Saliva testing procedure: Anigen Rapid™ PoC testing using blood or saliva as the diagnostic specimen. Saliva is collected from the caudal oral mucosa (A) (circled in red) using a clean cotton tip (B). The patient is held gently around the head so that the swab can be moved around freely to collect saliva (C) and (D). The swab is then held in the sample well and gently blotted while double the recommended test diluent is dropped onto the cotton tip of the swab (E) and (F). A result is read after 10 minutes, as per the manufacturer's instructions for blood testing (G). The top test strip in both Anigen Rapid™ kits pictured is the FIV result (two lines = positive), while the bottom strip is the FeLV result (one line = negative).



PCR testing to detect FIV infection is not recommended as a screening procedure since a negative PCR result does not rule out FIV infection. It is recommended by the Panel only in specific scenarios.

In one study, 14 FIV-infected cats (including 10 FIV-unvaccinated and 4 FIV-vaccinated cats) were tested with Anigen Rapid™, Witness™ and SNAP Combo™ kits using saliva instead of whole blood. The Anigen Rapid™ PoC kit performed superiorly to the other kits (14/14 correctly diagnosed as FIV-positive, i.e. 100% Se)[20].

Our experience is that although cats resent the cotton swab, they tolerate it. We repeat the saliva collection process a couple of times to ensure that the swab has sufficient sample on it, giving the cat a break between samplings.

The saliva-laden swab is held in the sample well of the Anigen Rapid™ PoC test kit while the diluent is dropped onto the cotton tip of the swab. We double the dose of diluent (i.e. 4 drops instead of 2 drops), then the swab is blotted in the well until the fluid begins to move across the test strip. The process is repeated for the feline leukaemia virus (FeLV) antigen test with a separate swab and saliva sample. The result is read after 10 minutes, as per the manufacturer's instructions for blood testing.

Note: None of the FIV antibody kit manufacturers endorse using saliva instead of blood as a diagnostic specimen.

FIV PCR testing

The Panel does not recommend FIV PCR testing as a screening or as a confirmatory diagnostic tool in FIV-unvaccinated cats.

PCR testing detects proviral DNA (FIV DNA inserted into the cat's genome), as well as viral RNA if a reverse-transcriptase (RT) step is performed as part of the PCR assay. In Australia, the commercially available FIV RealPCR™ (offered by IDEXX Laboratories) has a published Se and Sp in an independent study of 92% and 99%, respectively[17], and includes a RT step to amplify both DNA and RNA in testing. However, FIV-infected cats have low levels of both proviral DNA and viral RNA during the long subclinical phase of infection, thus even though PCR testing is able to detect very low levels of DNA/RNA, it may still fail to detect infection (i.e. produce a false-negative result in FIV-infected cats) (Figure 2).

In contrast, FIV antibodies usually rise to detectably high levels within 8 weeks of infection and remain high until the clinical phase of FIV infection. Even during the clinical phase of FIV infection, when FIV antibody levels may wane, they usually remain high enough to be detected by PoC test kits (Figure 2).

Thus, antibody testing is generally a more reliable method for detecting FIV infection than PCR testing. We are aware of several cases where cats have tested FIV antibody positive with PoC kits but have required multiple PCR tests at different time points to confirm FIV infection. It is expensive for the owner, and stressful for the cat, to have multiple samples taken, when testing with a second (and different) PoC antibody kit affords a much faster confirmatory result.

FIV PCR testing, however, is able to differentiate FIV-vaccinated and FIV-infected cats, and there are some scenarios when it may be useful to pursue. These include:

- Cats recently administered a primary course of FIV vaccination (< 6 months previously)
- Discordant FIV antibody test results (i.e. one positive and one negative FIV result using different PoC kits)
- Cats recently bitten by another cat when an urgent FIV test result is required (FIV-infected cats usually test PCR-positive within 4 weeks of being bitten, versus 8 weeks for a positive antibody test).

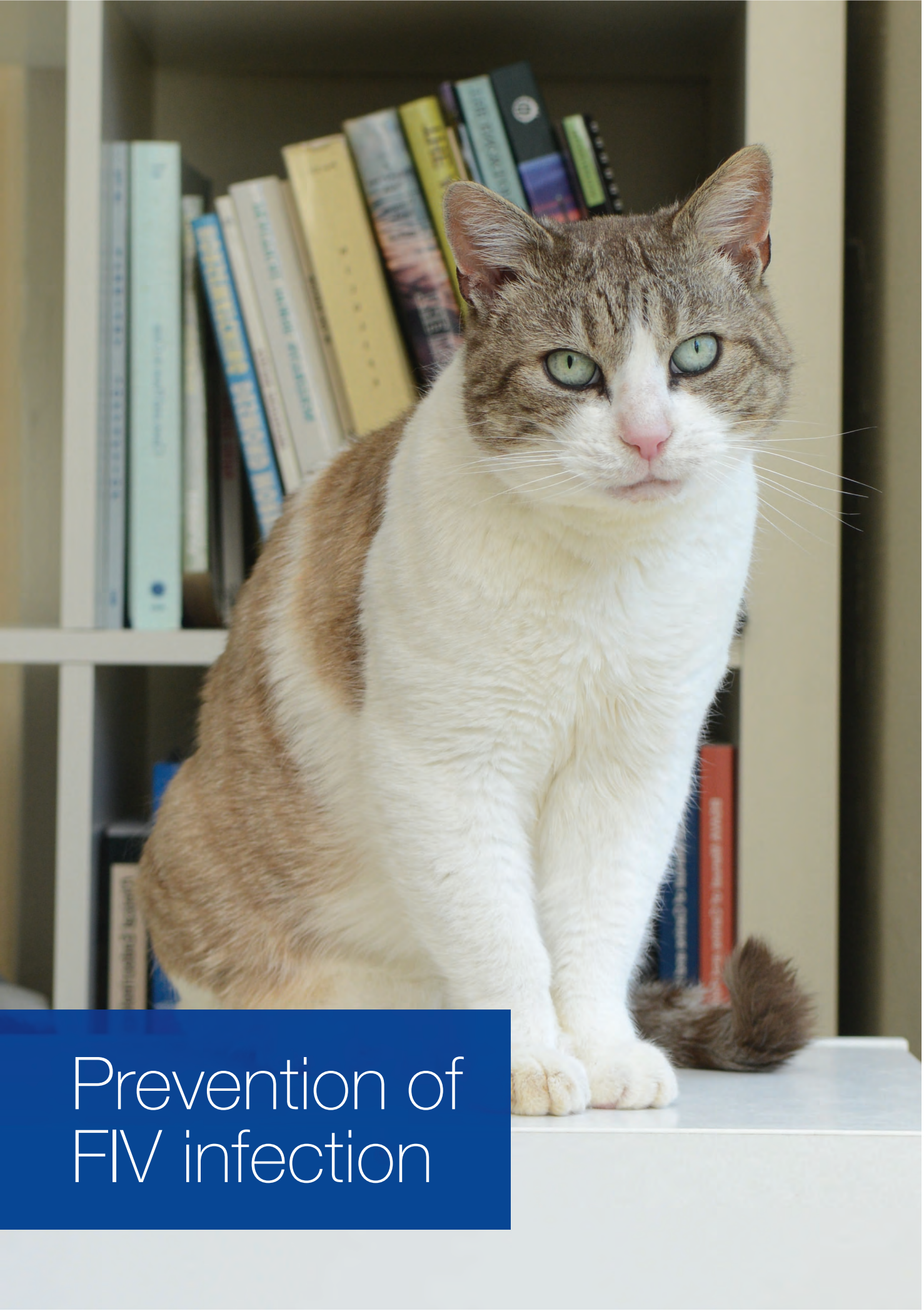
Table 1. FIV testing recommendations.

	FIV testing indication	Time of testing	Initial testing	Confirmatory testing (see Figure 6)
FIV-unvaccinated	Unwell cat (e.g. unexplained weight loss particularly in a young cat, diarrhoea, lymphadenomegaly, renal disease in a younger cat, behavioural issues, respiratory disease, uveitis, anaemia of unknown cause)	Concurrently with other blood tests (e.g. haematology and biochemistry)	Any PoC kit (EDTA whole blood)	Use a different PoC kit (EDTA whole blood)
	Blood donation (only enrol cats with no possibility of cat fights in previous 12 weeks)	During screening, prior to collecting transfusion blood (will also need blood for FeLV PCR testing)		
	Any new kitten or cat	At time of initial health check (see page 24 for discussion about minimum age for testing in kittens)	Any PoC kit (EDTA whole blood) or Anigen Rapid™ PoC kit (saliva)	
	Introduction of new cats to a household	Prior to introduction		
	Dental procedure	Before dental procedure commences		
	Cat fight abscess (CFA)	8 weeks after CFA		
	Primary FIV vaccination	At time of health check and prior to first FIV vaccine administration (including recently bitten cats; see page 19)		
FIV-vaccinated or unknown vaccine history	Unwell cat (e.g. unexplained weight loss particularly in a young cat, diarrhoea, lymphadenomegaly, renal disease in a younger cat, behavioural issues, respiratory disease, uveitis, anaemia of unknown cause)	Concurrently with other blood tests (e.g. haematology and biochemistry)	Anigen Rapid™ or Witness™ PoC kit (EDTA whole blood)	Anigen Rapid™ or Witness™ PoC kit – whichever was not used for initial testing (EDTA whole blood)
	Blood donation (only enrol cats with no possibility of cat fights in previous 12 weeks)	During screening, prior to collecting transfusion blood (will also need blood for FeLV PCR testing)		
	Annual (or lapsed) FIV vaccination	At time of health check and prior to annual FIV vaccination administration	Anigen Rapid™ PoC kit (EDTA whole blood or saliva) or Witness™ PoC (EDTA whole blood)	
	Cat fight abscess (CFA)	8 weeks after CFA		

Extra comments about when to test for FIV infection:

FIV testing should be prioritised in cats with sequential opportunistic infections, unexplained neutropenia and/or anaemia, or lymphoma.

Common sense should be applied to all other testing scenarios by the consulting veterinarian. If FIV testing is unnecessary, and won't change the treatment options, management plan or outcome for a cat, it shouldn't be performed. For example, a 6-month-old kitten, born to a known FIV-negative queen, and housed 100% indoors, does not need to be FIV tested prior to rehoming or commencement of FIV vaccination. However, a 6-month-old kitten born to a queen of unknown FIV status, or that has had some level of unsupervised outdoor access in the first 6 months of life, should be FIV tested prior to FIV vaccination or co-mingling with other cats. Similarly, a cat that has been kept 100% indoors since a previous FIV test does not need to be re-tested for FIV prior to a dental procedure or annual FIV vaccination.



Prevention of FIV infection

Preventing cats' exposure to the outdoors is the only sure way of preventing FIV transmission.

Keeping cats indoors

Bite wounds inflicted by FIV-infected cats have the potential to transmit FIV from one cat to the next. Such bite wounds are most likely to occur to pet cats that are allowed to go outdoors, unsupervised.

Indoor pet cats may occasionally squabble within their social groups, but are less likely to inflict bite wounds on one another. Even if the FIV status of all cats in a multi-cat household is not yet known, FIV transmission is relatively uncommon in stable, established groups kept indoors[21].

Keeping pet cats indoors, including secure outdoor enclosures, is the most practical way of preventing FIV transmission. It will also help prevent vehicular trauma, UV-induced skin cancer, snake bites and tick paralysis, while simultaneously minimising adverse impacts of pet cats on wildlife[22, 23].

If one or more cats in a multi-cat household becomes ill and is discovered to be FIV infected, it is advisable to test the remaining cats. Whether or not to advise separation of infected from uninfected cats depends on whether there is a history of inter-cat aggression and wounding within the indoor social group.

Meeting the welfare needs of cats kept 100% indoors is vital. This topic has been studied increasingly in recent years[24-28]. Familiarity with the American Association of Feline Practitioners (AAFP) and International Society of Feline Medicine (ISFM) Feline Environmental Needs Guidelines may help when advising and encouraging clients who may be weighing up whether or not to keep their pet cat(s) 100% indoors, or indoors with access to an outdoor secured enclosure. Their "Five Pillars of Feline Welfare" are helpful[26]. The Panel believes this is the cornerstone of FIV prevention and is the best way to ensuring longevity for owned cats.

Useful advice about play, exercise, weight control, environmental enrichment and avoidance of separation anxiety has been gathered and presented as part of the "Indoor Pet Initiative" (https://indoorpet.osu.edu)[29]. On this website, you and your clients will find an abundance of encouragement and advice about refuges, prey-preference-selected toys, perches, resting areas and much more[30, 31]. Indoor-outdoor secured enclosures can be home-made, or purpose designed. They can be lavish and extensive[32].

Not all clients can manage to house their cat(s) 100% indoors, while managing to completely fulfill their welfare requirements[15]. Consequently, FIV vaccination may need to be considered, depending on individual risk factors for FIV infection (e.g. local FIV prevalence in owned and unowned cats, density of pet cats in the local area with outdoor access, size of the unowned cat population, etc.).

Figure 10: Keeping cats housed 100% indoors happy requires fulfilling each of the 'Five Pillars' of feline welfare.

FIV vaccination

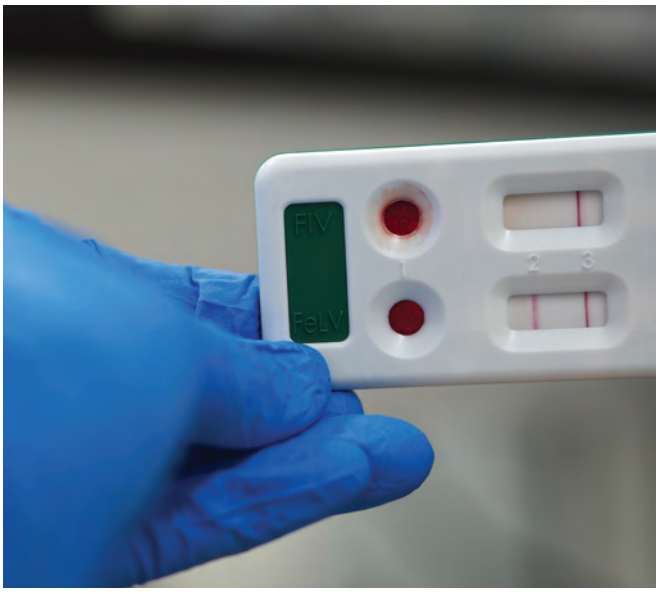
Fel-O-Vax® FIV (Boehringer Ingelheim Animal Health Australia) is an inactivated, whole-virus vaccine that contains two divergent subtypes of the virus, thought to broaden the protection it affords. The efficacy of this vaccine has been studied by multiple research groups over the last 20 years. Different methodologies and challenge doses and strains were used in these studies.

Widely varying results have been obtained. Several studies have demonstrated 100% protection, while one small study showed no efficacy at all[5, 33-39]. A case-control field study by Sydney-based researchers published in 2016 showed a vaccine protective rate of 56%[40]. Stringent inclusion criteria were applied in this study, reducing the number of cases and controls, leaving the study statistically underpowered. Nevertheless, this provided sufficient evidence for the World Small Animal Veterinary Association's (WSAVA) Vaccination Guidelines Group to redesignate this vaccine as "Non-Core"; whereas it had previously been designated as "Not Recommended". Non-core vaccines can be recommended after careful risk-benefit analysis has been performed by the veterinarian and pet owner in consultation.

A field study from New Zealand recently reported no protection from FIV infection in FIV-vaccinated cats[41]. The definition for FIV-positivity was more relaxed in the NZ study and there were biases with case recruitment that impacted study results. For example, the rate of FIV infection in controls was half that of vaccinates, suggesting differences between the recruited groups. Despite this, the result is important and might reflect differences in NZ subtypes of FIV. Further field investigations of FIV vaccine efficacy clearly should be undertaken to explore these differences.

Use of this vaccine can be recommended for pet cats whose owners are unable to, or cannot be persuaded to, keep their cats away from the risk of being bitten by an FIV-infected cat. Unfortunately, many cats fall into this category because a majority of cats in Australia are allowed to go outdoors on their own, unsupervised, and FIV infection is prevalent in such cats across the country[10, 15, 42].

Since Fel-O-Vax® FIV only has a reported field effectiveness of 56% in Australia, the Panel recommends that cats vaccinated against FIV should undergo annual testing prior to annual FIV re-vaccination, to check infection has not occurred in the preceding year, using an Anigen Rapid™ or Witness™ antibody kit.



Suggested FIV vaccination procedure for recently bitten cats:

Since FIV is most commonly transmitted during fighting, it is the cats that constantly get into fights and being bitten who are at the greatest risk of becoming FIV-infected. It is these cats who have the most to benefit from FIV vaccination. It can be hard to know when to vaccinate these cats, as some owners will not bring their cat back to the clinic for testing. Waiting 8 weeks to use a PoC antibody test kit might result in another cat fight bite in the intervening period, with the 8-week countdown for antibody testing re-starting.

For this reason, we suggest vaccinating 'brawlers' against FIV at the first possible opportunity (even if recently bitten), using the following protocol. As soon as cat fight injury has resolved:

- Conduct FIV testing with PoC kit to ensure the cat was not previously FIV-infected (note, however, that this may not detect infection caused by the most recent fight); administer the first primary FIV dose
- 2-4 weeks later: administer 2nd primary FIV dose.
- 2-4 weeks later: administer 3rd primary FIV dose.
- 12 months later: FIV testing with an Anigen Rapid™ or Witness™ PoC kit immediately prior to administration of the first annual FIV vaccine.

The alternative to this regimen is to build a modular pet park that prevents the cat's access to outdoors, and the cost to do this is possibly not dissimilar to the cost of a lifetime of FIV vaccination.

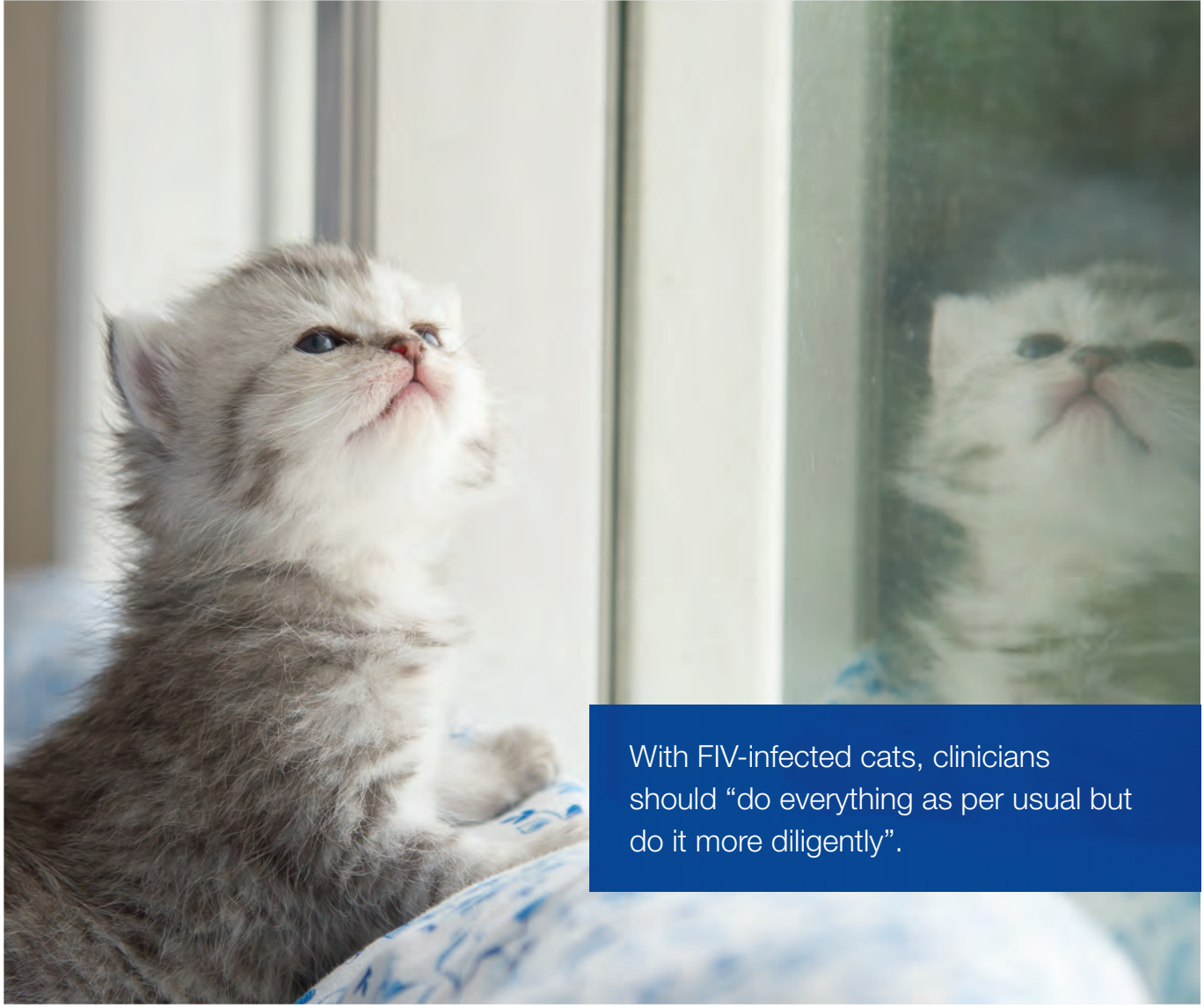
Note: If the 'brawler' cat tests FIV-positive at the first annual FIV vaccination, it will be impossible to determine if the cat became FIV-infected prior to or during the completion of the primary FIV vaccination course, or if a lack of efficacy event has occurred and FIV infection has established following primary FIV vaccination and before annual FIV re-vaccination.

If a kitten/cat does not receive the full set of three Fel-O-Vax® FIV vaccine doses on schedule, or an adult cat is late for its annual FIV booster, seek advice from the vaccine manufacturer as to the optimal vaccination regimen.

There is no demonstrated benefit to administering Fel-O-Vax® FIV to an already FIV-infected cat.

The most serious risk of vaccination (and other injections) in cats is feline injection site sarcoma (FISS) formation. This is a very rare, malignant neoplasm thought to be attributable to injection of vaccines and other substances into the "scruff". It was first described in the USA and reported shortly afterwards in Australia[43]. It is thought to be much less prevalent in Australia than the USA, in part due to absence of rabies vaccination, but good quality Australian epidemiological data are lacking. Nevertheless, the consequences for affected cats are catastrophic. Given the apparent rarity of these tumours in Australia, the Panel does not currently encourage distal limb or tail vaccination. However, avoiding the interscapular furrow, and injecting approximately 4 cm lateral to the dorsal midline, over the convexity of the muscles covering the scapula spine, would allow earlier detection and diagnosis of any mass subsequent to vaccination. Although the role of adjuvants in the pathogenesis of FISS is unresolved, the Panel suggests varying the site of injection of adjuvanted vaccines from year to year (i.e. left side one year, right side the next). The site of injection of each vaccine should be recorded in the medical record.

Management of FIV-positive cats



With FIV-infected cats, clinicians should “do everything as per usual but do it more diligently”.

Whilst many owners will try to make comparisons between the clinical course, therapeutic interventions, and outcomes for HIV and FIV infections, key differences exist. Importantly, most FIV-infected cats reach reasonable longevity without antiretroviral drugs where there is diligent attention to husbandry and management of concurrent disease[44-48].

Top tip

The best way to enhance quality of life and life expectancy is to optimise basic husbandry and to detect and treat any concurrent conditions early in the disease course.

It is important to stress to owners that FIV is not a death sentence and does not constitute grounds for euthanasia.

When approaching management of FIV-infected cats, the guiding principles are:

- Clinicians should “do everything as per usual but do it more diligently” and err on the side of investigation sooner rather than later (see checklist of health recommendations below).
- Owners should be encouraged to take an “if in doubt get it checked out” approach and act as soon as any concerning clinical signs or behaviours are noted.
- Diseases that would be considered possible/likely in cats without FIV infection should be excluded via thorough clinical investigation before consigning any clinical problem to the virus itself.

> **“Importantly, FIV positivity is not a reason to stop thinking hard about why a cat is sick and pursuing further diagnostic testing. A treatable underlying disease could well be present.”**
>
> – The late Vic Menrath, known by many as “The Father of Feline Medicine in Australia”

Monitoring for immunodeficiency

A complete blood count can be performed on FIV-infected cats at the time of diagnosis and annually thereafter to monitor for haematologic abnormalities such as leukopenia and anaemia[49-52].

The presence of lymphopenia in particular may signal declining immune function, but it is a common finding in stressed sick cats[8, 51]. Cat owners may be aware of the use of CD4+ T lymphocyte, plasma viral RNA load, and acute phase protein quantification to monitor immune status and disease progression in people infected with HIV. Whilst monitoring of equivalent measurements has been reported for cats naturally infected with FIV[8, 53, 54], it is not currently utilised widely by clinical veterinarians. Maybe we should be doing more flow cytometry to stage FIV-positive cats.

Measurement of plasma viral RNA load and concentrations of acute phase proteins such as serum amyloid A and C-reactive protein may prove to be useful in staging of disease and prognostication of cats infected with FIV[54], but criteria are yet to be defined. Cats can live with low CD4+ T lymphocyte counts for prolonged periods without developing problems, a fact that remains an enigma to feline immunologists!

Checklist of recommendations for basic health care and husbandry measures for all FIV-infected cats

- ✓ Screen cohabitating cats and vaccinate for FIV if FIV negative.
- ✓ House indoor only +/- enclosed or supervised outdoor access.
- ✓ Feed a nutritionally balanced and complete feline-specific diet.
- ✓ Reduce behavioural stress within the current living environment.
- ✓ Minimise number of cats in the household or facility and do not introduce new cats!
- ✓ Regular, twice-yearly veterinary health checks, with attention to body weight and body condition score assessment.
- ✓ Good attention to dental and oral cavity health.
- ✓ Prompt investigation of any health issues that emerge e.g. vomiting, diarrhoea, weight loss.
- ✓ Maintain core vaccination schedules and routine parasite prevention.

Antiretroviral and immunomodulatory agents: Which drugs might we consider?

Critically, the Panel deplores use of the term Feline AIDS to describe FIV-infected cats.

Antiretroviral drugs are not currently indicated for the majority of infected cats, with any decision to implement antiretroviral treatment comprising a risk-benefit decision that must be made on a case-by-case basis. In fact, the Panel would suggest that at this stage any drug treatment of FIV infection is best considered experimental.

Discussion of drug therapy for FIV must reflect existing survival data for infected cats as well as the health status of the individual cat. With regard to specific antiviral treatment for FIV, major barriers to potential success include limited drug availability and absent field trial data, frequent toxic side-effects, high cost, impractical administration frequency and duration of therapy. A decision to treat remains a risk-benefit decision to be made on a case-by-case basis, and in many instances, antiretroviral viral therapy may present more risks than benefits[55].

Importantly, the Panel is unaware of feline clinicians in Australia who currently use specific antiretroviral therapy to manage cats with FIV infections.

Of the antiretroviral drugs investigated, zidovudine (also known as azidothymidine; AZT), a nucleoside analogue reverse transcriptase inhibitor, holds the most promise for use in FIV-infected cats. AZT has been shown to reduce viral load, with improvements in immunologic status (including CD4+/CD8+ ratios), quality of life, life-expectancy and clinical status, particularly in neurologic presentations of FIV or FIV-associated stomatitis[55-58]. Drug resistance has been reported, as has bone marrow suppression, primarily manifesting as non-regenerative anaemia. AZT is consequently NOT recommended for use in cats with evidence of pre-existing bone marrow suppression. Vomiting and anorexia have been reported but occur infrequently and the drug otherwise appears to be well tolerated. A regimen comprising 5-10 mg/kg PO q12h with weekly monitoring of CBC for the first month, then monthly monitoring thereafter, may be recommended[57, 58].

At the time of publishing, AZT is available in Australia via prescription (S4) under the trade name Retrovir (50 mg/5 mL 200 mL strawberry-flavoured oral suspension) at a cost of approximately $60 AUD (100 mg and 250 mg capsules are manufactured but appear to be frequently unavailable). Compounded AZT is also available and may be preferable.

Interferons (human and feline) mediate and enhance innate immunity as a means of reducing susceptibility to secondary infections and viral replication[53]. Well-designed clinical trials are lacking, although Gomez-Lucia et al (2020) reported that oral administration of human interferon-alpha for a period of 4 months improved haematologic parameters (including CD4+:CD8+ ratios) and was well tolerated. Feline interferon omega (Virbagen Omega, Virbac Animal Health, Australia) has also been utilised and has been well tolerated. A small number of trials have shown evidence of clinical improvement in FIV-infected cats[59, 60], although its true therapeutic effect requires further demonstration.

Human interferon alpha has been previously available as Roferon A (3 million IU/0.5 mL vials costing approximately $40 AUD), but at the time of writing, this has been discontinued by the supplier.

Note: None of the drugs discussed are registered for the treatment of FIV.

FIV testing in shelters

It is useful to know the FIV status of any new kitten or cat upon entry to a shelter to assist with individual management and to limit FIV transmission. This includes all kittens (>12 weeks of age) and cats rehomed from pounds, shelters, and other rescue facilities.

Top tip

All animal holding facilities should aim to individually house cats in order to limit the spread of FIV and FeLV infection in groups of animals that are stressed and do not have established social hierarchies, to reduce fighting, and to reduce other aggressive interactions that promote the spread of FIV.

It is not as simple, however, as saying all shelters should FIV test all kittens and cats, all of the time. The cost of FIV testing is prohibitive for many organisations. Some organisations, particularly in the USA, have decided that the resources spent on FIV testing are better allocated to other programs, and that the cost of testing should be paid for by the new owner. In addition, identifying FIV-infected cats can affect length-of-stay for those animals, which is detrimental to their overall health and welfare, and some argue that not knowing FIV infection status is better for these animals[61]. In contrast, one study of cats rehomed from a shelter in Canberra, ACT, did not find any difference with regards to the length-of-stay of FIV-infected versus FIV-uninfected cats[62].

The Panel does not promote the euthanasia of healthy FIV-infected cats. We therefore suggest shelters should seriously question the need for FIV testing of healthy cats going to single cat households.

If group housing of cats is practised at the shelter, the FIV status of all those co-housed should be determined, so that FIV-infected cats can be housed individually, and FIV-infected cats ideally placed into indoor-only single cat households. If shelters opt not to test animals for FIV prior to adoption, new owners should be made aware and a waiver signed to indicate that they understand that the cat's FIV infection status is unknown.

Table 1 provides a summary of general FIV testing recommendations. Shelters are usually rehoming kittens and young healthy animals, often with an unknown FIV vaccination history, and therefore the following key recommendations should be followed where possible:

- FIV antibody testing using PoC kits is more reliable and cheaper than PCR testing and should be used for both initial disease screening and confirmation of any positive FIV test results (using a different manufacturer's test kit).
- Anigen Rapid™ and Witness™ kits (not SNAP Combo™) accurately detect FIV infection in FIV-vaccinated cats (excluding cats who have recently received a primary vaccination course), and therefore are ideal to use in cats with a history of FIV vaccination or unknown vaccination history.
- If a cat tests FIV-positive with an Anigen Rapid™ and Witness™ FIV kit, the result should be confirmed with the other FIV test kit (i.e. ideally shelters should stock both kits).
- For some cats, collection of saliva for FIV testing with an Anigen Rapid™ kit reduces sampling stress and should be pursued instead of blood collection.
- If blood collection is needed (e.g. for confirmatory testing with Witness™ after a positive Anigen Rapid™ result using saliva), ear tip bleeding, or foot pad bleeding, are low stress options for some cats.
- Kittens can be tested for FIV from 12 weeks. If a positive result is obtained, our recommendation is to re-test in 1 month using blood and another test kit to confirm (see below).
- FIV testing should be performed on all animals prior to dental procedures. Freshly autoclaved dental instruments should be used for each cat, irrespective of the FIV result (in case of early FIV infection prior to seroconversion). Thorough cleaning of all non-autoclavable equipment should be undertaken at the conclusion of every dental procedure.
- Spays and castrations should never be done using a single kit for multiple cats.

It is important for shelters to remember that identifying FIV infection is not a death sentence or a reason to euthanise animals. Alarmingly, 4/17 Australian shelters responding to a questionnaire indicated that they euthanised all FIV-positive cats regardless of health status[63]. Many FIV-infected cats will live normal, happy, healthy lives with appropriate management, and many people will willingly adopt FIV-infected cats.

Age of testing: Kittens can be tested for FIV antibodies from 12 weeks. This is younger than most major retroviral guidelines suggest; however, in one study involving 55 kittens born to 12 FIV-vaccinated queens, all 55 kittens tested FIV-negative with two different commercial FIV kits by 12 weeks of age[64]. In the same study, 35/55 kittens (64%) tested FIV-positive at 8 weeks with one of the commercial FIV kits, demonstrating persistence of maternally-derived antibodies (MDA) against FIV for at least 8 weeks in kittens[64]. Presumably, persistence of MDA is comparable for kittens born to FIV-vaccinated and FIV-infected queens. Some Australian shelters now perform FIV testing in litters of kittens less than 12 weeks old; in this scenario, negative FIV results can be trusted, but positive FIV results must be confirmed by either PCR testing or repeat PoC testing when the kitten is older.

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