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PATHOGENESIS AND IMMUNOLOGIC RESPONSE OF HIV

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ABSTRACT
HIV belongs to a large family of ribonucleic acid (RNA) lentiviruses. These viruses are characterized by association with diseases of immunosuppression or central nervous system involvement and with long incubation periods following infection before manifestations of illness become apparent. Retroviruses are unable to replicate outside of living host cells and do not contain deoxyribonucleic acid (DNA). HIV primarily infects cells that have CD4 cell-surface receptor molecules, using these receptors to gain entry. Once the HIV proviral DNA is within the infected cell's genome, it cannot be eliminated or destroyed except by destroying the cell itself. Though the pharmacologic therapies exist for prolonging the lives of persons infected with HIV. Such therapies are expensive and out-of-reach for many persons worldwide. All infected persons are at risk for illness and death from opportunistic infections and neoplastic complications because of the inevitable manifestations of AIDS. Considerable effort has been placed into education of persons potentially at risk for acquiring HIV. A proper understanding of AIDS issues, including the nature of HIV and its means of spread, should precede decisions regarding allocation of health care resources and control measures. Prevention strategies for HIV will require ongoing education, despite a general public perception, particularly among young persons, that AIDS is a peripheral threat that does not call for changes in lifestyle.

KEYWORDS: CD4 cell-surface receptor, Immunosuppression, Lentivirus, Retrovirus.

INTRODUCTION
Human immunodeficiency virus (HIV) and its subtypes are retroviruses and the etiologic agents of AIDS. HIV belongs to a large family of ribonucleic acid (RNA) lentiviruses.[1] Lentiviruses similar to HIV have been found in a variety of primate species, and some of these are associated with a disease process called simian AIDS. Unlike other retroviruses, the primate lentiviruses are not transmitted through the germ line, and no endogenous copies of the virus exist in the genome of susceptible species.[2] Molecular epidemiologic data suggest that HIV type 1 (HIV-1) is the most common subtype of HIV that infects human. It has been derived from the simian immunodeficiency virus, called SIVcpz, of the *Pan troglodytes troglodytes* subspecies of chimpanzee. The lentivirus strain SIVcpz is highly homologous with HIV-1. Other form of simian immunodeficiency virus found in sooty mangabeys (SIVsm) has similarities as well and likely gave rise to HIV-2.[3] There are four subtypes of HIV-1 called groups M, N, O, and P, and each of these groups appears to have arisen from an independent cross-species transmission event. One additional major human retrovirus, called HIV-2, has more similarity to simian immunodeficiency virus (SIV) than to HIV-1. HIV-2 is mostly found in West Africa, with its highest prevalence rates recorded in Guinea-Bissau and Senegal.[4]

STRUCTURE OF HIV
The mature virus consists of a bar-shaped electron dense core containing the viral genome two short strands of ribonucleic acid (RNA) about 9200 nucleotide bases long-along with the enzymes reverse transcriptase, protease, ribonuclease, and integrase, all encased in an outer lipid envelope derived from a host cell. This envelope has 72 surface projections, or spikes, containing an antigen, gp120 (envelope glycoprotein) that aids in the binding of the virus to the target cells with CD4 receptors. A second glycoprotein, gp41, binds gp120 to the lipid envelope.[5] The genome of HIV, similar to retroviruses in general, contains three major genes- *gag*, *pol*, and *env*. These genes code for the major structural and functional components of HIV, including envelope proteins and reverse transcriptase. The structural components encoded by *env* include the envelope glycoproteins: outer envelope glycoprotein gp120 and transmembrane glycoprotein gp41 derived from glycoprotein precursor gp160. Components

encoded by the *gag* gene include core nucleocapsid proteins p55 (a precursor protein), p40, p24 (capsid, or "core" antigen), p17 (matrix), and p7 (nucleocapsid); the important proteins encoded by *pol* are the enzyme proteins p66 and p51 (reverse transcriptase), p11 (protease), and p32 (integrase).[6] Although, most of the major HIV viral proteins, which include p24 (core antigen) and gp41 (envelope antigen), are highly immunogenic. The antibody responses vary according to the virus load and the immune competence of the host. The antigenicity of these various components provides a means for detection of antibody, the basis for most HIV testing.[7] Accessory genes carried by HIV include *tat*, *rev*, *nef*, *vif*, *vpr*, and *vpu* (for HIV-1) or *vpx* (for HIV-2).

The *rev* gene encodes for a regulatory protein which switches the processing of viral RNA transcripts to a pattern that predominates with established infection, leading to production of viral structural and enzymatic proteins. The long terminal repeat (LTR) serves as a promoter of transcription.[8] The *tat* (trans-activator of transcription) gene plays multiple roles in HIV pathogenesis. It produces a regulatory protein that speeds up transcription of the HIV provirus to full-length viral mRNAs. It functions in trans-activation of viral genes. In addition, *tat* modulates host cell gene expression. The effects of such modulation may include enhanced immune suppression, apoptosis, and oxidative stress.[9]

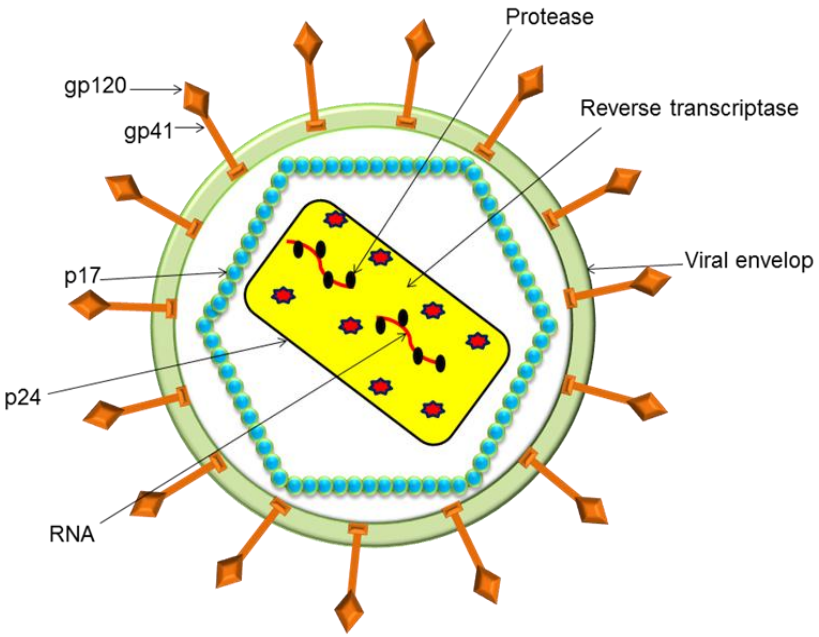

Fig. 1: Structure of HIV.

The *nef* (negative factor) gene produces a regulatory protein that modifies the infected cell to make it more suitable for producing HIV virions, by accelerating endocytosis of CD4 from the surface of infected cells. The *vif*, *vpr*, and *vpu* genes encode proteins that appear to play a role in generating infectivity and pathologic effects. *Vif*, *vpu*, and *vpr* protein products link to members of a superfamily of modular ubiquitin ligases to induce the polyubiquitylation and proteasomal degradation of their cellular targets. More specifically, *vpr* (viral protein r) has the ability to delay or arrest infected cells in the G2/M phase of the cell cycle and facilitates infection of macrophages, and it promotes nuclear transport of the viral preintegration complex. *Vif* antagonizes the antiviral effect of apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3G, or the protein product of the gene *APOBEC3G* (*A3G*). *Vpu* enhances efficient release of virions from infected cells.[10]

HUMAN IMMUNODEFICIENCY VIRUS-1

There are four major groups of HIV-1, based upon phylogenetic analysis, which likely arose from different transmission events in history among chimpanzee and gorilla primates and humans. These groups are defined as M (major), N (nonmajor and nonoutlier), O (outlier), and P(nonmajor). These groups are very similar to simian immunodeficiency viruses SIVcpz (M and N) and SIVgor (O and P).[11] Within these HIV-1 groups are subtypes that developed in the latter half of the 20th century. The predominant group M has recognized subtypes A, B, C, D, F, G, H, J, and K.[12] Group O is distinctly different and genetically more closely related to simian immunodeficiency virus (SIV) and HIV-2.[13] Group N appears to have arisen from interaction between a group M and a group O virus.[14] The vast majority of HIV-1 infections have been with group M. In contrast, only about 100,000 infections with group O have occurred, and group N and P infections are rare. Even within HIV-1 subtypes, genetic diversity can average 8 to 17% but reach 30%; between subtypes, it is 17 to 35% but up to 42%.

Table 1: Subtypes of HIV-1.

HIV GROUP	SUBTYPES	REGION
Group M	A	East and Central Africa; Central Asia; Eastern Europe
	AE	Southeast Asia
	AG	West Africa
	B	Americas; Western Europe; East Asia; Oceania
	C	India; Southern and Eastern Africa
	D	East Africa
	G	West Africa
	H	Central Africa
Group N	------	Cameroon
Group O	------	West Africa
Group P	------	Cameroon

Variability of HIV subtypes may also confound testing strategies, because diagnostic sensitivity and specificity of laboratory tests may not be the same across all subtypes.[15] Different subtypes of HIV-1 that have arisen and will continue to arise in the course of the AIDS pandemic have been identified with certain geographic distributions, though movement of individuals among populations creates more variability over time.

HUMAN IMMUNODEFICIENCY VIRUS TYPE-2

The numerous strains of HIV-1 isolated from various geographic regions of the world are all immunologically similar and differ only slightly in their DNA sequences. A second retrovirus designated HIV-2 has been isolated from a number of patients with AIDS, first in 1986 in West African countries and subsequently in locations in Western Europe (principally Portugal and France), India, the United States, and elsewhere that migration from West Africa occurred. Worldwide there are 1 to 2 million cases of HIV-2 infection, and most cases have appeared in West Africa and but only sporadically in other parts of the world.[16,17] HIV-2 is believed to have been present in Africa as early as the 1940's. HIV-2, which has greater homology to simian immunodeficiency virus (SIV) than to HIV-1, appears to have become established in human populations as a zoonotic infection from the primate reservoir of sooty mangabeys (*Cercocebus atys*), originating from SIVsmm.[18] Persons infected with HIV-2 infection have a longer asymptomatic phase, higher CD4 cell counts, lower viral RNA levels, and slower progression to AIDS than HIV-1 infection. The risk factors for transmission are the same as for HIV-1, but heterosexual transmission and maternal transmission is less efficient. Though HIV-2 has a higher mutation rate, it does not have a selective advantage over HIV-1. Rather, the immunologic response with broadly neutralizing antibodies, rare in HIV-1 infection, are present with HIV-2 infection and their presence is equivalent to a vaccine response to reduce viral replication.[17] The diminished virulence of HIV-2, compared with HIV-1, explains the slower progression to AIDS and progression at higher CD4 counts. The cellular immune responses to HIV-2 tend to be more polyfunctional. Once persons with HIV-2 infection have progressed to clinical AIDS, the manifestations are similar to those of persons with AIDS from HIV-1 infection. In endemic regions for HIV-2, tuberculosis is a frequent complication of AIDS. Clinical findings more common with HIV-2 include severe multi-organ cytomegalovirus infection, encephalitis, cholangitis, chronic bacterial diarrhoeal illness, and wasting syndrome. Findings less common with HIV-2 include Kaposi sarcoma and oral candidiasis. Viral load testing for HIV-2 is not routinely available, but viral loads tend to be low. Just as HIV-1 has a distinct subtype, so does HIV-2. There are 8 strains labeled A through H, but groups A and B account for pandemic spread, and group A accounts for most infections worldwide. There is up to a 25% difference in genetic homology among these subtypes. All subtypes can be detected by enzyme immunoassay (EIA) and confirmatory assays for HIV-2 similar to those for HIV-1. The reverse transcriptase enzyme is similar in structure and function in both HIV-1 and HIV-2. Infection with HIV-2 eventually leads to AIDS, albeit in 10 to 20 years on average. Fourth generation immunoassays remain the mainstay for diagnosis of HIV-2 infection.[19,20] The genetic sequences of HIV-1 and HIV-2 are only partially homologous. HIV-1 has a *vpu* gene, similar to simian immunodeficiency virus, while HIV-2 has the *vpx* gene like sooty mangabey retrovirus. These difference affect treatment strategies, of antiretroviral agents, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) are less likely to be effective against HIV-2, while nucleoside reverse transcriptase inhibitors (NRTIs) and proteasome inhibitors (PIs) are effective. The potential problem of genetic variation with HIV was illustrated in 1994 with the detection of a strain of HIV-1 (designated MVP-5180, or subtype O), a new HIV variant originating in the region of West-Central Africa, which showed only slightly more homology with other HIV-1 strains than with HIV-2. This variant is detectable with many testing methods for HIV-1, but false negative results may occur. This subtype O of HIV-1 demonstrates higher heterogeneity in *env* sequences than the more prevalent HIV-1 subtypes such as B.[13,21] The appearance of additional HIV subtypes requires more complex testing schemes in locations where HIV-2, or other possible HIV virus subtypes, are prevalent. The natural history of HIV-2 infection is characterized by a longer latent period before the appearance of AIDS, a less aggressive course of AIDS, and a lower viral load

with higher CD4 lymphocyte counts and lower CD4 cell turnover than HIV-1 infection until late in the course of the disease, when clinical AIDS is apparent. Thus, the pathogenicity of HIV-2 appears to be lower than that of HIV-1. This may explain the more limited spread of HIV-2, compared to HIV-1both in West African countries and elsewhere, due to less efficient transmission, particularly via heterosexual and perinatal modes.[17,19]

PATHOGENESIS OF HIV INFECTION

Retroviruses are unable to replicate outside of living host cells and do not contain deoxyribonucleic acid (DNA). After entering the body, the viral particle is attracted to a cell with the appropriate CD4 receptor molecules where it attaches by fusion to a susceptible cell membrane or by endocytosis and then enters the cell. The probability of infection is a function of both the number of infective HIV virions in the body fluid which contacts the host as well as the number of cells available at the site of contact that have appropriate CD4 receptors.[6] HIV infection can occur through oropharyngeal, cervical, vaginal, and gastrointestinal mucosal surfaces, even in the absence of mucosal disruption. Routes of HIV entry into mucosal lamina propria include dendritic cells, epithelial cells, and microfold (M) cells. Dendritic cells can bind to gp120 through a C type lectin, suggesting that dendritic cells that squeeze between "tight" epithelium may capture HIV and deliver it to underlying T cells, resulting in dissemination to lymphoid organs. HIV can transmigrate across fetal oral mucosal squamous epithelium that has few layers, 5 or less. HIV-infected macrophages, but not lymphocytes, are able to transmigrate across fetal oral epithelia. HIV-infected macrophages and, to a lesser extent, lymphocytes can transmigrate across fetal intestinal epithelia. However, efficient viral transmission through adult mucosal epithelia is difficult because of a mechanical barrier of stratified epithelia with tight junctions that prevent penetration of virions into the deeper layers of the epithelium, and from expression of the anti-HIV innate proteins HBD2, HBD3, and SLPI that inactivate virions.[22] HIV primarily infects cells that have CD4 cell-surface receptor molecules, using these receptors to gain entry. Many cell types share common receptor epitopes, though CD4 lymphocytes play a crucial role. Cells with CD4 receptors susceptible to HIV infection may include cells of the mononuclear phagocyte system, principally blood monocytes and tissue macrophages, as well as T lymphocytes, natural killer (NK) lymphocytes, dendritic cells (epithelial Langerhans cells and follicular dendritic cells in lymph nodes), hematopoietic stromal cells, and microglial cells in brain. HIV entry into cells can occur independently of CD4 receptor interaction. Such entry is less efficient and less extensive. Such entry has been described for renal tubules, gut enterocytes, vascular endothelium, cardiac myocytes, and astrocytes. Infection of these cells may play a role in the pathogenesis of HIV-related diseases occurring at tissue sites with those cells.[23] In addition to the CD4 receptor, a coreceptor known as a chemokine enables HIV entry into cells. Chemokines are cell surface membrane-bound fusion-mediating molecules found on many cells. A diagrammatic representation of the relationship of the chemokine receptor to the CD4 receptor is shown below.

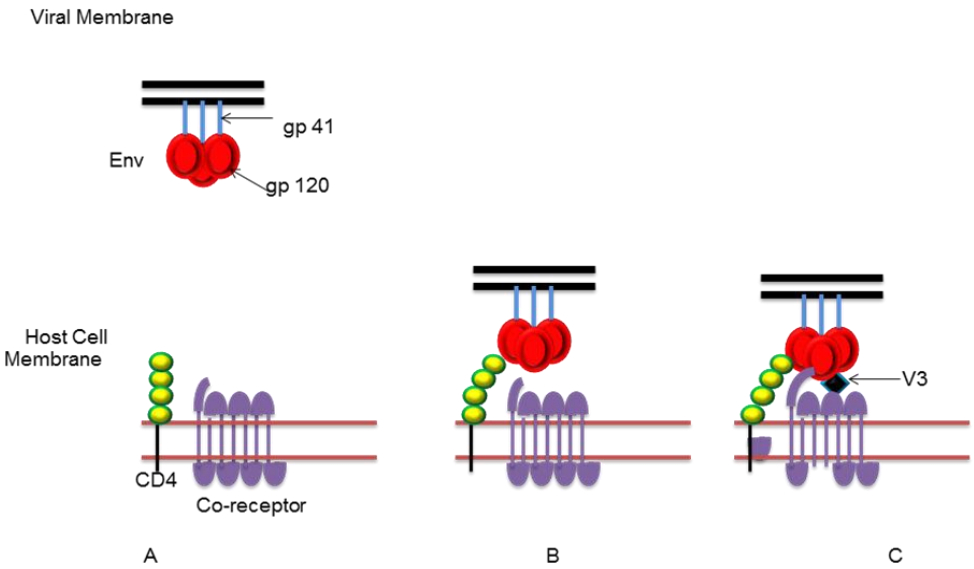

Fig. 2: Diagrammatic representation of the relationship of the chemokine receptor to the CD4 receptor.

HIV entry into a host cell begins with gp120 binding to CD4 receptor, which induces a conformational change in gp120, exposing co-receptor binding sites. The V3 loop region of gp120 determines whether the host cell CCR5 or CXCR4 chemokine co-receptor will be engaged. After the chemokine co-receptor is engaged, the gp41 on the HIV surface undergoes a conformational change. The gp41 transmembrane co-receptor consists of HR1 and HR2 helical regions along with a fusion peptide. Conformational change in gp41 through HR1 and HR2

interaction leads to formation of a stable structure that allows fusion of HIV and host cell membranes, with a fusion pore through which the viral core enters the host cell. These cores can utilize host cell microtubules to move toward the cell nucleus.[24,25]

The differences in chemokine coreceptors that are present on a cell also explain how different strains of HIV may infect cells selectively. There are strains of HIV known as T-tropic strains, which selectively interact with the CXCR4 ("X4") chemokine coreceptor to infect lymphocytes. The M-tropic strains of HIV interact with the CCR5 ("R5") chemokine coreceptor, and also CCR2 and CCR3, to infect macrophages and dendritic cells. CCR8 has been identified as a cofactor to permit infection by either T-cell tropic or by M-tropic strains of HIV. Dual tropic HIV strains have been identified that can use more than one chemokine coreceptor.[26] Over time, mutations in HIV may increase the ability of the virus to infect cells via these routes, beginning with dominance of CCR5 tropic strains of virus, then CCR5/CXCR4 dual tropic virus, and finally the more cytopathic CXCR4 tropic strain predominance. CCR5 tropic virus predominates early in HIV infection because it more readily infects dendritic cells and macrophages, has a high rate of replication, and is less visible to cytotoxic lymphocytes.[8] The gastrointestinal tract is a preferential site for HIV infection because most CD4 cells at that location are expressing CCR5.[27]

Cellular localization of chemokine receptors may help explain how HIV infection can occur. Macrophages and monocytes, as well as subpopulations of lymphocytes, can express the CCR5 receptor. Neurons, astrocytes, and microglia in the central nervous system also express this chemokine receptor. In other tissues, CCR5 is expressed on epithelium, endothelium, vascular smooth muscle, and fibroblasts. Areas of inflammation contain increased numbers of mononuclear cells with CCR5, and this may facilitate transmission of HIV at those sites.[28] The principal constituent of HIV-1 is Gag, accounting for half the entire virion mass. Viral membrane lipids account for about a third of the mass, and other viral and cellular proteins together contribute an additional 20%. The HIV-1 genomic RNA and other small RNAs comprise only 2.5% of virion mass. The Gag, Gag-Pro-Pol, Env, the two copies of genomic RNA, the tRNA primer, and the lipid envelope are all necessary for viral replication. HIV gene products are encoded on the genomic RNA, which also serves as mRNA for Gag and Gag-Pro- Pol, whereas singly or multiply spliced RNAs are translated to produce Env and accessory proteins, respectively. The HIV Gag and Gag-Pro-Pol proteins move from cytoplasmic sites of synthesis to the infected cell plasma membrane. These proteins then sort into detergent-resistant membrane microdomains. Virion production is cholesterol and sphingolipid dependent, and the virus is enriched in “raft”-associated proteins and lipids from the host cell membrane. The viral Env glycoproteins reach the plasma membrane independently of Gag.[6,29] Dendritic cells play a key role in HIV infection. Two populations of dendritic cells have been characterized. The conventional dendritic cells such as Langerhans cells are found in epithelia and mark with CD11c. They become infected with HIV, and they can transport HIV via lymph and blood to multiple sites within the body. They secrete interleukin-12 that induces cytotoxic lymphocyte responses to infection. In contrast, plasmacytoid dendritic cells mainly circulate in blood but can migrate to many tissue sites. These cells are CD123 positive and produce type I interferons that can stimulate conventional dendritic cells. Dendritic cells circulating in blood tend to decrease inversely in proportion to the increase in HIV viremia. This may be due to apoptosis of HIV-infected dendritic cells, redistribution to lymphoid organs, or to decreased production.[30] Dendritic cells express high amounts of the HIV entry receptors CCR5 and CXCR4 but relatively low amounts of CD4 which allow gp120 binding and attachment of HIV virions. When dendritic cells mature they upregulate CXCR4 but downregulate CCR5. Though HIV poorly infects DC, the virions carried by dendritic cells can infect nearby CD4+ T cells. Dendritic cells may promote initial HIV infection and dissemination through chemokine secretion.[31] Infection of the central nervous system by HIV requires that HIV-infected peripheral blood mononuclear cells cross the blood-brain barrier. Then infection of macrophages and microglial cells can occur. The immune activation leads to release of neurotoxic factors that further stimulate microglial activation along with neuronal apoptosis.[32]

IMMUNOLOGIC RESPONSE OF HIV

Once the HIV proviral DNA is within the infected cell's genome, it cannot be eliminated or destroyed except by destroying the cell itself. The HIV proviral DNA then directs its replication by infected host cells. This replication may first occur within inflammatory cells at the site of infection or within peripheral blood mononuclear cells (CD4 lymphocytes and monocytes) but then the major site of replication quickly shifts to lymphoid tissues of the body (lymph nodes and gastrointestinal tract). The initial burst of viral replication that follows infection is followed by replication at a lower level, which accounts for the clinically apparent latency of infection. However, viral replication is stimulated by a variety of cytokines such as interleukins and tumor necrosis factor, which activate CD4 lymphocytes and make them more susceptible to HIV infection.[33] Macrophages and dendritic (Langerhans) cells in epithelial tissues of the body, such as the genital tract, are also important as both reservoirs and vectors for spread of HIV in the body. Macrophages originate from blood monocytes and give rise to the body's mononuclear phagocyte system. Persons on antiretroviral therapy who are otherwise healthy may have demonstrable HIV-1 within their alveolar macrophages.[34] Langerhans cells (a subset of blood dendritic cells) originate in bone marrow and migrate to peripheral epithelial locations in skin and mucus

membranes, acting as antigen presenting cells for lymphocytes. Dendritic cells can cross endothelium and circulate freely into both lymphoid and mucosal tissues. HIV can be replicated within dendritic cells for up to 45 days.[35] Both macrophages and Langerhans cells can be HIV-infected but are not destroyed. Dendritic cells can capture HIV in their processes, providing a focus for infection of other cells. In experimental cell cultures, the two pathways of HIV-1 spread are: (1) fluid-phase diffusion of cell-free virions, and (2) cell–cell spread of virus. The latter is potentially more efficient, and this is likely the case in vivo. Cell-cell transfer can include budding with fusion of closely opposed cell membranes occurs as well as cell-cell fusion to give syncytia. Viral particles may undergo endocytosis, may be stored in a cell surface-accessible compartment, or just directly infect a cell via receptors. Though long-term transmission of HIV from dendritic cells to CD4 cells can be the result of active infection of the dendritic cells rather than just trapping and presenting virion, short-term transmission occurs principally through cell surface HIV interaction. There are pockets of plasma membrane that harbor virions on dendritic cells that provide the means to present virions to CD4 cells via a so-called "infectious synapse".[36] When HIV is carried to sites in the body, particularly to regional lymph nodes and to gut associated lymphoid tissue (GALT), the antigen-presenting cells such as macrophages or dendritic cells act as a "Trojan horse".[37] In the host, HIV continues to replicate, mainly within lymphoid tissues. Germinal centers of lymph nodes and GALT contain many follicular dendritic cells (FDCs). GALT becomes a persistent reservoir for HIV infection.[7] Lymphoid tissue FDCs not only have CD4 receptors on their surface membranes, but also express a surface protein, CD-SIGN, to which HIV envelope protein can bind. The FDCs can accumulate high numbers of HIV virions, acting as virion "warehouses".[38]

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