




EPIDEMIOLOGY

Prevalence and risk factors





Hi I'm Charlie. I don't have FIV but I'm enrolled in the Madeline Purdue FIV Study because I'm a match for Jojo



Prevalence and risk factors

- **Worldwide**
 - Prevalence varies 1-14% in healthy cats; higher in sick cats, but exact % depends on study design
 - USA, 2004 – 345 veterinary clinics (3.1% of 9970 cats) and 145 animal shelters (1.7% of 8068 cats)¹
 - Canada – 4.3% of 11,144 cats tested in 2007²
- **Major risk factors**
 - Age - Adult
 - Gender – Male (MN 4.3%, MI 3.3%) and intact status¹
 - Lifestyle –
 - Free-roaming/outdoor access
 - Shelter – Relinquished 1.4%, Stray 1.6%, Feral 3.9%¹
 - Health status – Current illness (6.1%)¹

1. Levy et al., J Am Vet Med Assoc 2006;228:371–376
2. Little et al., Can Vet J 2009; 50:644-648



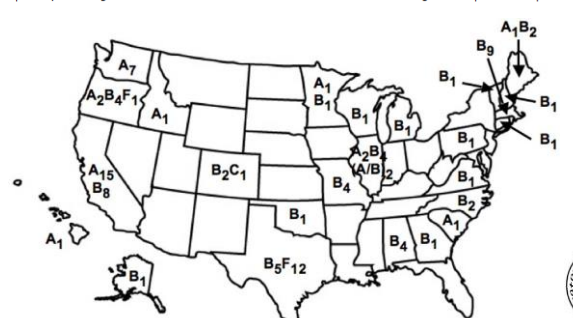


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A Detailed Phylogenetic Analysis of FIV in the United States

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TRANSMISSION



Hi I'm Domino. I have FIV and I'm enrolled in the Maddie's Purdue FIV Study.

Modes of FIV transmission¹

- **Most common**
 - Bite wounds
- **Also documented but *much* less common**
 - Infected mother to kittens – during pregnancy, birth or lactation
 - Blood donation from infected cat
- **Only demonstrated under laboratory conditions**
 - Mucosal transmission via oral, rectal or vaginal mucosa
 - Mucosal infection requires up to 10,000x more virus than other routes
- **Fomite transmission not important**
 - FIV loses infectivity outside the host
 - Susceptible to all disinfectants
- **Strain differences can be important**



1. Burkhard and Dean, Curr HIV Res 2003;1:15-29.

Published studies of closed 'mixed' populations

FIV-positive (n)	FIV-negative in-contact (n)	In-contact cats infected (n)	Laboratory/ Home	Observation period
18	14	0	Laboratory	4-14 months ¹
16	31	0	Home	Median 2 years ²
5	68	0	Home	3.5 years ³
NR	20	1 10/19 FIV PCR+	Laboratory	2-4 years ⁴
9	17	6	Home	10 years ⁵

1. Yamamoto et al., AJVR 1988;49:1246-1258.
 2. Shelton et al., 1989;25:7-12.
 3. Shelton et al., J Ac Imm Def Syn 1990;3:623-630.
 4. Dandekar et al., J Virol 1992;66:4040-4049.
 5. Addie et al., Vet Rec 2000;146:419-424.

Maddie's Purdue FIV Transmission Study

Aim

- To document the FIV serological status of cats living long-term in a stable multi-cat household containing FIV-positive and FIV-negative cats

Hypothesis

- That viral transmission would not occur from FIV-positive to FIV-negative cats



FIV Transmission Study - Protocol

Cats

- Stable multi-cat household of 138 cats with unrestricted access to one another
- All cats indoor only except for -
 - 1 FIV-positive indoor/outdoor cat
 - 1 FIV-negative cat that escaped for a 12-month period, then returned

Testing

- **FIV SNAP Test 1 - All cats FIV ELISA tested on intake¹**
 - 8 FIV-positive – 6MN 2FS; Median age - 28 months (Range 5mths-10 years)
 - 130 FIV-negative – 71MN 59FS; Median age - 4 months (Range 2mths-12 years)
 - All cats FeLV-negative
- **FIV SNAP Test 2 –**
 - ELISA testing repeated in 5 FIV-positive and 45 FIV-negative cats (SNAP Test 1 results)
 - FIV SNAP Test 2 performed median 28 months after Test 1 (Range 1-106 months)



1 – IDEXX FIV SNAP Combo; 2 – IDEXX FIV PCR.

Results of FIV SNAP Test 2

FIV ELISA test results in all 50 cats were unchanged from the FIV SNAP Test 1 results

- 5 FIV-positive cats and 45 FIV-negative cats

FeLV ELISA test results from SNAP Test 2 –

- One cat was FeLV-positive FIV-negative

A further 5 of the 50 cats were tested a 3rd time

- Results were the same as at FIV SNAP Test 2 – 1 FIV-positive cats and 4 FIV-negative cats
- The 3rd FIV SNAP test was performed median 3 months after FIV SNAP Test 2 (Range 1-45 months)
- All 5 cats were FeLV-negative



Cumulative exposure to FIV

- Cumulative exposure to FIV-positive cats (n=8) calculated for each FIV-negative cat with ≥ 2 FIV ELISA test results (n=45)
- Date calculations performed using XL -
 - Entry date to last negative test date for all FIV-negative cats
 - Number of days exposure to each FIV-positive cat calculated individually by comparing residence dates
- Median cumulative exposure duration of each FIV-negative cat to FIV-positive cats = 11.98 years (3.9-13.7 years)



FIV Transmission Study – Conclusions

- Mutual grooming, mild aggression, shared food bowls, litter boxes etc. did not transmit FIV over many years of cumulative exposure in a mixed group of FIV-negative and FIV-positive cats kept in a stable multi-cat household
- Viral load and phenotype could be important in risk of transmission
- Feline behavior, virology, immunology underpin recommendations for ‘mixed’ housing



PATHOGENESIS

*Hi I'm Clarence.
I don't have FIV but I'm enrolled in the Maddie's Purdue FIV study
because I'm a match for Ace. I live with Booth.*



Pathogenesis

- **Acute infection**
 - Often clinically silent; perhaps mild fever, lymphadenopathy
 - Large amounts of virus circulating
 - CD4 (helper) and CD8 (cytotoxic) T-lymphocytes decline
- **Response to initial infection**
 - FIV antibody production
 - Reduced amounts of circulating virus
 - Increased CD8 T-lymphocyte count → CD4:CD8 is reduced
- **Long asymptomatic period**
 - Progressive dysfunction of immune system
 - CD4 T-lymphocyte count declines → CD4:CD8 is reduced, but does not always cause clinical signs
 - Non-regenerative anemia, lymphopenia and neutropenia can occur
 - Because cell-mediated immunity is reduced, antibody-mediated immunity can be stimulated → increased serum globulin concentration
 - FIV-positive cats respond adequately to vaccination, unless advanced disease is present



CLINICAL SIGNS

Hi I'm Athena. I have FIV and I'm enrolled in the Maddie's Purdue FIV Study. I live with Apollo.



Clinical signs

- Clinical signs might take years to develop, if at all
 - 41/89 FIV-positive cats enrolled in the Maddie's Purdue FIV Study had no clinical signs at enrollment
 - Asymptomatic period can last for years and clinical signs are generally seen in older cats
- **Chronic inflammation**
 - Oral cavity
 - Skin
- **Secondary infections**
 - Viral, bacterial, fungal, protozoal
- **Neoplasia**
 - Lymphoma
- **Signs of neurological or renal disease**
- **Slow, progressive weight loss**



Hair loss without skin inflammation





Hair loss with inflamed skin




Chronic wounds






Chronic upper respiratory tract disease






Chronic inflammation in the oral cavity






DIAGNOSIS

Hi I'm Huckleberry. I don't have FIV but I'm enrolled in the Maddie's Purdue FIV Study because I'm a match for Orangello. I live with Menuchin






Diagnosis – Antibody tests

- IDEXX SNAP test**
 - In-shelter test on serum, plasma or whole blood
 - Highly sensitive and specific – up to 100%¹
 - Detects antibodies to FIV core proteins - p15 p24 gag proteins
 - Use within 2 hours of opening foil pack and read in 10 mins
- Western blot test**
 - Send-out test
 - Have been used to confirm SNAP-positive result, but might not be as sensitive or specific as the original SNAP test!
 - When** - Most cats produce antibodies within 60 days of exposure, but it may take much longer (12 months) if viral exposure is low
 - False positive results** - Positive FIV antibody test results can sometimes occur in uninfected cats -
 - Antibody tests cannot distinguish between antibodies that are produced in response to a natural infection and those that are
 - Produced in response to **FIV vaccination** (persist at least 1 year after vaccination; perhaps up to 9 years), or
 - Received by **kittens (<6 months old)** when their mother is FIV-positive (infected or vaccinated)



1. Levy et al., J Am Vet Med Assoc 2004;225:1558-1561 (n=124)



Diagnosis – Antigen tests

Tests that detect FIV viral protein

- IDEXX FIV RealPCR™ test**
 - Can potentially distinguish cats that are vaccinated but FIV-uninfected from FIV-infected cats
 - Relies on adequate amounts of certain amino acid sequences from field strains of FIV being 'recognized' by the test
 - Maddie's Purdue FIV Study found that both the sensitivity and specificity of this test was approximately 94%
 - Strain information is also provided
- Virus isolation –**
 - Performed at reference laboratories
 - 'Reference standard' method that takes at least 28 days to perform



FIV Diagnostic Testing Algorithm

Based on American Association of Feline Practitioners (AAFP) Guidelines¹

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    graph TD
      A[FIV antibody test (SNAP™ test or reference laboratory ELISA)] -- Negative --> B[Infection unlikely]
      A -- Positive --> C[Repeat test, using alternate method (EISA or Western blot tests)]
      C -- Negative --> D["If >6 months old, cat may be free of infection*"]
      C -- Positive --> E{Vaccinated?}
      E -- No --> F["If >6 months old, consider FIV infected*"]
      E -- Yes or unknown --> G[Inconclusive  
*Vaccinated cats will test antibody positive  
*Vaccinated cats may also be infected*]
      G --> H[FIV RealPCR™ test]
      H -- Negative --> I[Inconclusive  
Cat may be:  
- Free of infection  
- Infected, but DNA quantity below level of detection  
- Infected with FIV strain not detected by current assay]
      H -- Positive --> J[Cat is FIV infected]
      B -.-> C
      D -.-> E
      F -.-> J
      I -.-> J
  
```

Algorithm courtesy of IDEXX Laboratories Inc. 2009
1. Levy et al., JFMS 2008;10:300–316

Diagnosis – Which cats to test

- Sick cats
- Cats and kittens that will be group housed
- Cats and kittens at adoption, and a minimum of 60 days later if negative
- Cats with recent exposure to FIV-positive cat or cat of unknown FIV status, especially if there is a bite wound, and a minimum of 60 days later if negative
- Cats living with FIV-infected cats should be tested annually
- High risk cats – Outdoor, free-roaming cats, cats with bite wounds
- Before considering vaccination against FIV
- Blood donor cats



TREATMENTS FOR FIV

Hi I'm Menuchin. I don't have FIV but I'm enrolled in the Maddie's Purdue FIV Study because I'm a match for Rocky. I live with Huckleberry.

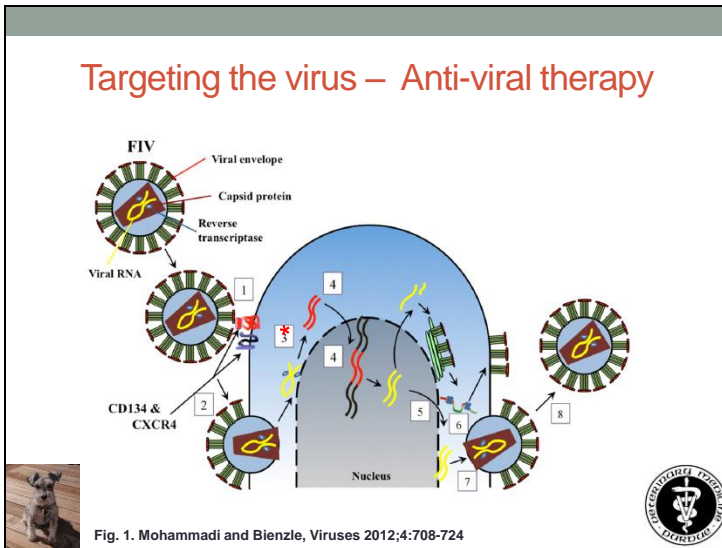


Targeting the immune system Interferon therapy

- **Recombinant feline interferon¹**
 - Not available in US naturally infected FIV-positive cats A
 - 7 naturally infected FIV-positive cats; 3 healthy, 4 unhealthy
 - 5 untreated FIV-positive cats as controls; 8-week treatment period
 - Healthy/mildly unhealthy cats remained stable (4 cats)
 - Unhealthy cats had improved clinical scores (3 cats)
- **Oral human interferon – low-dose oral treatment²**
 - 30 naturally infected unhealthy FIV-positive cats; 24 treated, 6 placebo
 - Total 14 months treatment
 - Clinical improvement in the first 2 months
 - Treated cats had significantly longer survival than placebo
 - No change in CD4:CD8 or other hematological parameters



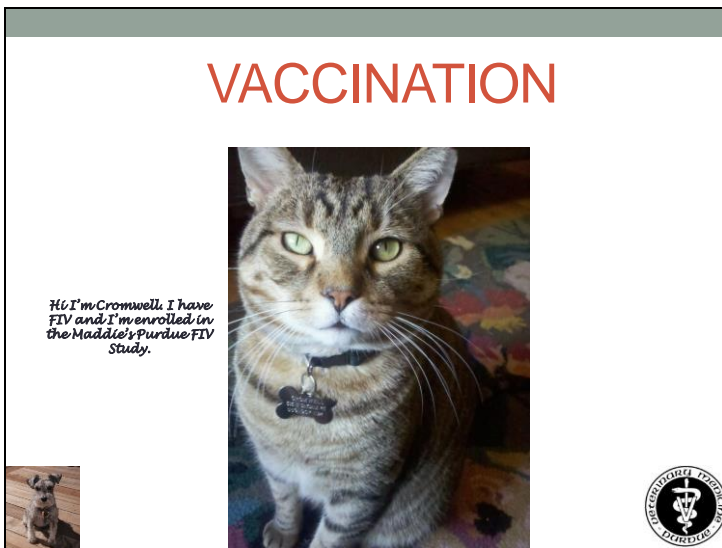
1. Doménech et al., Vet Immunol Immunopathol 2011;143:301-306
 2. Pedretti et al., Vet Immunol Immunopathol 2006;109:245-254



Targeting the virus – Anti-viral therapy

- **PMEA and Zidovudine (AZT)** – Work on Step 3
- **Zidovudine (AZT)**¹
 - Placebo-controlled study showed stomatitis and CD4:CD8 improved ; 3 weeks treatment used
 - Can cause dose-dependent anemia; anemia often resolves in the first 3 weeks of treatment
 - AZT-resistant strains of FIV can arise
 - Not suitable for cats with signs of bone marrow suppression
- **PMEA**¹
 - Associated with clinical improvement in one placebo-controlled study; 3 weeks treatment used
 - Caused more severe anemia than AZT-treated cats

1. Hartmann et al., *Vet Immunol Immunopathol* 1992;35:167-175



Vaccination against FIV

- Classified as a non-core vaccine by AAFP Vaccine Guidelines¹
 - Only administered to cats in specific risk categories
 - AAFP Vaccine Guidelines do not recommend shelter use¹
- Might be considered for cats with high risk lifestyles
 - Outdoor cats that fight
 - Cats living with FIV-positive cats, in unstable relationships
- Antibody tests can't distinguish between vaccinated and infected cats
- FIV vaccination must be performed in conjunction with microchipping so that cats are properly identified
- Efficacy –
 - Killed vaccine against subtypes A and D
 - Also protects against subtype B
 - Challenge studies have shown 0-82-100% 'preventable fraction' (proportion protected by vaccination in excess of proportion that is naturally resistant)



1. Richards et al., JAVMA 2006;229:1405-1441.



FIV Vaccination in Shelters?

FIV vaccination is not recommended for use in shelters or free-roaming cats¹

- Resources are better used elsewhere, such as spay/neuter/rabies vaccination programs
- FIV vaccination requires at least 3 doses to be effective and protection is strain-dependent
- Reduced aggression in spayed/neutered cats makes FIV transmission less likely
- Free-roaming cats are more likely to be presented as strays at veterinary hospitals and shelters where it might be assumed that they are FIV-infected

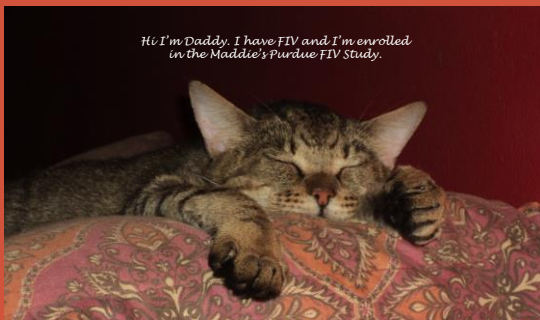


1. Levy et al., JFMS 2008;10:300-316






WHAT WE NEED MORE EVIDENCE ABOUT FOR CATS NATURALLY INFECTED WITH FIV

Hi I'm Daddy, I have FIV and I'm enrolled in the Maddie's Purdue FIV Study.



MARKERS OF DISEASE PROGRESSION



Hi I'm Neut. I don't have FIV but I'm enrolled in the Maddie's Purdue FIV Study because I'm a match for TJ.



Factors associated with disease progression




- **Clinical staging not well characterized or widely adopted**
- **Changes in the immune response**
 - CD4 T-lymphocyte count and CD4:CD8 decline in terminal stages
 - Decreased IL-2 and increased TNF- α
- **Changes in viral proteins¹**
 - Errors occur during viral replication, resulting in 'evolution' of the virus over time
 - 'Natural selection' of viral variants that resist the host immune response and lead to progression of disease
- **Viral load²**
 - Study of 33 naturally infected cats divided into High and Low viral load groups at enrollment
 - Survival of High viral load group was significantly reduced over the next 4 years and the viral loads increased just prior to death

1. Kraase et al., Vet Immunol Immunopathol 2010; 134:96-106
2. Goto et al., 2002 J Virol;76:10079



PROGNOSIS

Hi I'm Amos. I don't have FIV but I'm enrolled in the Maddie's Purdue FIV Study because I'm a match for Stormy.



Study Protocol

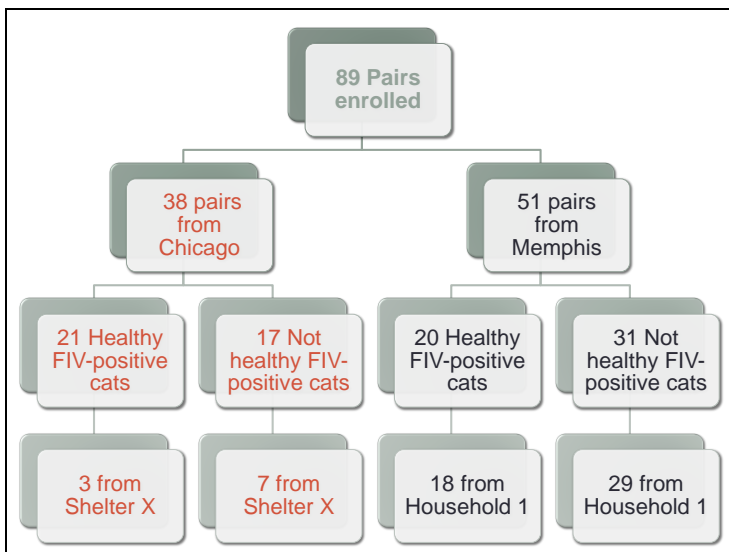
- Five-year controlled study of naturally-infected FIV-positive cats, starting January 1 2010
- Data collection every 6 months for FIV-infected cats and every 12 months for age- and sex-matched FIV-negative control cats
- Clinical history, general physical exam, gingival score, serum biochemistry, CBC, CD4/CD8, UA
- Cat owners receive reports to discuss with their regular DVM
- Virology data provided by University of Glasgow Retrovirus Research Laboratory and IDEXX West Sacramento
- Necropsies performed by one pathologist at Purdue
- Memphis FIV-positive cats weighed monthly
- Three-monthly email/phone check-in with all cat owners



Study Enrollments

- Two-year enrollment period – January 2010-January 2012
- All cats classified as 'Healthy' or 'Not healthy' at the time of enrollment
- Healthy = No abnormalities found on a physical examination by AL
- Not healthy = One or more abnormalities found on a physical examination by AL
- All Control cats must be 'Healthy'
- FIV-positive cats can be 'Healthy' or 'Not healthy'





Some results so far ...

Mortalities – FIV-positive cats

- **Chicago** - 4/38 cats enrolled (10.5%) have died
 - **Healthy group** – 3 cats – 1 death FIV-related, 2 deaths not FIV-related
 - **Not healthy group** – 1 cat died of FIV-related disease from Shelter X
- **Memphis** - 34/51 cats enrolled (66.7%) have died
 - **Healthy group (20 cats enrolled)** – 10 cats died of FIV-related disease; 9 were from Household 1 and 1 was from a large, multi-cat household
 - **Not healthy group (31 cats enrolled)** – 24 cats died of FIV-related disease; all were from Household 1

Mortalities - FIV-negative cats

- **Chicago** – 0/51 cats have died
- **Memphis** – 4/51 cats died
 - 2/4 accidental deaths
 - 2 illness-related – One from Household X and one from large multi-cat household



FIV-Positive Cats - Chicago and Memphis Comparisons

	Chicago (n=38)	Memphis (n=51)	P value
Age at enrollment	Median 4 years (1.5-11)	Median 5.5 years (2-10)	0.02
No. enrolled in Healthy group	55% (21/38)	39% (20/51)	
No. enrolled in Not Healthy Group	45% (17/38)	61% (31/51)	Not significant
Time from first FIV diagnosis to enrollment	Median 6 months (1 month-5 years)	Median 2 years (1 month-8 years)	<0.0001
Length of time enrolled	Median 1.9 years (1.3-2.9 years)	Median 3.2 years (1.2-3.2 years)	<0.0001
Housed with >5 cats	10/38	51/51	0.01

FIV-positive cats enrolled in Memphis are older; have been known to be FIV-positive longer; have been enrolled in the study longer; and are housed differently to FIV-positive cats from Chicago.



More results ...

Lymphoma -

- Of the 38 FIV-positive cats that have died so far, 13 (34.2%) have had lymphoma identified at necropsy
- 9/13 were from the Not Healthy group and 4/13 were from the Healthy group
- Lymphoma was always found in the bone marrow; often in other sites also

Weight loss –

- Weight loss usually precedes FIV-related death
- Often >10%/month for at least 3 months

Viral transmission

- Three cats originally enrolled in the FIV-negative group have become FIV-positive
- All 3 had significant bite wounds and required hospitalization
- Two were from large multi-cat households with mixed populations
- One was a territorial outdoor cat



Clinical and laboratory results ...

FIV subtypes

- FIV subtypes A, B, D and F have been identified
- No associations have been made so far between subtype and health status

Physical exam findings

- Stomatitis, faucitis, bowel thickening on palpation, allergic skin disease and non-inflammatory alopecia are common in the FIV-positive cats

Lab results

- CD4 T-lymphocyte count and CD4:CD8 are lower in FIV-positive cats at enrollment and over the study period so far



Shelter medicine research solving practical problems

- Which factors provide **early** information about **naturally infected** cats to predict outcomes so we can advise potential adopters or foster parents?
- Are there particular co-morbidities that are important and/or common in FIV-infected cats?
- Are changes to the immune response and viral loads the cause and/or the result of clinical progression?
- What are the optimal management plans for FIV-infected cats in shelters and adoptive homes?



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