EVS

PROJECT REPORT

ON

HIV AIDS

SUBMITTED BY:

D-11 ETRX

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HIV

Human immunodeficiency virus (HIV) is a lentivirus (slowly replicating retrovirus) that causes acquired immunodeficiency syndrome(AIDS), a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic infections andcancers to thrive. Infection with HIV occurs by the transfer of blood, semen, vaginal fluid, pre-ejaculate, or breast milk. Within these bodily fluids, HIV is present as both free virus particles and virus within infected immune cells.

HIV infects vital cells in the human immune system such as helper T cells (specifically $CD4^+$ T cells), macrophages, and dendritic cells. HIV infection leads to low levels of $CD4^+$ T cells through a number of mechanisms including: apoptosis of uninfected bystander cells, direct viral killing of infected cells, and killing of infected $CD4^+$ T cells by CD8 cytotoxic lymphocytes that recognize infected cells. When $CD4^+$ T cell numbers decline below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections.

History

AIDS was first clinically observed in 1981 in the United States. The initial cases were a cluster of injection drug users and gay men with no known cause of impaired immunity who showed symptoms of Pneumocystis carinii pneumonia (PCP), a rare opportunistic infection that was known to occur in people with very compromised immune systems.Soon thereafter, additional gay men developed a previously rare skin cancer called Kaposi's sarcoma (KS). Many more cases of PCP and KS emerged, alerting U.S. Centers for Disease Control and Prevention (CDC) and a CDC task force was formed to monitor the outbreak.

In the beginning, the CDC did not have an official name for the disease, often referring to it by way of the diseases that were associated with it, for example, lymphadenopathy, the disease after which the discoverers of HIV originally named the virus. They also used Kaposi's Sarcoma and Opportunistic Infections, the name by which a task force had been set up in 1981. In the general press, the term GRID, which stood for gay-related immune deficiency, had been coined. The CDC, in search of a name, and looking at the infected communities coined “the 4H disease, ” as it seemed to single out Haitians, homosexuals, hemophiliacs, and heroin users. However, after determining that AIDS was not isolated to the gay community, it was realized that the term GRID was misleading and AIDS was introduced at a meeting in July 1982. By September 1982

the CDC started using the name AIDS.

In 1983, two separate research groups led by Robert Gallo and Luc Montagnier independently declared that a novel retrovirus may have been infecting AIDS patients, and published their findings in the same issue of the journal Science. Gallo claimed that a virus his group had isolated from an AIDS patient was strikingly similar in shape to other human T-lymphotropic

viruses (HTLVs) his group had been the first to isolate. Gallo's group called their newly isolated virus HTLV-III. At the same time, Montagnier's group isolated a virus from a patient presenting with swelling of the lymph nodes of the neck and physical weakness, two classic symptoms of AIDS. Contradicting the report from Gallo's group, Montagnier and his colleagues showed that core proteins of this virus were immunologically different from those of HTLV-I. Montagnier's group named their isolated virus lymphadenopathy-associated virus (LAV). As these two viruses turned out to be the same, in 1986, LAV and HTLV-III were renamed HIV.

Origins

Both HIV-1 and HIV-2 are believed to have originated in non-human primates in West-central Africa and to have transferred to humans (a process known as zoonosis) in the early 20th century.HIV-1 appears to have originated in southern Cameroon through the evolution of SIV(cpz), a simian immunodeficiency virus (SIV) that infects wild chimpanzees(HIV-1 descends from the SIVcpz endemic in the chimpanzee subspecies Pan troglodytes troglodytes). The closest relative of HIV-2 is SIV (smm), a virus of the sooty mangabey (Cercocebus atys atys), an old world monkey living in litoral West Africa (from southern Senegal to western Côte d'Ivoire). New World monkeys such as the owl monkey are resistant to HIV-1 infection, possibly because of a genomic fusion of two viral resistance genes. HIV-1 is thought to have jumped the species barrier on at least three separate occasions, giving rise to the three groups of the virus, M, N, and O.

There is evidence that humans who participate in bushmeat activities, either as hunters or as bushmeat vendors, commonly acquire SIV. However, SIV is a weak virus, and it is typically suppressed by the human immune system within weeks of infection. It is thought that several transmissions of the virus from individual to individual in quick succession are necessary to

allow it enough time to mutate into HIV.Furthermore, due to its relatively low person-to-person transmission rate, it can only spread throughout the population in the presence of one or more of high-risk transmission channels, which are thought to have been absent in Africa prior to the 20th century.

Specific proposed high-risk transmission channels, allowing the virus to adapt to humans and spread throughout the society, depend on the proposed timing of the animal-to-human crossing. Genetic studies of the virus suggest that the most recent common ancestor of the HIV-1 M group dates back to circa 1910. Proponents of this dating link the HIV epidemic with the emergence of colonialism and growth of large colonial African cities, leading to social changes, including a higher degree of sexual promiscuity, the spread of prostitution, and the concomitant high frequency of genital ulcer diseases (such as syphilis) in nascent colonial cities. While transmission rates of HIV during vaginal intercourse are low under regular circumstances they are increased many fold if one of the partners suffers from a sexually transmitted infection resulting in genital ulcers. Early 1900s colonial cities were notable due to their high prevalence of prostitution and genital ulcers to the degree that as of 1928 as many as 45% of female residents of eastern Kinshasa were thought to have been prostitutes and as of 1933 around 15% of all residents of the same city were infected by one of the forms of syphilis.

An alternative view holds that unsafe medical practices in Africa during years following World War II, such as unsterile reuse of single use syringes during mass vaccination, antibiotic and anti-malaria treatment campaigns, were the initial vector that allowed the virus to adapt to humans and spread.

The earliest well documented case of HIV in a human dates back to 1959 in the Congo. The virus may have been present in the United States as early as 1966.

Virology

Classification:

HIV is a member of the genus Lentivirus, part of the family Retroviridae. Lentiviruses have many morphologies andbiological properties in common. Many species are infected by lentiviruses, which are characteristically responsible for long-duration illnesses with a long incubation period. Lentiviruses are transmitted as single-stranded, positive-sense,enveloped RNA viruses. Upon entry into the target cell, the viral RNA genome is converted (reverse transcribed) into double-stranded DNA by a virally encoded reverse transcriptase that is transported along with the viral genome in the virus particle. The resulting viral DNA is then imported into the cell nucleus and integrated into the cellular DNA by a virally encoded integrase and host co-factors. Once integrated, the virus may become latent, allowing the virus and its host cell to avoid detection by the immune system. Alternatively, the virus may

be transcribed, producing new RNA genomes and viral proteins that are packaged and released from the cell as new virus particles that begin the replication cycle anew.

Two types of HIV have been characterized: HIV-1 and HIV-2. HIV-1 is the virus that was initially discovered and termed both LAV and HTLV-III. It is more virulent, more infective,and is the cause of the majority of HIV infections globally. The lower infectivity of HIV-2 compared to HIV-1 implies that fewer of those exposed to HIV-2 will be infected per exposure. Because of its relatively poor capacity for transmission, HIV-2 is largely confined to West Africa.

Subtypes of HIV

One of the obstacles to treatment of the human immunodeficiency virus is its high genetic variability.HIV can be divided into two major types, HIV type 1 (HIV-1) and HIV type 2 (HIV-2). HIV-1 is related to viruses found in chimpanzees and gorillas living in western Africa, while HIV-2 viruses are related to viruses found in the endangered west African primate sooty mangabey.HIV-1 viruses may be further divided into groups. The HIV-1 group M viruses predominate and are responsible for the AIDS pandemic. Group M can be further subdivided into subtypes based on genetic sequence data. Some of the subtypes are known to be more virulent or are resistant to different medications. Likewise, HIV-2 viruses are thought to be less virulent and transmissible than HIV-1 M group viruses, although HIV-2 is known to cause AIDS.

HIV-1:

HIV-1 is the most common and pathogenic strain of the virus. Scientists divide HIV-1 into a major group (Group M) and two or more minor groups. Each group is believed to represent an independent transmission of SIV into humans (but subtypes within a group are not).Total 39 ORFs are found in all six possible reading frames (RFs) of HIV-1 complete genome sequence. But only few of them are functional.

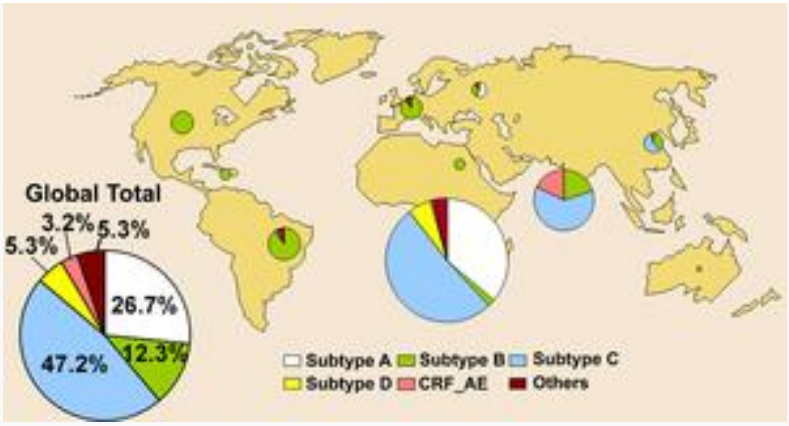
Group M

With 'M' for "major", this is by far the most common type of HIV, with more than 90% of HIV/AIDS cases deriving from infection with HIV-1 group M. The M group is subdivided further into clades, called subtypes, that are also given a letter. There are also "circulating recombinant forms" or CRFs derived from recombination between viruses of different subtypes which are each given a number. CRF12_BF, for example, is a recombination between subtypes B and F.

- Subtype A is common in West Africa.
- Subtype B is the dominant form in Europe, the Americas, Japan, Thailand, and Australia.
- Subtype C is the dominant form in Southern Africa, Eastern Africa, India, Nepal, and parts of China.

- Subtype D is generally only seen in Eastern and central Africa.
- (Subtype E) has never been identified as a nonrecombinant, only recombined with subtype A as CRF01_AE.
- Subtype F has been found in central Africa, South America and Eastern Europe.
- Subtype G (and the CRF02_AG) have been found in Africa and central Europe.
- Subtype H is limited to central Africa.
- (Subtype I) was originally used to describe a strain that is now accounted for as CRF04_cpx, with the cpx for a "complex" recombination of several subtypes.
- Subtype J is primarily found in North, Central and West Africa, and the Caribbean
- Subtype K is limited to the Democratic Republic of Congo and Cameroon.

These subtypes are sometimes further split into sub-subtypes such as A1 and A2 or F1 and F2. This is not thought to be a complete or final list, and further types are likely to be found.



HIV-1 subtype prevalence in 2002

Group N

The 'N' stands for "non-M, non-O". This group was discovered in 1998 and has only been seen in Cameroon. As of 2006, only 10 Group N infections had been identified.

Group O

The O ("Outlier") group is not usually seen outside of West-central Africa. It is reportedly most common in Cameroon, where a 1997 survey found that about 2% of HIV-positive samples were from Group O. The group caused some concern because it could not be detected by early versions of the HIV-1 test kits. More advanced HIV tests have now been developed to detect both Group O and Group N.

Group P

In 2009, a newly analyzed HIV sequence was reported to have greater similarity to a simian immunodeficiency virus recently discovered in wild gorillas (SIVgor) than to SIVs from chimpanzees (SIVcpz). The virus had been isolated from a Cameroonian woman residing in France who was diagnosed with HIV-1 infection in 2004. The scientists reporting this sequence placed it in a proposed Group P "pending the identification of further human cases".

HIV-2:

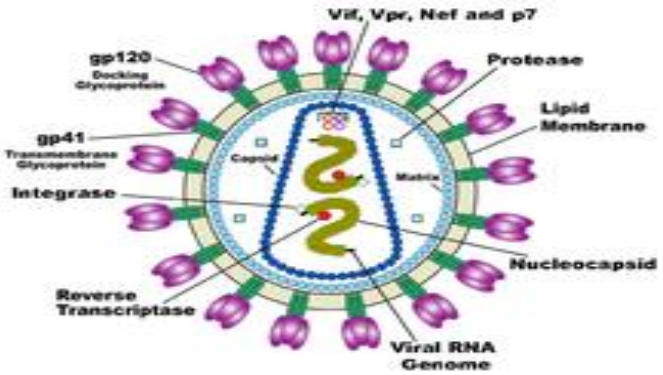
HIV-2 has not been widely seen outside of Africa. The first case in the United States was in 1987. Many test kits for HIV-1 will also detect HIV-2.

As of 2010, there are 8 known HIV-2 groups (A to H). Of these, only groups A and B are epidemic. Group A spread mainly in West Africa, but also to Angola, Mozambique, Brazil,India, and very limitedly to Europe or the US. Group B is mainly confined to West Africa.

HIV-2 is mostly related to simian immunodeficiency virus endemic in sooty mangabeys (Cercocebus atys atys) (SIVsmm), a monkey species inhabiting the forests of littoral West Africa. Phylogenetic analyses show that the viruses most closely related to the two strains of HIV-2 which spread considerably in humans (HIV-2 groups A and B) are the SIVsmm found in the sooty mangabeys of the Tai forest, in western Ivory Coast.

There are six additional known HIV-2 groups, each having been found in just one person. They all seem to derive from independent transmissions from sooty mangabeys to humans. Groups C and D have been found in two people from Liberia, groups E and F have been discovered in two people from Sierra Leone, and groups G and H have been detected in two people from the Ivory Coast. Each of these HIV-2 strains, for which humans are probably dead-end hosts, is most closely related to SIVsmm strains from sooty mangabeys living in the same country where the human infection was found.

Structure and genome



HIV is different in structure from other retroviruses. It is roughly spherical with a diameter of about 120 nm, around 60 times smaller than a red blood cell, yet large for a virus. It is composed of two copies of positive single-stranded RNA that codes for the virus's ninegenes enclosed by a conical capsid composed of 2,000 copies of the viral protein p24. The single-stranded RNA is tightly bound to nucleocapsid proteins, p7, and enzymes needed for the development of the virion such as reverse transcriptase, proteases, ribonucleaseand integrase. A matrix composed of the viral protein p17 surrounds the capsid ensuring the integrity of the virion particle.

This is, in turn, surrounded by the viral envelope that is composed of two layers of fatty molecules called phospholipids taken from the membrane of a human cell when a newly formed virus particle buds from the cell. Embedded in the viral envelope are proteins from the host cell and about 70 copies of a complex HIV protein that protrudes through the surface of the virus particle.This protein, known as Env, consists of a cap made of three molecules called glycoprotein (gp) 120, and a stem consisting of three gp41 molecules that anchor the structure into the viral envelope. This glycoprotein complex enables the virus to attach to and fuse with target cells to initiate the infectious cycle. Both these surface proteins, especially gp120, have been considered as targets of future treatments or vaccines against HIV.

The RNA genome consists of at least seven structural landmarks (LTR, TAR, RRE, PE, SLIP, CRS, and INS), and nine genes (gag, pol, and env, tat, rev, nef, vif, vpr, vpu, and sometimes a tenth tev, which is a fusion of tat env and rev), encoding 19 proteins. Three of these genes, gag, pol, and env, contain information needed to make the structural proteins for new virus particles. For example, env codes for a protein called gp160 that is broken down by a cellular protease to form gp120 and gp41. The six remaining genes,tat, rev, nef, vif, vpr, and vpu (or vpx in the case of HIV-2), are regulatory genes for proteins that control the ability of HIV to infect cells, produce new copies of virus (replicate), or cause disease.

The two Tat proteins (p16 and p14) are transcriptional transactivators for the LTR promoter acting by binding the TAR RNA element. The TAR may also be processed intomicroRNAs that regulate the apoptosis genes ERCC1 and IER3.The Rev protein (p19) is involved in shuttling RNAs from the nucleus and the cytoplasm by binding to theRRE RNA element. The Vif protein (p23) prevents the action of APOBEC3G (a cell protein that deaminates DNA:RNA hybrids and/or interferes with the Pol protein). The Vpr protein (p14) arrests cell division at G2/M. The Nef protein (p27) down-regulates CD4 (the major viral receptor), as well as the MHC class I and class II molecules.

Nef also interacts with SH3 domains. The Vpu protein (p16) influences the release of new virus particles from infected cells. The ends of each strand of HIV RNA contain an RNA sequence called the long terminal repeat (LTR). Regions in the LTR act as switches to control production of new viruses and can be triggered by proteins from either HIV or the host cell. The Psi element is involved in viral genome packaging and recognized by Gag and Rev proteins. The SLIP element (TTTTTT) is involved in the frameshift in the Gag-Pol reading frame required to make functional Pol

Tropism

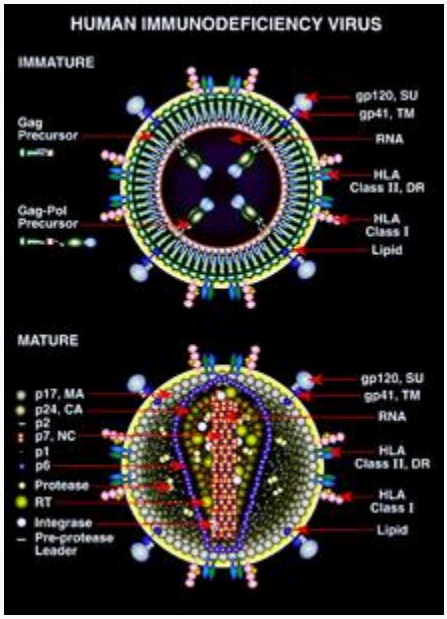


Diagram of the immature and mature forms of HIV

The term viral tropism refers to the cell types a virus infects. HIV can infect a variety of immune cells such as $CD4^+$ T cells,macrophages, and microglial cells. HIV-1 entry to macrophages and $CD4^+$ T cells is mediated through interaction of the virion envelope glycoproteins (gp120) with the CD4 molecule on the target cells and also with chemokine coreceptors.

Macrophage (M-tropic) strains of HIV-1, or non-syncitia-inducing strains (NSI) use the β-chemokine receptor CCR5 for entry and are, thus, able to replicate in macrophages and $CD4^+$ T cells. This CCR5 coreceptor is used by almost all primary HIV-1 isolates regardless of viral genetic subtype. Indeed, macrophages play a key role in several critical aspects of HIV infection. They appear to be the first cells infected by HIV and perhaps the source of HIV production when $CD4^+$ cells become depleted in the patient. Macrophages and microglial cells are the cells infected by HIV in the central nervous system. In tonsils and adenoids of HIV-infected patients, macrophages fuse into multinucleated giant cells that produce huge amounts of virus.

T-tropic isolates, or syncitia-inducing (SI) strains replicate in primary $CD4^+$ T cells as well as in macrophages and use the α-chemokine receptor, CXCR4, for entry. Dual-tropic HIV-1 strains are thought to be transitional strains of HIV-1 and thus are able to use both CCR5 and CXCR4 as co-receptors for viral entry.

The α-chemokine SDF-1, a ligand for CXCR4, suppresses replication of T-tropic HIV-1 isolates. It does this by down-regulating the expression of CXCR4 on the surface of these cells. HIV that

use only the CCR5 receptor are termed R5; those that use only CXCR4 are termed X4, and those that use both, X4R5. However, the use of coreceptor alone does not explain viral tropism, as not all R5 viruses are able to use CCR5 on macrophages for a productive infection[22] and HIV can also infect a subtype of myeloid dendritic cells, which probably constitute a reservoir that maintains infection when $CD4^+$ T cell numbers have declined to extremely low levels.

Some people are resistant to certain strains of HIV.For example, people with the CCR5-Δ32 mutation are resistant to infection with R5 virus, as the mutation stops HIV from binding to this coreceptor, reducing its ability to infect target cells.

Sexual intercourse is the major mode of HIV transmission. Both X4 and R5 HIV are present in the seminal fluid, which is passed from a male to his sexual partner. The virions can then infect numerous cellular targets and disseminate into the whole organism. However, a selection process leads to a predominant transmission of the R5 virus through this pathway. How this selective process works is still under investigation, but one model is that spermatozoa may selectively carry R5 HIV as they possess both CCR3 and CCR5 but not CXCR4 on their surface and that genital epithelial cells preferentially sequester X4 virus. In patients infected with subtype B HIV-1, there is often a co-receptor switch in late-stage disease and T-tropic variants appear that can infect a variety of T cells through CXCR4. These variants then replicate more aggressively with heightened virulence that causes rapid T cell depletion, immune system collapse, and opportunistic infections that mark the advent of AIDS.Thus, during the course of infection, viral adaptation to the use of CXCR4 instead of CCR5 may be a key step in the progression to AIDS. A number of studies with subtype B-infected individuals have determined that between 40 and 50 percent of AIDS patients can harbour viruses of the SI and, it is presumed, the X4 phenotypes.

HIV-2 is much less pathogenic than HIV-1 and is restricted in its worldwide distribution. The adoption of "accessory genes" by HIV-2 and its more promiscuous pattern of coreceptor usage (including CD4-independence) may assist the virus in its adaptation to avoid innate restriction factors present in host cells. Adaptation to use normal cellular machinery to enable transmission and productive infection has also aided the establishment of HIV-2 replication in humans. A survival strategy for any infectious agent is not to kill its host but ultimately become a commensal organism. Having achieved a low pathogenicity, over time, variants more successful at transmission will be selected.

Replication Cycle

HIV enters macrophages and $CD4^+$ T cells by the adsorption of glycoproteins on its surface to receptors on the target cell followed by fusion of the viral envelopewith the cell membrane and the release of the HIV capsid into the cell.[37][38]

Entry to the cell begins through interaction of the trimeric envelope complex (gp160 spike) and both CD4 and a chemokine receptor (generally either CCR5or CXCR4, but others are known to

interact) on the cell surface. gp120 binds to integrin $\alpha_4\beta_7$ activating LFA-1 the central integrin involved in the establishment of virological synapses, which facilitate efficient cell-to-cell spreading of HIV-1. The gp160 spike contains binding domains for both CD4 and chemokine receptors.

The first step in fusion involves the high-affinity attachment of the CD4 binding domains of gp120 to CD4. Once gp120 is bound with the CD4 protein, the envelope complex undergoes a structural change, exposing the chemokine binding domains of gp120 and allowing them to interact with the target chemokine receptor. This allows for a more stable two-pronged attachment, which allows the N-terminal fusion peptide gp41 to penetrate the cell membrane.Repeat sequences in gp41, HR1, and HR2 then interact, causing the collapse of the extracellular portion of gp41 into a hairpin. This loop structure brings the virus and cell membranes close together, allowing fusion of the membranes and subsequent entry of the viral capsid.

After HIV has bound to the target cell, the HIV RNA and various enzymes, including reverse transcriptase, integrase, ribonuclease, and protease, are injected into the cell.[37] During the microtubule-based transport to the nucleus, the viral single-strand RNA genome is transcribed into double-strand DNA, which is then integrated into a host chromosome.

HIV can infect dendritic cells (DCs) by this CD4-CCR5 route, but another route using mannose-specific C-type lectin receptors such asDC-SIGN can also be used.DCs are one of the first cells encountered by the virus during sexual transmission. They are currently thought to play an important role by transmitting HIV to T-cells when the virus is captured in the mucosa by DCs.The presence ofFEZ-1, which occurs naturally in neurons, is believed to prevent the infection of cells by HIV.

Replication And Transcription:

Shortly after the viral capsid enters the cell, an enzyme called reverse transcriptase liberates the single-stranded (+)RNA genome from the attached viral proteins and copies it into a complementary DNA (cDNA) molecule.The process of reverse transcription is extremely error-prone, and the resulting mutations may cause drug resistance or allow the virus to evade the body's immune system. The reverse transcriptase also has ribonuclease activity that degrades the viral RNA during the synthesis of cDNA, as well as DNA-dependent DNA polymerase activity that creates a sense DNA from the antisense cDNA. Together, the cDNA and its complement form a double-stranded viral DNA that is then transported into the cell nucleus. The integration of the viral DNA into the host cell's genome is carried out by another viral enzyme called integrase.

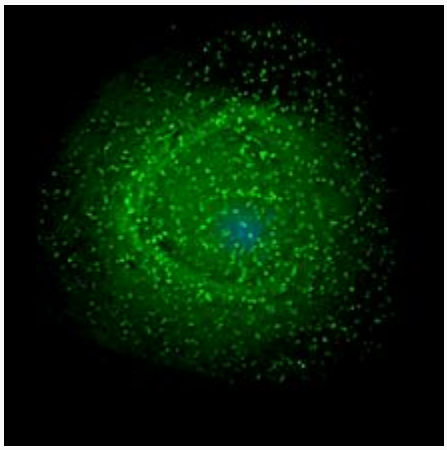
This integrated viral DNA may then lie dormant, in the latent stage of HIV infection. To actively produce the virus, certain cellulartranscription factors need to be present, the most important of

which is NF-κB (NF kappa B), which is upregulated when T-cells become activated. This means that those cells most likely to be killed by HIV are those currently fighting infection.

During viral replication, the integrated DNA provirus is transcribed into mRNA, which is then spliced into smaller pieces. These small pieces are exported from the nucleus into the cytoplasm, where they are translated into the regulatory proteins Tat (which encourages new virus production) and Rev. As the newly produced Rev protein accumulates in the nucleus, it binds to viral mRNAs and allows unspliced RNAs to leave the nucleus, where they are otherwise retained until spliced.At this stage, the structural proteins Gag and Env are produced from the full-length mRNA. The full-length RNA is actually the virus genome; it binds to the Gag protein and is packaged into new virus particles.

HIV-1 and HIV-2 appear to package their RNA differently; HIV-1 will bind to any appropriate RNA, whereas HIV-2 will preferentially bind to the mRNA that was used to create the Gag protein itself. This may mean that HIV-1 is better able to mutate (HIV-1 infection progresses to AIDS faster than HIV-2 infection and is responsible for the majority of global infections).

Assembly and release

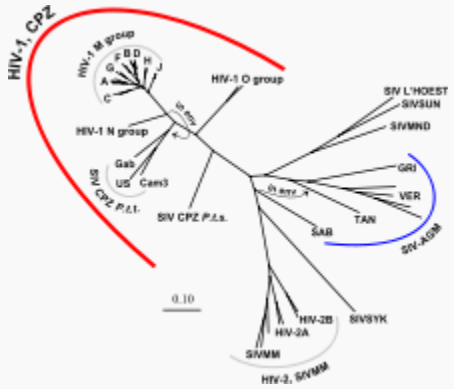


HIV assembling on the surface of an infected macrophage.

The final step of the viral cycle, assembly of new HIV-1 virions, begins at the plasma membrane of the host cell. The Env polyprotein (gp160) goes through the endoplasmic reticulum and is transported to the Golgi complex where it is cleaved by furin resulting in the two HIV envelope glycoproteins, gp41 and gp120. These are transported to the plasma membrane of the host cell where gp41 anchors gp120 to the membrane of the infected cell. The Gag (p55) and Gag-Pol (p160) polyproteins also associate with the inner surface of the plasma membrane along with the HIV genomic RNA as the forming virion begins to bud from the host cell. The budded virion is still immature as the gag polyproteins still need to be cleaved into the actual matrix, capsid and

nucleocapsid proteins. This cleavage is mediated by the also packaged viral protease and can be inhibited by antiretroviral drugs of the protease inhibitor class.

Genetic variability



The phylogenetic tree of the SIV and HIV

HIV differs from many viruses in that it has very high genetic variability. This diversity is a result of its fast replication cycle, with the generation of about 10^{10} virions every day, coupled with a high mutation rate of approximately 3×10^{-5} per nucleotide base per cycle of replication and recombinogenic properties of reverse transcriptase.

This complex scenario leads to the generation of many variants of HIV in a single infected patient in the course of one day. This variability is compounded when a single cell is simultaneously infected by two or more different strains of HIV. When simultaneous infection occurs, the genome of progeny virions may be composed of RNA strands from two different strains. This hybrid virion then infects a new cell where it undergoes replication. As this happens, the reverse transcriptase, by jumping back and forth between the two different RNA templates, will generate a newly synthesized retroviral DNA sequence that is a recombinant between the two parental genomes.This recombination is most obvious when it occurs between subtypes.

The closely related simian immunodeficiency virus (SIV) has evolved into many strains, classified by the natural host species. SIV strains of the African green monkey (SIVagm) and sooty mangabey (SIVsmm) are thought to have a long evolutionary history with their hosts. These hosts have adapted to the presence of the virus, which is present at high levels in the host's blood but evokes only a mild immune response, does not cause the development of simian AIDS,and does not undergo the extensive mutation and recombination typical of HIV infection in humans.

Three groups of HIV-1 have been identified on the basis of differences in the envelope (env) region: M, N, and O.Group M is the most prevalent and is subdivided into eight subtypes (or clades), based on the whole genome, which are geographically distinct. The most prevalent are subtypes B (found mainly in North America and Europe), A and D (found mainly in Africa), and C (found mainly in Africa and Asia); these subtypes form branches in the phylogenetic tree representing the lineage of the M group of HIV-1. Coinfection with distinct subtypes gives rise to circulating recombinant forms (CRFs). In 2000, the last year in which an analysis of global subtype prevalence was made, 47.2% of infections worldwide were of subtype C, 26.7% were of subtype A/CRF02_AG, 12.3% were of subtype B, 5.3% were of subtype D, 3.2% were of CRF_AE, and the remaining 5.3% were composed of other subtypes and CRFs. Most HIV-1 research is focused on subtype B; few laboratories focus on the other subtypes. The existence of a fourth group, "P", has been hypothesised based on a virus isolated in 2009.The strain is apparently derived from gorilla SIV (SIVgor), first isolated from western lowland gorillas in 2006.The genetic sequence of HIV-2 is only partially homologous to HIV-1 and more closely resembles that of SIVsmm.

Diagnosis

A generalized graph of the relationship between HIV copies (viral load) and CD4 counts over the average course of untreated HIV infection; any particular individual's disease course may vary considerably. $CD4^+$ T cell count

Many HIV-positive people are unaware that they are infected with the virus. For example, in 2001 less than 1% of the sexually active urban population in Africa had been tested, and this proportion is even lower in rural populations.Furthermore, in 2001 only 0.5% of pregnant women attending urban health facilities were counselled, tested or receive their test results. Again, this proportion is even lower in rural health facilities.Since donors may therefore

be unaware of their infection, donor blood and blood products used in medicine and medical research are routinely screened for HIV.

HIV-1 testing is initially by an enzyme-linked immunosorbent assay (ELISA) to detect antibodies to HIV-1. Specimens with a nonreactive result from the initial ELISA are considered HIV-negative unless new exposure to an infected partner or partner of unknown HIV status has occurred. Specimens with a reactive ELISA result are retested in duplicate. If the result of either duplicate test is reactive, the specimen is reported as repeatedly reactive and undergoes confirmatory testing with a more specific supplemental test (e.g., Western blot or, less commonly, an immunofluorescence assay(IFA)). Only specimens that are repeatedly reactive by ELISA and positive by IFA or reactive by Western blot are considered HIV-positive and indicative of HIV infection. Specimens that are repeatedly ELISA-reactive occasionally provide an indeterminate Western blot result, which may be either an incomplete antibody response to HIV in an infected person or nonspecific reactions in an uninfected person.

Although IFA can be used to confirm infection in these ambiguous cases, this assay is not widely used. In general, a second specimen should be collected more than a month later and retested for persons with indeterminate Western blot results. Although much less commonly available, nucleic acid testing (e.g., viral RNA or proviral DNA amplification method) can also help diagnosis in certain situations. In addition, a few tested specimens might provide inconclusive results because of a low quantity specimen. In these situations, a second specimen is collected and tested for HIV infection.

Research

HIV/AIDS research includes all medical research which attempts to prevent, treat, or cure HIV/AIDS as well as fundamental research about the nature of HIV as an infectious agent and AIDS as the disease caused by HIV.

Currently, no cure for HIV/AIDS exists. The most universally recommended method for the prevention of HIV/AIDS is to avoid blood-to-blood contact between people and to otherwise practice safe sex. The most recommended method for treating HIV is to receive attention from a doctor who would coordinate the patient's management of HIV/AIDS.

Many governments and research institutions participate in HIV/AIDS research. This research includes behavioral health interventions, such as research into sex education, and drug development, such as research into microbicides for sexually transmitted diseases, HIV vaccines, and antiretroviral drugs. Other medical research areas include the topics of pre-exposure prophylaxis, post-exposure prophylaxis, and Circumcision and HIV.

A hybrid virus, simian human immunodeficiency virus (SHIV), combining parts between HIV and SIV, was created in order to further study different aspects of HIV.