Article

Naturally acquired feline immunodeficiency virus (FIV) infection in cats from western Canada: Prevalence, disease associations, and survival analysis

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Abstract — This retrospective study evaluated epidemiologic features and disease associations of feline immunodeficiency virus (FIV) infection in client owned cats from western Canada. Among 1205 cats that were tested 66 (5.5%) were positive for FIV antibody (FIV^+) with a higher prevalence in males than females. FIV^+ cats were older than the overall population. Epidemiologic features and disease associations were compared between 58 FIV^+, but feline leukemia virus negative ($FeLV^-$) cats and 58 age and sex matched FIV-negative (FIV^-), $FeLV^-$ cats. FIV positivity was associated with a history of bite wounds, increasing age, and male gender. Lethargy and oral diseases were significantly associated with FIV positivity. Although several FIV^+ cats were euthanized, the survival time of FIV^+ cats after diagnosis was not significantly different from that of FIV^- cats. In summary, FIV prevalence was low in cats from western Canada, clinical signs/diseases were mild, and lifespan was not different in FIV^+ cats.

Résumé — Infection naturelle par le virus de l'immunodéficience féline (VIF) chez les chats de l'Ouest canadien : prévalence, associations de maladies et analyse de survie. Cette étude rétrospective a évalué les caractéristiques épidémiologiques et les associations de maladies de l'infection par le virus de l'immunodéficience féline (VIF) chez des chats appartenant à des clients de l'Ouest canadien. Parmi 1205 chats qui ont été testés, 66 (5,5 %) étaient positifs pour l'anticorps du VIF (VIF^+) avec une prévalence supérieure chez les mâles par rapport aux femelles. Les chats VIF^+ étaient plus âgés que la population globale. Les caractéristiques épidémiologiques et les associations de maladies ont été comparées entre 58 chats VIF^+, mais qui étaient séronégatifs pour le virus de la leucémie féline ($FeLV^-$) et 58 chats séronégatifs pour le VIF (FIV^-) et le virus de la leucémie féline. La séropositivité pour le VIF était associée à de longs antécédents de morsures, à un âge grandissant et au sexe mâle. La léthargie et les maladies buccales étaient souvent associées à la séropositivité pour le VIF. Même si plusieurs chats VIF^+ ont été euthanasiés, le taux de survie des chats VIF^+ après le diagnostic n'était pas significativement différent de celui des chats VIF^-. En résumé, la prévalence du VIF est faible chez les chats de l'Ouest canadien, les signes cliniques et la maladie étaient légers et l'espérance de vie n'était pas différente chez les chats VIF^+.

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Introduction

Feline immunodeficiency virus (FIV), a Lentivirus within the *Retroviridae* family, was first isolated in 1987 from a colony of group-housed cats with a high prevalence of opportunistic infections and degenerative diseases (1). Since then, various clinical diseases and syndromes have been associated with FIV infection in cats (2–4). Retrospective serosurveys suggest that FIV has been present in the domestic cat population at least since 1966 (5). This virus is now recognized worldwide as endemic in the domestic cat population (6). Typically, cats are tested for FIV antibody in a dual enzyme-linked immunosorbent assay (ELISA) that also detects feline leukemia virus (FeLV) antigen. Western blot, polymerase chain reaction (PCR), or virus isolation can be used to confirm FIV positivity (7,8). Seroprevalence of FIV among sick cats varies from 2.5% to 43.9%, which are higher rates than those of healthy cats (3,9–13). Multivariate analysis indicates that age, sex, health status, cat's lifestyle, and source of the cat (stray, relinquished, or feral) are significantly associated with risk of seropositivity (6,12).

The hallmark of experimental and natural FIV infection is progressive disruption of immune function by virus-induced depletion of CD4+ T lymphocytes in peripheral blood, leading to lowering of the CD4 to CD8 lymphocyte ratio as seen with

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HIV infection in people (14–16). Loss of CD4+ T lymphocytes impairs immune function resulting in increased susceptibility to opportunistic infectious and degenerative diseases. Naturally infected FIV-positive (FIV^+) cats exhibit clinical signs of fever, hemopoietic disorders, dermatitis, otitis, lymphadenopathy, stomatitis, gingivitis, neurological diseases, ocular diseases, weight loss, lethargy, anorexia, emaciation, vomition, cystitis, nephritis, diarrhea, abscesses, skin diseases, renal insufficiency/failure, hepatic disease, and upper respiratory tract infections (4,17–22). Clinical signs are most often a reflection of opportunistic infections, neoplasia and/or myelosuppression, as the disease progresses (22).

Few studies have compared the prevalence of clinical signs and diseases in FIV-infected and uninfected cats. Although a higher prevalence of FIV in sick cats suggests that FIV contributes to disease development, many veterinarians hold the opinion that FIV^+ cats are clinically indistinguishable from FIV-negative (FIV^-) cats. Further, FIV may produce only subtle manifestations of immune-dysregulation resulting in long periods of subclinical infections, and a fairly normal life span and quality of life (15). Studies from Australia have found equal prevalence of FIV in healthy and systemically ill cats (13), with no statistically significant association between FIV-positivity and the occurrence of anemia, mucosal inflammation and infection, neoplasia, lymphadenomegaly, pyrexia, or opportunistic infections (23). Another study reported that FIV infection did not adversely affect life expectancy in closed household pet cats (24). There are limited studies on FIV seroprevalence in Canada and no studies have compared the prevalence of various diseases/clinical entities in naturally infected FIV^+ and FIV^- cats from western Canada. The purpose of this retrospective study was to determine the seroprevalence of FIV in client-owned cats from western Canada, and to compare clinical signs, diseases, and survival times in FIV^+ and FIV^- cats.

Materials and methods

Sample population of cats

The test group for this retrospective study consisted of 1205 domestic cats, from the western Canadian provinces of Saskatchewan, Manitoba, and Alberta that were evaluated for FIV/FeLV infection at the Veterinary Teaching Hospital (VTH), Western College of Veterinary Medicine (WCVM), between January 1996 and December 2006, inclusive. Cats were tested for FIV/FeLV for 1 of the following reasons: to establish retrovirus status before introduction to a new household; to evaluate possible underlying infection; to evaluate potential exposure to these viruses after a known fight with another cat; to establish retrovirus status before vaccinating for FeLV. None of these cats had been vaccinated for FIV as the FIV vaccine was approved for use in 2005 in Canada. Cats that tested FeLV-positive ($FeLV^+$) were eliminated from the study of association between clinical variables and FIV status.

Fifty-eight cats were positive for FIV and negative for FeLV. Therefore, 58 FIV^-/FeLV-negative ($FeLV^-$), randomly selected, age and sex-matched uninfected cats were identified from the test group of cats which was stratified into groups based on age and sex to compare clinical signs, disease associations, and survival times with FIV^+ cats. No distinction was made between cats that were sexually intact or neutered. Health records of these 116 cats were reviewed to obtain history, signalment, clinical signs, clinicopathological diagnoses at the time of testing, lifestyle (indoor/outdoor activity), living status (alive or dead), and reason for death. Cat owners were surveyed to determine additional clinical problems; current status (living or dead); if dead, age at the time of death and reason for death.

Table 1. Prevalence of feline immunodeficiency virus (FIV) antibody in cats that were also tested for the presence of feline leukemia virus (FeLV) antigen

Group by age (y) and sex	Number tested	$FeLV^-$ FIV^+ (%)	$FeLV^+$ FIV^+ (%)
< 1 y			
Male	78	1 (1.3)	0 (0)
Female	70	0 (0)	0 (0)
Total	148	1 (0.7)	0 (0)
1 to 5 y			
Male	230	10 (4.3)	2 (0.9)
Female	133	7 (5.3)	1 (0.8)
Total	363	17 (4.7)	3 (0.8)
6 to 10 y			
Male	142	17 (12)	4 (2.8)
Female	91	1 (1)	0 (0)
Total	233	18 (7.7)	4 (1.7)
11 to 15 y			
Male	86	8 (9.3)	0 (0)
Female	70	1 (1.4)	0 (0)
Total	156	9 (5.8)	0 (0)
≥ 16 y			
Male	18	4 (22.2)	1 (5.6)
Female	27	0 (0)	0 (0)
Total	45	4 (8.9)	1 (2.4)
Unknown age			
Male	164	8 (4.9)	0 (0)
Female	96	1 (1)	0 (0)
Total	260	9 (3.5)	0 (0)
Male	718	48 (6.7)	7 (1.0)
Female	487	10 (2.1)	1 (0.2)
Total	1205	58 (4.8)	8 (0.7)

Testing protocol

All 1205 cats were tested for FeLV antigen and FIV antibody by the immunology laboratory of Prairie Diagnostic Services Inc., Saskatoon, using a commercially available ELISA kit (SNAP Combo FeLV antigen/FIV antibody; IDEXX laboratories, Maine, USA). The reported sensitivities of the assay for detection of FeLV and FIV are 98.6% and 98.2%, respectively; and the reported specificities are 98.2% and 100%, respectively (Dietz M, IDEXX Laboratories, personal communication, 2005).

Statistical analysis

Clinical data were stored in a database (Microsoft Access, 2003) and analyzed to determine the associations between clinical variables and FIV status using chi-squared analysis with Epi Info software (version 3.4.1). The strength of association between FIV infection and individual or combination of clinical variables was determined by calculating the crude

Table 2. Summary of results for 1205 serum samples tested for feline immunodeficiency virus (FIV) antibody and feline leukemia virus (FeLV) antigen

Sex and mean age	$FeLV^-/FIV^+$	$FeLV^+/FIV^+$	$FeLV^-/FIV^-$	$FeLV^+/FIV^-$	Total
Males *(n)*	48 (6.7%)	7 (1%)	635	28 (3.9%)	718
Mean age (y)	7.9	7.8	5.8	4.1	5.8
Females *(n)*	10 (2.1%)	1 (0.2%)	462	14 (2.9%)	487
Mean age (y)	4.3	1.8	6.3	5.0	6.3

Table 3. Clinical signs, disease conditions, and lifestyle of FIV^+ and FIV^- cats

Clinical signs, diseases, and lifestyle	FIV^+ (n = 58)	FIV^- (n = 58)	Odds ratio (95% CI)	P-value
Prior bite wounds	17	5	4.4 (1.37–14.98)	0.004[a]
Anorexia	13	14	0.91 (0.35–2.34)	0.83
Lethargy	13	5	3.06 (0.92–10.76)	0.04[a]
Weight loss	7	11	0.59 (0.19–1.81)	0.3
Gastrointestinal signs (vomition and diarrhea)	4	10	0.36 (0.0–1.35)	0.08
Fever	3	0	∞0.24	
Lymphadenopathy	2	2	1 (0.1–10.38)	1
Oral disease (stomatitis/gingivitis/ periodontal disease)	23	6	5.7 (1.94–17.52)	0.0006[a]
Ocular disease	11	4	3.16 (0.85–12.72)	0.053
Respiratory disease	10	11	0.89 (0.3–2.5)	0.8
upper respiratory tract infection	7	10	0.66 (0.2–2.08)	0.43
lower respiratory tract infection	3	1	3.11 (0.27–8.05)	0.31
Renal disease[b]	9	14	0.67 (0.25–1.76)	0.37
Endocrinopathies	7	4	1.85 (0.4–8.1)	0.34
diabetes mellitus	3	2	1.53 (0.2–13.68)	1
hyperthyroidism	4	2	2.07 (0.31–17.1)	0.68
Skin disease	6	5	1.22 (0.31–4.99)	0.75
Otitis externa	6	2	3.23 (0.55–24.34)	0.27
Neoplasia	2	4	0.48 (0.06–3.25)	0.68
Anemia	2	1	2.04 (0.14–5.9)	0.56
Cardiac disease	1	4	0.24 (0.01–2.37)	0.36
Lifestyle[c]				
outdoor	21	9	2.72 (0.7–10.41)	0.14
indoor	6	7	0.37 (0.08–1.69)	0.17

[a] $P < 0.05$ considered significant.
[b] Renal failure was diagnosed in 6 of 9 FIV^+ cats and 2 of 14 FIV^- cats.
[c] Lifestyle information available for 27 FIV^+ and 16 FIV^- cats.

odds ratios and their 95% confidence intervals (CI). Survival analysis was done to determine the effect of FIV status on cats' longevity irrespective of reasons for euthanasia or death using Kaplan-Meier product-limit method which compares the survival curves using both the Logrank test and the Gehan-Wilcoxon test using Graph Pad Prism (Ver. 5). The end point in the survival analysis was death/euthanasia. The data for 19 FIV^+ cats and 36 FIV^- cats were excluded from the survival analysis as they were lost to follow-up. Data for cats that were still alive at the end of the study were censored in the survival analysis because survival beyond the censoring day was an unknown future event (25). Statistical significance was set at $P < 0.05$.

Results

FeLV/FIV ELISA results by age group and sex are shown in Table 1. Among 1205 cats, comprising 718 males and 487 females, 58 (5.5%; 95% CI: 4.2–6.8) were positive for FIV antibody but negative for FeLV antigen, 8 (0.7%; 95% CI: 0.2–1.2) were positive for both FIV and FeLV (Table 1) and 42 (3.5%; 95% CI: 2.5–4.5) were positive for FeLV antigen but negative for FIV antibody (Table 2). Prevalence of FIV infection in male cats (n = 55; 7.7%; 95% CI: 5.5–9.6) was greater than in female cats (n = 11; 2.3%; 95% CI: 0.1–3.6). Prevalence increased with age, with the greatest prevalence (8.9%) in the ≥ 16 y age group (Table 1). The mean age of male FIV^+ cats (7.9 y; range: 8 mo to 19 y) was greater than the population mean for males (mean 5.8 y; range 0 to 21 y). The mean age of female FIV^+ cats (4.3 y; range 2 to 11 y) was less than the population mean for females (6.3 y; range: 0 to 21 y) (Table 2). Clinical signs and diseases for the 58 FIV^+, $FeLV^-$ cats and the 58 FIV^-, $FeLV^-$ cats are summarized in Table 3. Bite wounds, lethargy, and oral diseases (stomatitis, gingivitis, and periodontal disease) were significantly associated with FIV seropositivity ($P < 0.05$). Although the proportion of FIV^+ cats with ocular disease (n = 11) and fever (n = 3) appeared higher, the associations were not statistically significant ($P > 0.05$). Inflammatory, endocrine, neoplastic and degenerative conditions were not significantly associated with FIV positivity.

Table 4. Summary of reasons for euthanasia and mode of death of FIV$^+$ ($n = 28$) and FIV$^-$ cats ($n = 12$).

Number of cats	Reasons for euthanasia
FIV$^+$ cats[a]	
9	FIV positivity
6	Gingivitis, periodontal disease, stomatitis
4	Renal failure
3	Vomition and diarrhea
3	Unknown
1	Abdominal abscess
1	Lymphosarcoma
1	Hit by a car
FIV$^-$ cats	
2	Clostridial colitis, clostridial enteritis
2	Lymphosarcoma
2	Renal failure, renal insufficiency
1	Unknown
1	Chronic urinary tract infection
1	Neoplasia
1	Chronic anorexia
1	Hepatic lipidosis
1	Abdominal mass

[a] Four FIV$^+$ cats died naturally, 1 of renal failure, 1 of diabetic complications, 1 of diabetes and congestive heart failure, and 1 of unknown cause.

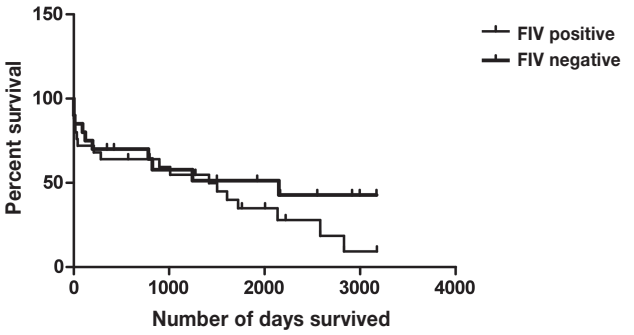

Figure 1. Kaplan-Meier survival curve comparison for FIV positive cats ($n = 39$) and FIV$^-$ cats ($n = 22$). The median survival times for FIV$^+$ and FIV$^-$ cats are 1416 and 2147 days, respectively. This difference is not statistically significant ($P > 0.05$). Ticks on the lines indicating censored items represent the data of cats that were alive at the end of the study.

Survival after FIV positive diagnosis

By the end of the study, 12 FIV$^-$ cats (euthanized, n = 12) and 32 FIV$^+$ cats (euthanized, n = 28) were dead. Among the 28 FIV$^+$ cats that were euthanized, 17 had been euthanized immediately after determining FIV seropositivity, and 3 cats had been euthanized within 30 d of diagnosis. The reasons for euthanasia/death and mode of death of FIV$^+$ and FIV$^-$ cats are summarized in Table 4. The mean age at the time of death for FIV$^+$ cats whose birthdates were available (n = 26) was 9.8 y (range: 8.6 mo to 17 y) while that for FIV$^-$ cats (n = 12) was 12.9 y (range: 7 to 21.5 y). The mean age of FIV$^+$ cats that were still alive (n = 7) at the end of the study was 13.2 y (range: 2.5 to 23.7 y) while that for FIV$^-$ cats (n = 10) was 9.6 y (range: 5 to 15.9 y). The clinical information available for 6 of 7 FIV$^+$ cats that were still alive by the end of the study is as follows: 4 cats were reported healthy although 1 was blind; 1 cat had renal failure and another cat had a heart murmur. The FIV status had no significant effect ($P > 0.05$) on the cats' longevity (Figure 1). The median survival times of FIV$^+$ (n = 39) and FIV$^-$ cats (n = 22) after FIV testing were 3.9 y and 5.9 y, respectively.

Discussion

This study examined seroprevalence of FIV infection in client-owned cats from western Canada and compared the prevalence of various clinical signs and disease entities as well as survival times in FIV$^+$ and FIV$^-$ cats. Several studies have reported a wide range of clinical signs associated with FIV infection; however, few studies have compared clinical signs and disease entities between age and sex matched FIV$^+$ and FIV$^-$ cats (17,23,24). Bias may have been introduced in the selection of cats to be tested for FeLV/FIV in this study as all cases were from a single teaching hospital and the criteria for retroviral testing may vary among clinicians. In addition, the prevalence of FIV may have been overestimated since most cats were presented with a clinical problem. Vaccination for FIV was not considered to be an explanation for a positive test result due to timing of the study relative to the release of FIV vaccine in Canada, lack of promotion of FIV vaccination at the WCVM VTH, and lack of history of FIV vaccination in individual medical records.

The reported sensitivity and specificity of the SNAP combo ELISA kit are high, but false positive and false negative test results can occur due to undetermined reasons. In a recent study, the performance of 7 FIV tests was compared, with the finding that the lowest sensitivity and specificity of the SNAP Combo test were 93.1% and 98.5%, respectively (26). Based on the reported test performance, the prevalence in the present study is likely overestimated and the true prevalence would be likely lower. In general, Western blot assay is recommended to confirm FIV ELISA results; however, confirmatory analyses were not performed given the retrospective nature of the study and the fact that the reported sensitivity and specificity for the SNAP combo ELISA kit are high.

The overall rate of FIV infection among 1205 cats tested in this study was 5.5%, which is comparable to prevalence studies for North America (2.5%) (12), Ontario, Canada (5.9%) (27), and Atlantic Canada (7.6%) (28). However, the prevalence was less than that reported in Germany (10%) (8), Australia (20.8%) (11), Turkey (22.3%) (29), Italy (24%) (10), and Japan (43.9%) (3). The findings of greater prevalence in male and adult cats ($\geq$ 6 years old) are in agreement with previous studies (3,8,9,12,13,29).

In contrast to the general opinion that FIV infection significantly reduces a cat's life span, FIV status did not affect the cats' survival times significantly ($P > 0.05$) in this study despite the number of FIV$^+$ cats that were euthanized at or shortly after FIV diagnosis. Relatively high numbers of cats were excluded in the survival analysis because they were lost to follow-up after FIV testing. Their inclusion as censored items in the survival analysis did not affect the end result ($P > 0.05$) (data not shown). The results of survival time data analysis are in agreement with another study on the long-term impact of

FIV infection in a closed household of naturally infected pet cats (24). The fact that life span was not reduced with FIV infection may relate to a long incubation period for this virus after initial infection as cats may remain relatively disease-free for 8 y or more (30). Alternatively, the cats may have been infected with less virulent strains (such as, Subtype B) of FIV or may not have been exposed to infectious/opportunistic agents after acquiring FIV infection. There are 5 subtypes (A to E) of FIV isolates based on sequence diversity in variable regions (V3 to V5) (31–35) and FIV subtypes exhibit considerable geographic clustering. Subtype A is found in the western United States and Europe, subtype B is found in Japan and the central and eastern United States, while subtype C is found in California and British Columbia (31,35). Subtypes D and E have been reported from Japan (36) and Argentina (34), respectively. A study from Ontario, Canada identified A, B, and C FIV subtypes with subtype A being the most frequent (37). Despite the heterogeneous geographic distribution, most FIV isolates belong to either subtype A or B. Studies have hypothesized that subtype B is in a more advanced state of host adaptation and may, therefore, be less pathogenic than subtype A (31,35). An observational and comparative study of specific pathogen-free cats experimentally infected with FIV subtypes A and B, demonstrated that a cat infected with subtype A virus developed progressive immunological abnormalities and severe clinical signs of immunodeficiency syndrome 8 y and 8 mo after infection, while cats infected with subtype B did not show any significant clinical signs of immunodeficiency syndrome during the same time period (30). No studies have been done to investigate the prevalence of various FIV strains in the western Canadian provinces comprising this study. This warrants further investigation.

FIV^+ cats in this study were significantly more likely to have had a history of bite wounds than were FIV^- cats. This virus is effectively transmitted through bite wounds and greater frequency of FIV infection in male cats may relate to fighting, territorial aggressiveness, and courtship fighting (9). The sample population herein was not segregated into neutered and entire animals. Although reports vary, there is evidence that neutering and spaying do not have a statistically significant effect on FIV prevalence (28,29). In addition, although neutered cats do not indulge in courtship fighting, they still retain territorial aggressiveness (29).

$FeLV^+$ cats were eliminated from the study of FIV and its clinical association as this virus has a severe influence on disease progression and life expectancy of FIV co-infected cats (16,38). Opportunistic infections by viruses, bacteria, protozoa and fungi have been reported in experimentally and naturally infected FIV^+ cats (3,39,40). There were no serious/life-threatening infections associated with FIV^+ cats in this study. The clinical course of FIV infection and pattern of opportunistic infections may vary with the patient and its lifestyle, geographic location, and strain of virus. Unlike previous reports, we found significant associations only with lethargy and oral disease in FIV^+ cats when compared with FIV^- cats. Although, anemia, hyperthyroidism, lower respiratory tract infection, renal failure, and outdoor lifestyle showed trends towards an association with FIV positivity (odds ratio > 2), the findings were not statistically significant ($P > 0.05$). To our knowledge no studies have compared clinical findings in FIV^+ cats with age and sex matched randomly selected FIV^- control cats. It has been reported that there is no significant disease association with naturally acquired FIV infection in Australian cats compared with uninfected cats (23), and that cats kept under hygienic conditions or infected by less pathogenic FIV strain(s) do not develop severe clinical signs (16).

Oral disease was significantly more common in FIV^+ cats than in FIV^- cats in this study. This agrees with earlier reports, and suggests that a systemic immunosuppressive effect of FIV may allow microbial invasion of the oral cavity (9,18,41). In this study, it was uncertain whether stomatitis was predisposed by other factors (dental disease, other viruses), as no additional diagnostic tests were done. Earlier reports suggest that increased ocular disease in FIV^+ cats could be due to direct damage from the virus or opportunistic infections (39,42,43) but ocular diseases were not significantly associated with FIV positivity in this study; despite a trend to increased numbers.

Lymph node enlargement is one of the most frequently reported abnormalities in cats with FIV infection. In our study, there appeared to be no association between FIV-positivity and lymph node enlargement, which is in agreement with the findings of Hosie et al (17) and Shaw et al (23). Further, there was no association between neoplasia and FIV infection in our study which agrees with the findings of Shaw et al (23) who analyzed the association of FIV infection with diseases in Australian cats. This is in contrast to Hopper et al (44) who determined that the prevalence of neoplasia in an FIV^+ cat population was increased.

In summary, FIV status did not significantly affect cats' longevity in this study. History of bite wounds, male sex, increasing age, lethargy, and oral diseases were associated with FIV positivity when compared with age- and sex-matched randomly selected FIV^- control cats. A significant proportion of cats that tested FIV positive were euthanized, perhaps prematurely. There may be geographical/strain-related variation in clinical signs, diseases, and opportunistic infections associated with FIV infection.

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