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Feline Immunodeficiency Virus (FIV) as A Model for Study of Lentivirus Infections: Parallels with HIV

John H. Elder[1], **Ying-Chuan Lin**[1], **Elizabeth Fink**[1], and **Chris K. Grant**[2]

[1]Department of Immunology and Microbial Sciences, The Scripps Research Institute, La Jolla, CA 92037

[2]Custom Monoclonals, Int'l. Corp., W. Sacramento, CA 95691

Abstract

FIV is a significant pathogen in the cat and is, in addition, the smallest available natural model for the study of lentivirus infections. Although divergent at the amino acid level, the cat lentivirus has an abundance of structural and pathophysiological commonalities with HIV and thus serves well as a model for development of intervention strategies relevant to infection in both cats and man. The following review highlights both the strengths and shortcomings of the FIV/cat model, particular as regards development of antiviral drugs.

Introduction

FIV-induced AIDS in Cats

FIV causes an AIDS-like syndrome in the domestic cat, with many similarities to HIV-induced AIDS in man (1;Table 1). Like HIV, FIV can be transmitted via mucosal exposure, blood transfer, and vertically via prenatal and postnatal routes. FIV is tropic for T cells (1–6) macrophages (7–10), and central nervous system cells (CNS (11,12)). *In vivo* tissue tropism studies (11,12) have demonstrated viral RNA in T cells, macrophages, and CNS cells. FIV RNA has also been demonstrated in association with follicular dendritic cells (FDC) (13–15). Although $CD4^+$ cell decline is a hallmark of FIV infection, FIV has a broader lymphocyte tropism than $CD4^+$ T cells, with infection also evident in at least a subset of $CD8^+$ T cells and B cells *in vitro* and *in vivo* (16–18). The course of the disease is also similar in cats and man, with a relatively short acute phase measure in weeks and denoted by increasing viral loads, febrile episodes, weight loss, lymphadenopathy, and neutropenia. During this time, $CD4^+$ T cells decline as well as neutrophils and a percentage of cats will not recover and require humane euthanasia in experimental infections. However, most infected cats exhibit an increase in $CD8^+$ T cells along with a strong humoral antibody response which allows them to weather this initial phase of the infection (19,20). The acute phase is followed by what is often referred to as an “asymptomatic”, or Latent phase denoted by relative quiescence of the infection in the face of strong antiviral immune responses, with lower viral titers and minimal clinical symptoms. As with HIV infections in man, this latent phase can be quite protracted in the cat, lasting from several months to several years. The rate of progression of the disease can dependant on the genotype of the infecting FIV and is also likely influenced by undefined genetic determinants of the particular cat. As with HIV-infected people, FIV-infected cats vary in the response to infection, with some animals remaining phenotypically normal throughout the course of the infection, while others suffer from assorted maladies including oral lesions, febrile episodes, bouts of diarrhea, and dehydration. The terminal phase is marked by further

Correspondence to: John H. Elder.

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decline in the antiviral response, with resultant increase in plasma viral load and onset of clinical symptoms of immunodeficiency. Lymphoid tissue alterations are similar to those noted with primate lentivirus infections, including thymic depletion, lymphoid hyperplasia, plasmacytosis, and terminal lymphoid depletion (2,8–10,13,19,21). Neurological manifestations are often evident (12 22–25), noted by delays auditory evoked and visual evoked potential changes (22,23) and marked alterations in sleep patterns in experimentally infected animals (26). As with human AIDS, FIV-infected cats ultimately succumb to opportunistic infections.

Given the above parallels with HIV infection, both from the standpoint of target tissues and course of disease, study of FIV infection of cats can serve as a useful tool for identifying and understanding the immunological and cellular pressures that occur in the course of both lentivirus infections. As will be seen below, many facets of the virus life cycle are shared between the two lentiviruses, although distinct courses are taken in specific elements of the virus life cycle. Hopefully, the commonalities may lead to development of broad-based interventions that will block progression of the disease in both systems.

The Virus Genome

FIV and HIV share many features in their genomes, but also have important differences that influence the utility of comparative studies (27–29). The length of the FIV genome is around 9400 nucleotides, approximating that of HIV and other lentiviruses. The integrated provirus is bordered by long terminal repeats (LTRs) and possesses *gag*, *pol*, and *env* genes, common elements of all retroviruses. Also like other lentiviruses, FIV uses a $tRNA_{lys}$ primer-binding site to prime first strand synthesis by reverse transcriptase (RT). Transport of full-length and multiply spliced mRNAs is regulated by Rev, but the *cis* element acted on by Rev, the RRE, as well as second coding exon of Rev are located 3' of *env* instead of overlapping the TM coding region as in primate lentiviruses (30). FIV does not encode the *vpr*, *vpu*, or *nef* genes present in HIV and also lacks a Tat/Tar system for regulating viral gene transcription. FIV does encode a small gene product expressed along with Rev from a bicistronic mRNA, termed OrfA (or Orf2). Expression of OrfA is necessary for productive growth of FIV in T cells and it's expression results in a net increase in translation of gene products whose transcription is driven by the FIV LTR (31–33). However, OrfA does not act via a TAR element, as is the case with HIV-1 Tat and does not function in the manner of tradition gene activators (34). Gemeniano et al. (2003,2004) carried out studies that indicated that there is no wholesale increase in transcription in the presence of OrfA and thus, the increase in net translation may be the consequence of downstream action (35–36). They also showed that OrfA may have relatedness to Vpr and present indications of involvement in virus release from the cell and influence on cell cycle, similar to HIV Vpr (36). Thus, OrfA may be a multi-functional protein capable of substituting for more than one gene product lacking from FIV relative to HIV-1. Interestingly, OrfA shows the greatest sequence variability of all the viral genes, surpassing even the highly variable Env region when compared across viral clades. On one hand, if immunological pressure is driving this variability, it would be expected that the protein would reside on the surface of the cell or virion, which as far as we know is not the case. Alternatively. This variability might indicate a lack of any functional pressure to maintain sequence conservation. However, we know the protein plays an important role in virus replication in T cells and furthermore. Furthermore, a lack of function would likely result in even more variability and frequent appearance of stop codons and deletions, which is not the case. It remains to be determined the significance of this variability relative to the function of this interesting protein in the virus life cycle.

As for other lentiviruses, the Gag polyprotein of FIV is expressed from the full-length viral mRNA and is comprised of a myristoylated matrix (MA) protein, a capsid (CA) protein, and

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a nucleocapsid (NC) protein that has two copies of a zinc finger motif. FIV lacks a p6 protein between Gag and Pol, but contains instead a p2 protein (37) that has a P(S/T)AP domain necessary for virus budding (38). Thus, it is likely that p2 serves the same purpose as HIV-1 p6. It is now recognized that the PTAP domain in HIV p6 recruits TSG 101, a cellular protein involved in the virus budding process (39–43) and a similar role is likely in the FIV life cycle.

The FIV Pol proteins are expressed from the full-length viral mRNA as a large Gag/Pol polyprotein generated via a −1 frameshift approximately once every fifteen translational events (44). FIV Pol is comprised of protease (PR), reverse transcriptase (RT), and integrase (IN) genes that are common with HIV-1, but also encodes a gene for deoxyuridine pyrophosphatase (DU) between RT and IN that is lacking from the human lentivirus (45,46). FIVs lacking DU are incapable of successful propagation in cells that are not undergoing division, such as primary macrophages, whereas wild type FIV will productively infect such cells (46). These findings are also true for equine infectious anemia virus (EIAV), which is also a DU^+ lentivirus and primarily lives in macrophages (47,48). DU is not necessary for replication in rapidly dividing cells, due to high endogenous levels of DU in the replicating cell (46). The primary role of DU is to prevent mis-incorporation of uracil into DNA by limiting the concentration of dUTP through conversion to dUMP, a precursor for dTTP synthesis. If the virus is mutated to deactivate or remove DU, the mutant FIV shows a five- to eight-fold increase in G->A transition mutations compared to wild type FIV during replication in macrophages *in vivo*, consistent with mis-incorporation of uracil into viral DNA during reverse transcription. It is as yet unclear as to how HIV, which does not encode DU, avoids high-level mis-incorporation of uracil in viral DNA. However, Vpr may play a role via an association with uracil N-glycosylase (Ung), the enzyme responsible for excision of uracil mis-incorporated into DNA (49). Mutations of Vpr that knock out Ung association causes a phenotype remarkably similar to the DU^- phenotype noted in FIV and EIAV (50).

In common with HIV, FIV encodes viral infectivity factor (Vif) immediately 3' of *pol*, as in other lentiviruses, with the exception of EIAV which lacks a *vif* gene. The primary role of Vif appears to be to reduce G->A transition mutations by preventing cytidine deamination by the cellular deaminase, APOBEC-3G (51,52). Vif interacts with APOBEC-3G and directs the enzyme to the proteosome for degradation, thus preventing its incorporation into the virus particle. FIV Vif shows substantial sequence divergence from HIV Vif, but is the same size and retains the consensus sequence, SLQ(Y/F)LA critical to Vif function and common to all Vifs. The role of Vif in the FIV life cycle is yet to be fully elucidated, but has been shown to be essential for virus propagation in available cat cell lines (53). Experiments indicated that FIV Vif cannot transcomplement Vif-Defective HIV (54; other publications by Malim and colleagues). Thus, the function of the protein is influenced by species divergent elements in spite of the common consensus sequence.

The *env* gene of FIV encodes heavily glycosylated SU and TM proteins, with 5–30% amino acid sequence divergence, similar to HIV Env. There are 5 consensus variable regions (V1–V5) in SU (29,55) (Figure 1). The mechanism of virus entry for FIV closely parallels SU/receptor interactions noted with HIV from the standpoint of employing both a primary binding and entry receptor for infection and sequence variability in Env. Four *env* subtypes (clades) plus numerous outliers have been defined via Env sequences (56). The intra- and inter-clade variation of FIV follows a pattern similar to that noted in HIV clades, as assessed by heteroduplex mobility shift assays (57). Assessments using synonymous/non-synonymous base change ratios and level of mutational saturation have been used to define distinctions between the most commonly found FIV *env* clades, A and B (58,59).

In spite of the targeting of $CD4^+$ T cells in vivo, FIV does not use CD4 as a primary *binding* receptor. However, all domestic cat FIVs we have examined to date share with certain T cell-

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tropic HIVs the utilization of the chemokine receptor, CXCR4 as an *entry* receptor as judged by the universal sensitivity of infection to the X4 antagonist, AMD3100 (60,61). *Ex vivo* studies have shown that FIV infection of certain cells may occur solely mediated by CXCR4 if expression of the chemokine receptor is sufficiently high (62,63). As to the initial binding receptor, Shimojima et al (64) demonstrated that this molecule is the activation marker, CD134, confirmed and extended in other studies (18,62,63). The demonstration that CD134 is up-regulated on activated $CD4^+$ T cells (18) explains how FIV targets this cell population *in vivo* in spite of failure to bind CD4. Furthermore, soluble CD134 can interact with the virus to facilitate productive infection of $CD134^-$ $CXCR4^+$ target cells (65), indicating that the binding receptor alters the conformation of SU to promote high affinity binding to CXCR4. This observation parallels findings with CD4 binding to HIV SU and indicates that although different primary binding receptors are utilized, both viruses use very similar mechanisms to infect target cells. Furthermore, neutralizing monoclonal antibodies have been identified that only neutralize the virus when soluble CD134 is present (65,66). These antibody epitopes, as well as the CXCR4 binding domain, reside on the V3 loop of FIV SU (65,66;Figure 1). The V2 loop also has many antibody binding epitopes, but none of these antibodies have been found to inhibit to date. If the epitope repertoire recognized in mice is any indicator, the V4 and V5 domains are relatively quiet from an immunological sense, likely reflecting a relatively low exposure to the environment. The findings of neutralizing epitopes exposed after virus binding parallel observations of such masked epitopes on HIV that become available upon interaction of SU with the CD4 binding receptor (67–71). The striking similarity and conservation of entry mechanisms between the two divergent lentiviruses likely the result of common immunological pressures in the two hosts. Thus, the feline lentivirus offers a valuable venue to study the mechanisms of lentivirus infection of T cells and for development of strategies to compromise the virus' ability to escape immune surveillance.

FIV as A Model for Drug Design

As outlined above, HIV and FIV have evolved along unique pathways that have led to development of alternative mechanisms to deal with certain aspects of replication, including transcriptional transactivation and uracil mis-incorporation. However, there are sufficient similarities to make the cat/FIV model a valuable tool for several lines of direct experimentation. The utilization of CXCR4 by FIV as one of the receptors used to enter target cells is an important similarity to a subset of HIV that can be explored in development of intervention strategies. In addition, commonalities in the target cell populations between FIV and HIV and most enzymes and structural components critical to virus replication present similar obstacles for perpetuation of species.

The enzymes encoded by *pol*, including PR, RT, and IN have common functions in the two viruses and in many cases, respond to the same inhibitors. In addition, defining the structural basis for failures to broadly inhibit the lentiviruses can provide essential information relevant to designing broad-based inhibitors. Use of the cat for development of broad-based protease inhibitors has been successful and has yielded an abundance of information regarding the regions that control both substrate and inhibitor sensitivities (72). Nucleoside analogs that interact with the active site of reverse transcriptase have been found efficacious against both FIV and HIV (73). It is likely that a similar will evolve for development of anti-integrase drugs. The structural proteins of Gag may also provide broad-based targets, since all lentiviruses share common morphological features. Elements of the virus core are likely to maintain commonalities in their mechanisms of action and orientations in the particles. The matrix, capsid, and nucleocapsid proteins may thus present effective targets for broad-based intervention strategies. As pointed out above, the P2 protein of FIV (37) is an apparent functional homologue to the P6 protein of HIV and shares late domain homologies (39,40).

Both HIV and FIV encode Vif proteins, which may provide an additional target for intervention strategies to be used in both lentivirus systems.

Development of Inhibitors to FIV PR

The aspartic protease. PR, is responsible for viral Gag and Gag-Pol polyprotein processing into individual structural and enzymatic proteins during assembly and maturation (37,74–78). This processing step is highly specific, ordered, and essential to generate infectious retrovirus particles (77,79–81). Therefore, PR has been a very important target for antiviral therapies (82–85). Several approved protease inhibitors are available that are effective for treating HIV-1 infection (84–87) and combination drug therapies, termed highly active retroviral therapy (HAART), have been used successfully in suppressing HIV-1 replication to undetectable levels in patients (86–91). However, drug resistance development is a persistent problem (91–99). As many as 40% of the patients receiving HAART have a viral rebound within the first 3 years and this number is likely to be higher outside of controlled studies (100). In addition, transmission of resistant HIV has been observed and is likely to increase with more patients on combination therapy (100). Also, poor tolerance to current protease inhibitors by a significant number of patients may lead to increased non-compliance, which may be the leading reason for cases of failure of HAART therapy. Side effects resulting from long-term drug treatment have also been observed. Both of the latter problems might be allayed by development of drugs with better bioavailability and length of efficacy per dosage, which would reduce the drug regimen. Thus, there is a need to develop novel inhibitors with activities against drug-resistant isolates that exhibit delayed resistance development and show a high degree of specificity (95). Defining the determinants of substrate specificity of the lentiviral PRs is a logical first step in the development of such broad-based inhibitors.

FIV protease, like HIV-1 protease, is a homodimeric aspartic proteinase and the two enzymes are very similar at the crystallographic level, particularly within the substrate binding pocket (101). However, FIV is distinct in that each monomer is comprised of 116 amino acids, as opposed to 99 amino acids for HIV-1 protease, with only 27 conserved amino acids between FIV and HIV-1 PRs. Like HIV protease, FIV PR is responsible for processing Gag and Gag-Pol polyproteins (37). Similar to SIV and HIV-1 PRs, autoproteolysis of FIV protease is observed *in vitro* (102). Despite these similarities, FIV PR is specific to its respective substrates and inhibitors of HIV-1 protease currently employed in clinic do not inhibit FIV protease (103–105). FIV protease cleaves the FIV MA/CA cleavage junction efficiently. However, it does not appreciably cut the HIV-1 MA/CA cleavage junction, despite the presence of four identical residues in the P3-P3' position. HIV-1 protease prefers its own substrates as well, but can cleave FIV MA/CA cleavage junction to some degree. Important to the present discussion, there are at least 6 mutations found in HIV-1 proteases associated with drug resistance that are identical to structurally equivalent residues of wild type FIV protease (105). Two particularly interesting resistance mutations of HIV-1 protease, Val32→Ile (FIV Ile37) and Ile50→Val (FIV Val59), are located in the substrate binding pockets of the protease, which suggests they may play an important role in the inhibitor and substrate selectivity of retroviral protease. Studies (72,106) have shown that a major structural distinction between FIV and HIV-1 PRs is that the combined S1/S3 substrate binding pocket is restricted in size relative to the same site in HIV-1 PR. This finding offers a structural explanation for the failure of the current HIV-1 PR inhibitors, which possess bulky P3 groups, to inhibit FIV PR (72). Importantly, many drug-resistant HIV-1 PRs appear to have more restricted *S*1/S3 subsites as well (106), reducing inhibitor binding affinities in a manner similar to the feline enzyme. In addition, the nature of S2/S2' amino acids is particularly critical in directing PR substrate specificity as well as certain inhibitor efficacies. Thus, studies directed at understanding the structural basis for inhibitor and substrate specificity in the feline and human systems may lead to development of broad-based inhibitors with efficacy for a range of HIV variants.

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Both FIV and HIV-1 PRs recognize, approximately, the P4-P4' residues of peptide substrates via a long cavity in the middle of the protease, as analyzed by biochemical experiments (78, 107–111) and crystallographic analyses (112–114). Both homodimeric PRs utilize an acid-base hydrolysis mechanism in which aspartic acids 25 and 25' (of HIV-1 PR; 30 and 30' for FIV PR) activate a water to perform a nucleophilic attack on the amide carbonyl between the P1 and P1' positions in various peptide substrates (108). Like most aspartic proteases, optimal substrate cleavage occurs at approximately pH 4–5 (95,110,115).

There are three major structurally conserved regions that make up the substrate binding pockets of PR: 1) the active core region (residues 30–38 for FIV; 25–33 for HIV); 2) the flap (residues 54–60 for FIV; 45–51 for HIV); and 3) C-terminal "90s loop" region (residues 98–101 for FIV; "80s loop" for HIV, residues 80–84). Within these regions, there are 11 amino acids that differ between FIV and HIV-1 proteases. These residues have proved to be good candidate targets for mutational studies of substrate selectivity. The 11 different amino acid residues in the S4 - S4' subsites of FIV protease; Ile35, Ile37, Gln54, Asn55, Met56, Ile57, Val59, Ile98, Gln99, Pro100 and Leu101, most likely account for the specificity of the substrate/inhibitor binding. The corresponding residues in HIV-1 protease are Asp30, Val32, Lys45, Met46, Ile47, Gly48, Ile50, Pro81, Val82, Asn83 and Ile84, respectively. We have prepared a series of mutant FIV PRs in which HIV-1 amino acid residues have been substituted into the FIV PR background at equivalent positions. Confirmation of the involvement of several of these residues in both substrate and inhibitor specificities has been obtained. These wild type and mutant FIV PRs have, and will continue to serve, as a structural library for further defining substrate specificity and for inhibitor refinement in the proposed research.

Influence of Polyprotein Structure on Processing

An increasing body of evidence points to a pivotal role of the polyprotein folding/conformation in the temporal cleavage of the Gag and Gag-Pol proteins that is necessary for generation of infectious virus (77,79,116–118). The studies of Swanstrom and colleagues (77,79,80,119–121) pointed out that polyprotein cleavage occurs in a specific order and that alteration of the order by site-directed mutagenesis of certain sites resulted in production of non-infectious HIV. In particular, cleavage at the N-terminus of NC appeared to be the earliest cleavage event, at least *in vitro*, and subsequent studies have shown early cleavage on either side of NC (119). Differences in the rate of cleavage of synthetic substrates encompassing the cleavage sites suggested that the order of cleavage was in part, dictated by the relative cleavage efficacy of each junction. However, more recent studies have indicated that the availability of sites around NC, based on folding of the polyprotein relative to the "embedded" protease, is likely the critical trigger to the initiation of ordered processing. Interesting studies of Kaplan, Dunn, and colleagues have shown that subtle changes at the N-terminus of the embedded protease can markedly influence polyprotein processing in *cis* with no apparent influence on the ability of free protease to cleave the polyprotein in *trans* (119,121). This finding underscores the role of polyprotein conformation in processing and the importance of the temporal cleavage of Gag-Pol in the generation of infectious virus. Structural and biochemical analyses have been performed on FIV PR to define distinctions with HIV PR to aid in understanding of the basis for processing (122–124). The results show that similar events occur during processing of FIV Gag-Pol polyprotein and the critical nature of the proper temporal cleavage of Gag/Pol in generating infectious virus offers yet another important target for inhibitor development that can be pursued using FIV as a model system.

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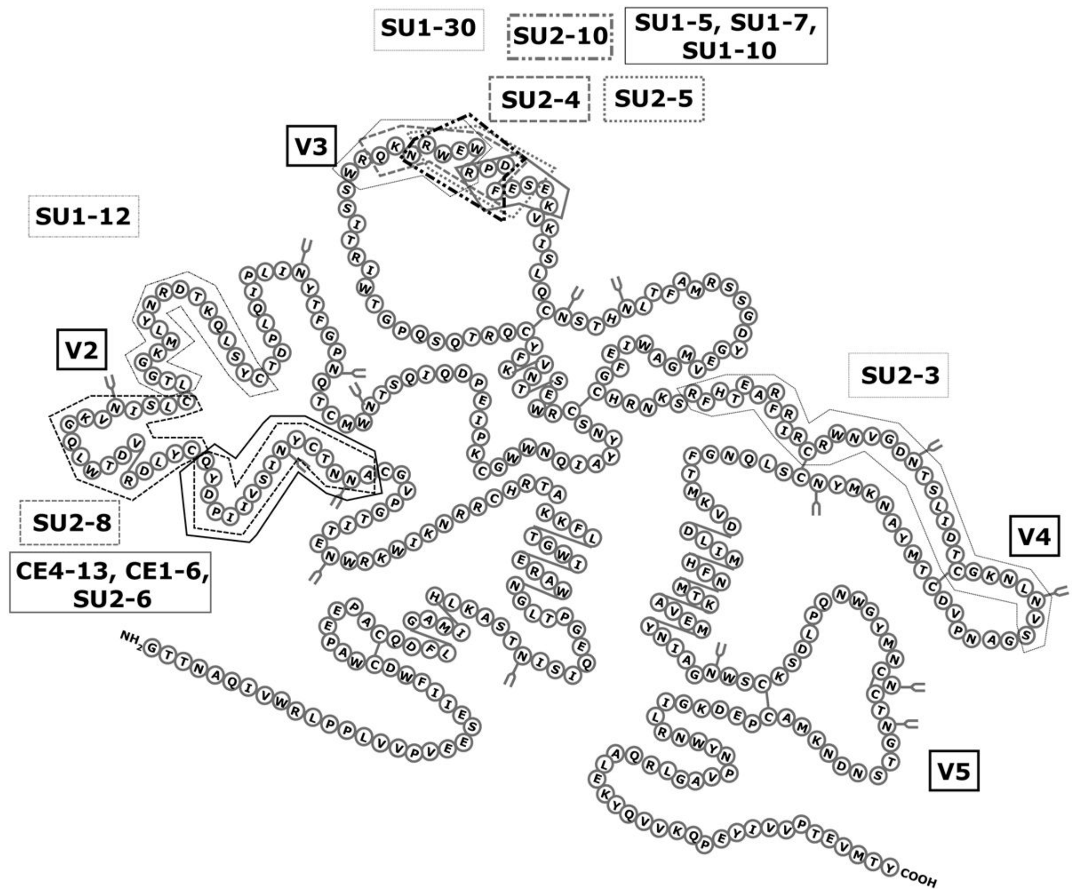

Figure 1.

Schematic diagram of the FIV SU, showing Variable (V) loops predicted from comparisons of multiple FIV Env sequences. Boxed areas in the structure indicate relative locations of the epitopes for a panel of monoclonal antibodies generated in mice using whole virions and mapped using nested synthetic peptides and deletion constructs (65,66; unpublished data)

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Table 1

COMPARATIVE PROPERTIES OF FIV AND HIV

	FIV	HIV
Transmission		
-blood contact	+	+
-mucosal contact	+	+
Target cell		
CD4$^+$ T cell	+	+
Macrophage	+	+
Dentritic cell,	+	+
Subset B cells	+	?
Microglia	+	+
Disease symptoms:		
Oral lesions	+	+
Lymphadenopathy	+	+
Neutropenia	+	+
CD4 T cell depletion	+	+
Hypergammaglobulinemia	+	+
Wasting, diahrrea	+	+
Secondary infections	+	+
CNS lesions	+	+
Viral genes encoded		
Gag,Pol,Env,LTRs	+	+
Vif	+	+
Rev/RRE	+	+
Tat/TAR	−	+
Vpr	−	+
Vpu	−	+
OrfA	+	−
DU	+	−
Receptors utilized		
-primary binding receptor		
CD4	−	+
CD134	+	−
Heparans	+	+
-entry receptor		
CXCR4	+	+
CCR5	−	+
-other chemokine receptors	?	+