

Coadaptation and immunodeficiency virus: lessons from the Felidae

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The emergence of pathogenic viruses in new species offers an unusual opportunity to monitor the coadaptation of viruses and their hosts in a dynamic ongoing process of intense biological selection. Tracking lentivirus epidemics in man, monkeys and cats reveals genomic struggles at three levels: quasispecies divergence within an individual; coadaptation of virus and host genomes subsequent to disease outbreaks; and transmission, spread and pathogenesis in related host species. Aspects of each level are revealed by examining the genetic diversity of feline immunodeficiency virus in domestic and wild cat species. This approach has been facilitated by the recent genetic characterization of a novel lentivirus in lions.

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Introduction

Feline immunodeficiency virus (FIV) causes an acquired immunodeficiency syndrome in domestic cats, involving depletion of the CD4 subset of T lymphocytes, susceptibility to opportunistic infections, and frequently death [1–6]. The presence of FIV-reactive antibodies in a number of other felid species has revealed the widespread occurrence of related viruses throughout the world [7,8•,9]. There is as yet no persuasive evidence, however, that FIV-related viruses cause disease in any of the wild cats. If FIV-infected wild cat species are healthy, then what differences among the viruses, their hosts, or virus–host interactions determine the lack of pathogenicity of FIV in various species? In this review, we address this question by looking at recent studies of feline viruses and by examining parallels from human and simian immunodeficiency virus studies that relate to the delicate balance of pathogenic viruses and their hosts in natural disease outbreaks.

Genetic variation of FIV among host species

Of twenty-seven felid species that have been examined, seventeen revealed the presence of FIV-reactive antibodies (Table 1). Lentiviruses genetically similar and morphologically analogous to FIV have been isolated from lions and pumas [8•,9]. (We refer to all the feline lentiviruses as FIV in this review, although *in vivo* all are not known to cause immunodeficiency.) Comparison of the complete DNA sequence of puma

FIV with that of FIV from domestic cats [10•,11,12] revealed the same major genes and genome organization with varying levels of gene sequence similarity (Fig. 1). The sequence similarity of the *env* gene and two open reading frames (*orf2* and *orf3*) between FIVs of pumas and domestic cats was very small (<39% nucleotide and <10% amino acid sequence identity) [10•]. This level of genetic divergence is substantial when compared to the divergence of viral genes in primate lentiviruses [13,14].

The amount of genetic variation among viruses from the same felid species was estimated by comparing sequences from the highly conserved *pol* gene isolated from several individuals (Table 2). The degree of intra-species variation was very high with as much variation within lions and within pumas as is observed between human immunodeficiency virus type 1 (HIV-1) and simian immunodeficiency virus (SIV) from chimpanzee, or between HIV-2 and SIV from small African monkey species [8•,9]. Overall, *pol* sequence variation in felids was lowest among FIV isolates from domestic cats. Assuming that viral genetic variation increases over time, this indicates a more recent infection of domestic cats than other feline species.

Phylogenetic analyses of sequences from the *pol* gene of FIV isolated from lions, pumas and domestic cats revealed that each feline species has its own species-specific strain of FIV [8•,9] (Fig. 2). These data indicate that there are significant differences between the viral strains, some of which may account for differences in pathogenicity among the feline species. Similarly, the large difference in *env* gene sequences among domestic cat FIV isolates offers a plausible explanation for the

Abbreviations

DIP—defective interfering particles; FIV—feline immunodeficiency virus; SIV—simian immunodeficiency virus.

Table 1. Seroprevalence of FIV antibodies in felids.

Species	Number positive	Number tested	% Positive	References
Lion (<i>Panthera leo</i>)	540	711	76	[7,20,35] (a)
Leopard (<i>Panthera pardus</i>)	7	169	4	[7,20,35] (a)
Tiger (<i>Panthera tigris</i>)	3	162	2	[7,20] (a)
Snow leopard (<i>Panthera uncia</i>)	3	77	4	[7,20] (a)
Jaguar (<i>Panthera onca</i>)	9	63	14	[7,20] (a)
Cheetah (<i>Acinonyx jubatus</i>)	17	473	4	[7,20,35] (a)
Puma (<i>Puma concolor</i>)	88	447	20	[7,20] (a)
Leopard cat (<i>Prionailurus bengalensis</i>)	1	55	2	[7] (a)
Jaguarondi (<i>Herpailurus yagouaroundi</i>)	6	33	18	(a)
Bobcat (<i>Lynx rufus</i>)	2	30	7	[7] (a)
Lynx (<i>Lynx sp.</i>)	0	3	0	[20]
Clouded leopard (<i>Neofelis nebulosa</i>)	0	21	0	[7] (a)
Serval (<i>Leptailurus serval</i>)	0	10	0	[7,20]
Flat headed cat (<i>Ictailurus planiceps</i>)	1	6	17	[7] (a)
Marbled cat (<i>Pardofelis marmorata</i>)	0	2	0	[7] (a)
Caracal (<i>Caracal caracal</i>)	0	1	0	[7]
Pallas cat (<i>Otocolobus manul</i>)	3	7	43	(a)
Domestic cat (<i>Felis catus</i>)	31	96	32	[7] (a)
European wild cat (<i>Felis silvestris</i>)	0	8	0	[7] (a)
Jungle cat (<i>Felis chaus</i>)	0	6	0	(a)
Sand cat (<i>Felis margarita</i>)	0	5	0	[7]
African wild cat (<i>Felis libyca</i>)	0	3	0	[a]
Ocelot (<i>Leopardus pardalis</i>)	10	85	12	[7,20] (a)
Margay (<i>Leopardus wiedi</i>)	4	67	6	[7] (a)
Tigrina (<i>Leopardus tigrina</i>)	2	32	6	(a)
Geoffroy's cat (<i>Oncifelis geoffroyi</i>)	3	44	7	(a)
Pampas cat (<i>Lynchailurus colocolo</i>)	0	3	0	(a)

(a) MA Carpenter, EW Brown, SJ O'Brien, unpublished data.

reported distinction in cell tropism and host range and may also determine the efficiency of each strain in disease induction [2,15*,16].

Table 2. Comparison of levels of *pol* gene sequence divergence in felid species.

Species	No. cats	% Nucleotide divergence		% Amino acid divergence		References
		Mean	Range	Mean	Range	
Domestic cat	15	8	0–17	5	0–11	[9,12,16,38] (a)
Lion	27	16	0–26	13	0–26	[8**]
Puma	26	18	0–27	10	0–24	[9] (a)

(a) MA Carpenter, SJ O'Brien, unpublished data.

Virus–host interaction

It is likely that differences in lentivirus infectivity are only part of the story. Variations in the host immune response to the virus would also affect the disease outcome, as has been demonstrated in studies of HIV and SIV. Unlike humans, chimpanzees persistently infected with HIV-1 fail to develop immunodeficiency, suggesting a difference between humans and chimpanzees in the host species permissiveness to disease [17]. Several strains of SIVsm have been isolated which are not pathogenic in their natural hosts, sooty mangabeys, but which cause AIDS-like disease when inoculated into species which have no natural SIV infection, such as Asian macaques [18*]. In addition, macaques develop AIDS when infected with some strains of SIV from sooty mangabey and African green monkey but not from others [18*,19]. These SIV studies indicate that pathogenicity is characteristic of specific virus–host combinations, suggesting dynamic coadaptation of host and viruses in the African monkey species in which SIV infection is widespread and non-pathogenic.

The effect of FIV–host interaction on pathogenicity might be evaluated by experimental infection of felids with FIV from a different species. For example, infection

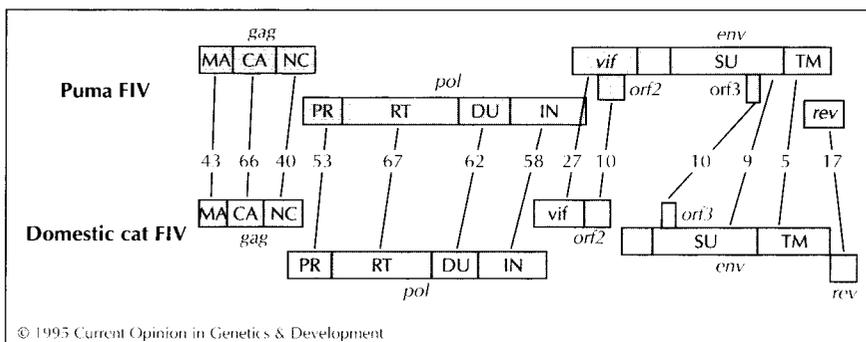


Fig. 1. Genome organization of feline lentiviruses. Shaded bars denote potential coding regions in each of the three reading frames. Numbers shown are the percentage of identical amino acids shared by the homologous genes of puma FIV and domestic cat FIV in each region [10]. MA, matrix; CA, capsid; NC, nucleocapsid; PR, protease; RT, reverse transcriptase/RNase H; DU, deoxyuridine triphosphatase; IN, integrase; SU, surface envelope glycoprotein; TM, transmembrane envelope glycoprotein.

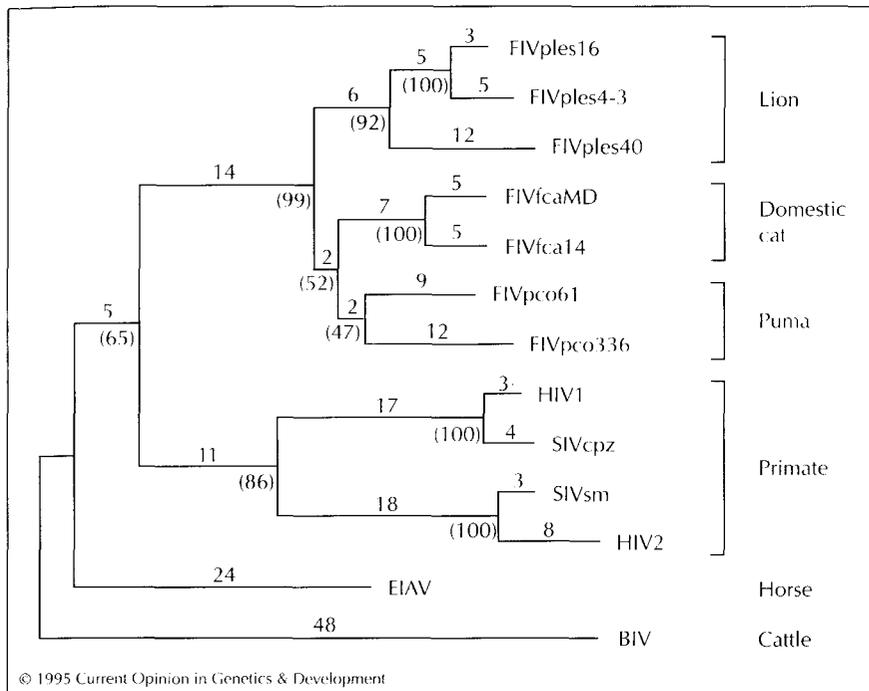


Fig. 2. Phylogenetic tree showing relationships between felid and primate lentiviruses, constructed from *pol* gene amino acid sequences using the neighbor joining method [53]. Branch lengths represent % genetic distance calculated using Dayhoff's PAM matrix. The number of bootstrap iterations out of 100 which support each node are shown in parentheses at the node. The felid sequences include representatives of the two domestic cat (fca) clades for which *pol* sequences are available, the three lion (ple) clades and two puma (pco) clades. BIV, bovine immunodeficiency virus; EIAV, equine infectious anemia virus.

of a specific pathogen free domestic cat with puma FIV resulted in the establishment of a persistent infection, but no pathogenicity was observed [9]. Inoculation of domestic cats with lion FIV failed to produce detectable infection [20]. Spontaneous occurrence of cross-species transmission could also prove informative; for example, FIV *pol* sequences characteristic of a domestic cat were recently detected in a captive puma (MA Carpenter, SJ O'Brien, unpublished data). It is not yet clear whether differences in disease outcome are determined primarily by characteristics of the strain of FIV or of its feline hosts.

The influence of host selective pressures on viral pathogenicity has been demonstrated by changes in the virulence of SIV strains that occur after passage through different hosts or cell types. For example, an SIVsm strain was observed to become more virulent after a macaque passage than after a passage through its natural host, the sooty mangabey [18•]. This suggests that the natural host can deter the evolution of more pathogenic strains, thereby avoiding immune deficiency.

Viral population dynamics

What is it about a pathogenic virus–host combination that distinguishes it from a non-pathogenic association? One key factor that appears to influence disease progression is viral load [18•]. Long-term survivors of HIV-1 infection who resist progression to AIDS for more than 10 years have been shown to maintain a reduced viral burden compared to people who rapidly progress to AIDS [21•,22•]. Similarly, naturally infected free-ranging African green monkeys, which do not

develop immunodeficiency, have a much lower viral load than immunodeficient SIV-infected macaques or AIDS patients [18•,19,23]. In addition, the more pathogenic strains of SIV tend to produce a higher *in vivo* viral titer than milder strains [24,25].

There is indirect evidence that viral load is similarly correlated with pathogenicity in felids. Amplification of FIV DNA from domestic cat lymphocytes usually requires only a single round of PCR, whereas the more sensitive nested PCR is generally required for samples from lions, pumas, and leopards ([8•,10•]; MA Carpenter, SJ O'Brien, unpublished data). This observation is consistent with a lesser viral load in the wild cats, in which FIV is not pathogenic.

The viral load of HIV (and probably FIV) is a product of continuous high viral replication balanced by an equally rapid virus removal through turnover of CD4 cells [26•,27•]. This dynamic process characterizes the asymptomatic phase of the disease, during which the immune system, far from being compromised, is actually extremely active. AIDS results when the immune system is eventually overwhelmed by the continuous barrage of virus. The decline of immune function in AIDS patients apparently reflects the overtaking of immune responses by virus evolving *in situ* until 'escape mutants' occur and predominate the viral population [28–30]. Viral escape from immune surveillance may be due to mutational acquisition of viral peptide motifs less easily recognized by the host major histocompatibility complex (MHC) [31,32]. Under such a model of viral load being a dynamic equilibrium between viral replication and removal, it would only take small alterations in either the rate of viral replication or in the efficiency

of virus removal by the immune system to change the disease outcome.

It may also be important that, in a situation with such rapid viral mutation and destruction, chance would have an enormous role in determining which viral mutations survived. Numerous functionally neutral new mutations would be carried along with the immune-selected variant in a viral version of molecular hitch-hiking. Empirical identification of the functionally operative mutation in the presence of all the hitch-hiking neutral variants is a difficult challenge that has yet to be accomplished.

Within an individual host, a rapidly replicating viral strain would soon predominate over a slower replicating strain. If a strain replicated too rapidly, however, it would risk killing the host prior to being transmitted to a new host. Therefore the rate of viral replication may be determined by a compromise between these two selective forces. If a virus mutated such that it were transmitted more readily between hosts, the rate of viral replication would be able to increase, together with the pathogenicity of the virus. Similarly, if the characteristics of the host population changed such that viral transmission was facilitated, rapidly replicating strains would be favored, and an increase in pathogenicity would result [33•]. It follows that the emergence of pathogenic immunodeficiency viruses in humans and domestic cats could be related to the population characteristics that these two domesticated species have in common, such as high population density and high population mobility. The lower pathogenicity of FIV in the wild cats could be seen as a more stable or 'normal' situation, which occurs in populations of a relatively low density and limited mobility. This may be true for the solitary cat species which appear to have low FIV seroprevalence [7,34]. It seems unlikely, however, to apply to lions in which the seroprevalence is high (80–90%) and social behavior would facilitate transmission of the virus [8•,35].

Developing host resistance to viral infection

By what mechanisms can a host species become resistant to a viral infection? The resistance is often already there among the natural genetic variation present in any population, but only in a proportion of the individuals. Resistance becomes endemic through selective elimination of the susceptible individuals and consequent increased reproductive success of the resistant individuals.

The relative virulence of a pathogenic agent in a species may be determined by the time that has been available for coadaptation of virus and host populations. Some estimates suggest that HIV-1 has been in the human population for less than 100 years [18•]. The severity of the HIV-1 epidemic therefore reflects the emergence of a novel virus into a large population of mostly

susceptible individuals, probably from a long infected but resistant primate host species, such as chimpanzees or other non-human primates [36,37].

The FIV pathology in domestic cats, but not in lions or pumas, may have a similar explanation. FIV sequence variation is lower in domestic cats than in lions or pumas ([38]; Table 1). If acquisition of genomic diversity is time dependent (as we believe it is) then the domestic cat probably became infected with FIV more recently than did pumas or lions. Yet the present world-wide prevalence of domestic cat FIV [2,39••], plus the high rate of synonymous substitution in the *env* gene, suggests that its introduction to cats preceded the emergence of HIV-1 in humans [39••,40]. A candidate for the donor species may become clear when more felid FIV strains are analyzed. In wild cat populations the susceptible individuals have been (or are being) eliminated, leaving a resistant population. The same outcome is likely for domestic cats and humans: the difference is that medical and veterinary clinicians are documenting the process.

There are several aspects of the host physiology which could conceivably confer resistance to viral infection, such as the degree of susceptibility of individual cells to viral replication, or by the ability of the MHC to mount an appropriate immune response [41]. Domestic cats have been shown to produce neutralizing antibodies to FIV, but these are only partially effective and do not prevent immunodeficiency [42•], possibly because of the production of neutralization escape mutants [43]. Perhaps the production of neutralizing antibodies is more effective in wild cats thus preventing FIV from causing immune suppression. Long-term survivors of macaque SIV infection (non-progressors to AIDS) have higher antibody titers than macaques which succumb to disease earlier [43], suggesting that the disease outcome is correlated with the strength of antibody production. An additional mechanism for achieving disease resistance is demonstrated by the CD8 cells of African green monkeys, which secrete a substance that suppresses SIV replication [44].

Studies of maternal transmission of HIV-1 suggest a way in which individuals can develop resistance to lentivirus infection. A number of healthy seronegative children born to seropositive mothers have HIV-1 infection detected by PCR, *in situ* hybridization or virus isolation [45•,46]. It was suggested that exposure of a fetus to HIV-1 could lead to a form of tolerance, such that no antibodies to HIV-1 are produced, and no destruction of infected CD4 cells occurs [45•]. As HIV-1 replicates only in activated cells this would provide fewer cells for HIV-1 to infect, thereby slowing viral replication. Healthy seronegative domestic cats which carry FIV nucleic acids have also been observed [47]. If this phenomenon is found in wild cats, this is another mechanism by which they may have developed resistance to FIV-associated pathogenesis.

Disease resistance can also be conferred by infection with a non-pathogenic strain of the same virus, which acts as a

vaccine. For example, it has been suggested that infection with HIV-2, which takes much longer to cause disease than HIV-1, may confer resistance to HIV-1 infection [48]. A non-pathogenic variant could originate through mutation or deletion, and if the deletion were substantial, would have little chance of reverting to a pathogenic strain. An example of such a deletion mutant is provided by a *nef*-deleted SIV isolate which successfully protected its hosts from infection by pathogenic SIV strains [49].

It is difficult to see how a non-pathogenic strain would ever originate from a rapidly replicating strain as it would be quickly outnumbered [50]. However, there is evidence for replication deficient deletion mutants that can compete effectively against rapidly replicating viruses. Known as defective interfering particles (DIPs), these spontaneous deletion mutants manage to replicate at the expense of the parent virus, while depending on the parent virus to enable them to complete their replication cycle. The advantage of the DIPs may reside in their shorter genomes being replicated more rapidly, but it has been suggested that more active means of interference occur, such that only DIPs are released from the infected host cell. The interaction of the parent virus and DIPs can theoretically result in a spontaneous cure through the elimination of the parent virus [51].

A non-pathogenic virus which becomes integrated in the germline of the host, an endogenous retrovirus, would be transmitted vertically from parent to offspring as a chromosomal element. If it conferred resistance to infection by related pathogenic viruses then it could easily spread through the population as a result of selection for disease resistance. At this stage, it is not even necessary for the complete viral genome to be present. This appears to have happened in a California wild mouse population in which a transcriptionally active truncated retrovirus has become a part of the genome [52]. The insertion consists of part of the *pol* gene, a transcriptionally active *env* gene, and the 3' long terminal repeat, and has 90% homology to an exogenous pathogenic retrovirus present in the mouse population. It is thought to confer resistance to the lethal virus by producing proteins which block the cell surface receptors normally used by the virus. Similar genomic adaptations may be found to confer resistance to FIV in the wild cats.

Conclusion

The information currently available suggests that wild cats are resistant to the FIV strains they carry, and that this immunity is likely to be due to coadaptation of the virus and host. There is no indication yet which parts of the felid and virus genomes were involved in coadaptation. Clues about the pathogenicity of FIV in wild cats may be obtained by examining other viruses, such as HIV-1 and SIV, in which parallel processes are

occurring. Information about the mechanisms which allow wild cats to tolerate FIV infection may be useful in finding ways to control infectious disease, particularly FIV in domestic cats and HIV-1 in man.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
 - of outstanding interest
1. Pedersen NC, Ho EW, Brown ML, Yamamoto JK: **Isolation of a T-lymphotropic virus from domestic cats with an immunodeficiency-like syndrome.** *Science* 1987, **235**:790-236.
 2. Pedersen NC: **The Feline Immunodeficiency Virus.** In *The Retroviridae*. Edited by Levy JA. New York: Plenum Press; 1993:181-228.
 3. English RV, Nelson P, Johnson CM, Nasisse M, Tompkins WA, Tompkins MB: **Development of clinical disease in cats experimentally infected with feline immunodeficiency virus.** *J Infectious Dis* 1994, **170**:543-552.
 4. Ackley CD, Yamamoto JK, Levy N, Pederson NC, Cooper MD: **Immunologic abnormalities in pathogen-free cats experimentally infected with feline immunodeficiency virus.** *J Virol* 1990, **64**:5652-5655.
 5. Torten M, Franchini M, Barlough JE, George JW, Mozes E, Lutz H, Pedersen NC: **Progressive immune dysfunction in cats experimentally infected with feline immunodeficiency virus.** *J Virol* 1991, **65**:2225-2230.
 6. Hoffman-Fezer G, Thum J, Ackley C, Herbold M, Mysliwicz J, Thefeld S, Hartmann K, Kraft W: **Decline in CD4+ cell numbers in cats with naturally acquired feline immunodeficiency virus infection.** *J Virol* 1992, **66**:1484-1488.
 7. Brown EW, Miththapala S, O'Brien SJ: **Prevalence of exposure to feline immunodeficiency virus in exotic felid species.** *J Zoo Wildlife Med* 1993, **24**:357-364.
 8. Brown EW, Yuhki N, Packer C, O'Brien SJ: **A lion lentivirus related to feline immunodeficiency virus: epidemiologic and phylogenetic aspects.** *J Virol* 1994, **68**:5953-5968.
- This paper reports the isolation of a novel feline lentivirus from the lion and presents an extensive analysis of the genetic diversity of this virus in free-ranging populations of African lions.
9. Olmsted RA, Langley R, Roelke ME, Goeken RM, Adger-Johnson D, Goff JP, Albert JP, Packer C, Laurenson MK, Caro TM *et al.*: **Worldwide prevalence of lentivirus infection in wild feline species: epidemiologic and phylogenetic aspects.** *J Virology* 1992, **66**:6008-6018.
 10. Langley RJ, Hirsch VM, O'Brien SJ, Adger-Johnson D, Goeken RM, Olmsted RA: **Nucleotide sequence analysis of puma lentivirus (PLV-14): genomic organization and relationship to other lentiviruses.** *Virology* 1994, **202**:853-864.

The complete nucleotide sequence of puma FIV is reported and compared to FIV from domestic cats in terms of genome organization and sequence similarity.

11. Talbot RL, Sparger EE, Lovelace KM, Fitch WM, Pederson NC, Luciw PA, Elder JH: **Nucleotide sequence and genomic organization of feline immunodeficiency virus.** *Proc Natl Acad Sci USA* 1989, **86**:5743–5747.
12. Olmsted RA, Hirsch VM, Purcell RH, Johnson PR: **Nucleotide sequence analysis of feline immunodeficiency virus: genome organization and relationship to other lentiviruses.** *Proc Natl Acad Sci USA* 1989, **86**:8088–8092.
13. Jin MJ, Rogers J, Phillips-Conroy JE, Allan JS, Desrosiers RC, Shaw GM, Sharp PM, Hahn BH: **Infection of a yellow baboon with Simian immunodeficiency virus from african green monkeys: evidence for cross-species transmission in the wild.** *J Virol* 1994, **68**:8454–8460.
14. Haesevelde MV, Decourt J-L, De Leys RJ, Vanderborgh B, Groen GVD, Heuverswijn HV, Saman E: **Genomic cloning and complete sequence analysis of a highly divergent african human immunodeficiency virus isolate.** *J Virol* 1994, **68**:1586–1596.
15. Pancino G, Castetot S, Sonigo P: **Differences in feline immunodeficiency virus host cell range correlate with envelope fusogenic properties.** *Virology* 1995, **206**:796–806.
This study highlights the role of the viral envelope in the infection process by comparing the ability of envelope glycoproteins from different strains of domestic cat FIV to cause syncytium formation in cultured cells.
16. Phillips TR, Talbot RL, Lamont C, Muir S, Lovelace K, Elder JH: **Comparison of two host cell range variants of feline immunodeficiency virus.** *J Virol* 1990, **64**:4605–4613.
17. Johnson BK, Stone GA, Godec MS, Asher DM, Gajdusek DC, Gibbs CJ: **Long-term observations of human immunodeficiency virus-infected chimpanzees.** *AIDS Res Hum Retroviruses* 1993, **4**:375–378.
18. Hirsch VM, Johnson PR: **Pathogenic diversity of simian immunodeficiency viruses.** *Virus Res* 1994, **32**:183–203.
A comprehensive review of SIV diversity with emphasis on pathogenesis.
19. Hirsch VM, Dapolito G, Johnson PR, Elkins WR, London WT, Montali RJ, Goldstein S, Brown C: **Induction of AIDS by simian immunodeficiency virus from an african green monkey: species-specific variation in pathogenicity correlates with extent of *in vivo* replication.** *J Virol* 1995, **69**:955–967.
20. Lutz H, Isenbugel E, Lenhmann R, Sabapara RH, Wolfensberger C: **Retrovirus infections in non-domestic felids: serological studies and attempts to isolate a lentivirus.** *Vet Immunol Immunopath* 1992, **35**:215–224.
21. Cao Y, Qin L, Zhang L, Safrit J, Ho DD: **Virologic and immunologic characterization of long-term survivors of human immunodeficiency virus type 1 infection.** *N Engl J Med* 1995, **332**:201–208.
See annotation [22*].
22. Pantaleo G, Menzo SM, Vaccarezza M, Graziosi C, Cohen OJ, Demarest JF, Montefiori D, Orenstein JM, Fox C, Schragar LK et al.: **Studies in subjects with long-term nonprogressive human immunodeficiency virus infection.** *N Engl J Med* 1995, **332**:209–216.
This paper and [21*] present studies of long-term survivors of HIV-1 infection which both report a low viral load and strong immune responses in these people.
23. Hartung S, Boller K, Cichutek K, Norley SG, Kurth R: **Quantitation of a lentivirus in its natural host: simian immunodeficiency virus in african green monkeys.** *J Virol* 1992, **66**:2143–2149.
24. Fultz PN, Zack PM: **Unique lentivirus–host interactions: SIV_{simmPBj14} infection of macaques.** *Virus Res* 1994, **32**:205–225.
25. Fultz PN: **SIV_{simmPBj14}: an atypical lentivirus.** *Curr Top Microbiol Immunol* 1994, **188**:65–76.
26. Wei X, Ghosh SK, Taylor ME, Johnson VA, Emini EA, Deutsch P, Lifson JD, Bonhoeffer S, Nowak MA, Hahn BH et al.: **Viral dynamics in human immunodeficiency virus type 1 infection.** *Nature* 1995, **373**:117–122.
See annotation [27*].
27. Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M: **Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infections.** *Nature* 1995, **373**:123–126.
Two exciting reports (see also [26*]) characterizing viral dynamics in HIV-1 infection as a situation of extremely rapid viral turnover accompanied by equally dynamic turnover of CD4 lymphocytes.
28. Nowak MA, Anderson RM, McLean AR, Wolfs TFW, Goudsmit J, Ray RM: **Antigenic diversity thresholds and the development of AIDS.** *Science* 1991, **254**:963–969.
29. Phillips RE, Rowland-Jones S, Nixon DF, Gotch FM, Edwards JP, Ogunlesi AO, Elvin JG, Rothbard JA, Bangham CRM, Rizza CR, McMichael AJ: **Human immunodeficiency virus genetic variation that can escape cytotoxic T cell recognition.** *Nature* 1994, **354**:453–459.
30. O'Brien SJ, Mann DL: **Adaptive chaos and AIDS.** *Curr Biol* 1992, **2**:203–205.
31. Engelhard VH: **Structure of peptides associated with MHC class I molecules.** *Curr Opin Immunol* 1994, **6**:13–23.
32. Rammensee H-G, Friede T, Stevanovic S: **MHC ligands and peptide motifs: first listing.** *Immunogenetics* 1995, **41**:178–228.
33. Ewald PW: **Evolution of mutation rate and virulence among human retroviruses.** *Philos Trans R Soc Lond [B]* 1994, **346**:333–343.
A thought-provoking analysis of the factors affecting the evolution of virulence in HIV-1, with implications for the control of the AIDS pandemic.
34. Brown EW, Olmsted RA, Martenson JS, O'Brien SJ: **Exposure to FIV and FIPV in wild and captive cheetahs.** *Zoo Biology* 1993, **12**:135–142.
35. Spencer JA, Van Dijk AA, Horzinek MC, Egberink HF, Bengis RG, Keet DF, Morikawa S, Bishop DHL: **Incidence of feline immunodeficiency virus reactive antibodies in free-ranging lions of the Kruger National Park and the Etosha National Park in southern Africa detected by recombinant FIV p24 antigen.** *Onderstepoort J Vet Res* 1992, **59**:315–322.
36. Franchinni G, Reitz MS: **Tenth anniversary perspectives on AIDS.** *AIDS Res Hum Retroviruses* 1994, **10**:1047–1060.
37. Janssens W, Franssen K, Peeters M, Heyndrickx L, Motte J, Bedjabaga L, Delaporte E, Piot P, Van der Groen G: **Phylogenetic analysis of a new chimpanzee lentivirus SIV_{cpz-gab2} from a wild-captured chimpanzee from Gabon.** *AIDS Res Hum Retroviruses* 1994, **10**:1191–1192.
38. Greene WK, Meers J, Chadwick B, Carnegie PR, Robinson WF: **Nucleotide sequences of Australian isolates of the feline immunodeficiency virus: comparison with other feline lentiviruses.** *Arch Virol* 1993, **132**:369–379.
39. Sodora DL, Shpaer EG, Kitchell BE, Dow SW, Hoover EA, Mullins JL: **Identification of three feline immunodeficiency virus (FIV) *env* gene subtypes and comparison of the FIV and human immunodeficiency virus type 1 evolutionary patterns.** *J Virol* 1994, **68**:2230–2238.
Sequences from the *env* gene of domestic cat FIV representing locations in British Columbia and the USA were analyzed with existing *env* sequences, providing evidence for three distinct subtypes of domestic cat FIV and giving insight into the duration and pattern of evolution of FIV in domestic cats.
40. Rigby MA, Holmes EC, Pistello M, Mackay A, Leigh Brown AJ, Neil JC: **Evolution of structural proteins of feline immunodeficiency virus: molecular epidemiology and evidence of selection for change.** *J Gen Virol* 1993, **74**:425–436.
41. Williams LM, Cloyd MW: **Polymorphic human gene(s) determines differential susceptibility of CD4 lymphocytes to infection by certain HIV-1 isolates.** *Virology* 1991, **184**:723–728.
42. Osborne R, Rigby M, Siebelink K, Neil JC, Jarret O: **Virus neutralization reveals antigenic variation among feline immunodeficiency virus isolates.** *J Gen Virol* 1994, **75**:3641–3645.
The antigenic variation among domestic cat FIV isolates was analyzed by testing for cross-reactivity to virus neutralizing antibodies in a study relevant to vaccine design.

43. Burns DPW, Desrosiers RC: **Envelope sequence variation, neutralizing antibodies, and primate lentivirus persistence.** *Curr Top Microbiol Immunol* 1994, **188**:185-219.
44. Ennen J, Findelee H, Duttmar MT, Norley S, Ernst M, Kurth R: **CD8⁺ T lymphocytes of african green monkeys secrete an immunodeficiency virus- suppressing lymphokine.** *Proc Natl Acad Sci USA* 1994, **91**:7207-7211.
45. Jehuda-Cohen T: **A new look at HIV transmission from seropositive mothers to their infants: the facts beyond serology.** *Israel J Med Sci* 1994, **30**:364-368.
- A provocative reinterpretation of HIV and SIV data regarding healthy, seronegative, but virus-positive, children born to HIV- and SIV-positive mothers.
46. Baur A, Schwarz N, Ellinger S, Korn K, Harrer T, Mang K, Jahn G: **Continuous clearance of HIV in a vertically infected child.** *Lancet* 1989, **ii**:1045.
47. Dandekar S, Beebe AM, Barlough J, Phillips T, Elder J, Torten M, Pedersen NC: **Detection of feline immunodeficiency virus (FIV) nucleic acids in FIV-seronegative cats.** *J Virol* 1992, **66**:4040-4049.
48. Travers K, Mboup S, Marlink R, Gueye-Ndiaye A, Siby T, Thior I, Traore I, Dieng-Sarr A, Sankale J-L, Mullins C *et al.*: **Natural protection against HIV-1 infection provided by HIV-2.** *Science* 1995, **268**:1612-1615.
- A long-term study of commercial sex workers which suggests that infection with the less pathogenic HIV-2 might confer a degree of protection from HIV-1.
49. Daniel MD, Kirchoff F, Czajak SC, Sehgal PK, Desrosiers RC: **Protective effects of a live attenuated SIV vaccine with a deletion in the *nef* gene.** *Science* 1992, **258**:1938-1941.
50. Kestler HW, Ringer DJ, Mori K, Panicali DL, Sehgal PK, Daniel MD, Desrosiers RC: **Importance of the *nef* gene for maintenance of high virus loads and for development of AIDS.** *Cell* 1991, **65**:651-662.
51. Kirkwood TBL, Bangham CRM: **Cycles, chaos, and evolution in virus cultures: a model of defective interfering particles.** *Proc Natl Acad Sci USA* 1994, **91**:8685-8689.
52. Gardner MB, Kozak CA, O'Brien SJ: **The Lake Casitas wild mouse.** *Trends Genet* 1991, **7**:22-27.
53. Felsenstein J: **PHYLIP: phylogeny inference package, version 3.5.** Seattle: University of Washington; 1993.

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