HIV stands for Human Immunodeficiency Virus, a pathogen that works by attacking the human immune system. It belongs to a class of viruses called retroviruses and more specifically, a subgroup called lentiviruses, or viruses that cause disease slowly. 1

HIV cannot replicate on its own, so in order to make new copies of itself, it must infect cells of the human immune system, called CD4 cells. CD4 cells are white blood cells that play a central role in responding to infections in the body. 2

Over time, CD4 cells are killed by HIV and the body’s ability to recognise and fight some types of infection begins to decline. If HIV is not controlled by treatment, the loss of CD4 cells leads to the development of serious illnesses, or ‘opportunistic infections’. In people with normal CD4 cell levels, these infections would be recognised and cleared by the immune system. 3
Experiencing a collection of these infections is the most advanced stage of HIV, which is when a person is also said to have AIDS (Acquired Immune Deficiency Syndrome). Effective testing and treatment of HIV means that the large majority of people living with HIV do not reach this stage. 

The structure of HIV

HIV is called a retrovirus because it works in a back-to-front way. Unlike other viruses, retroviruses store their genetic information using RNA instead of DNA, meaning they need to ‘make’ DNA when they enter a human cell in order to make new copies of themselves.

HIV is a spherical virus. The outer shell of the virus is called the envelope and this is covered in spikes of the ‘glycoproteins’ gp120 and gp41, which allow HIV to lock onto the CD4 receptor on CD4 T cells and enter the cell.
Inside the virus envelope is a layer called the matrix. The core of the virus, or nucleus, is held in the capsid, a cone-shaped structure in the centre of the virion. The capsid contains two enzymes essential for HIV replication, the reverse transcriptase and integrase molecules. It also contains two strands of RNA - which hold HIV’s genetic material.  

HIV’s RNA is made up of nine genes which contain all the instructions to make new viruses. Three of these genes – gag, pol and env – provide the instructions to make proteins that will form new virus particles. For example, env provides the code to make the proteins that form the envelope, or shell, of HIV. gag makes the structural proteins such as the matrix and the capsid, and pol makes the enzymes that are essential for making new viruses.

The other six genes, known as tat, rev, nef, vif, vpr and vpu, provide code to make proteins that control the ability of HIV to infect a cell, produce new copies of virus or release viruses from infected cells.  

The life-cycle of HIV

1. Attachment and entry

The process of producing new viruses begins when HIV gains entry to a cell. This process happens in two stages, attachment and fusion.

HIV infects immune system cells which have a CD4 receptor on the surface. These cells include T-lymphocytes (also known as t cells), monocytes, macrophages and dendritic cells. The CD4 receptor is used by the cell to signal to other parts of the immune system the presence of antigens.

When HIV makes contact with a CD4 cell, the gp120 spikes on the surface of HIV lock onto the CD4 receptor and another co-receptor, either CCR5 or CXCR4. The gp41 protein is used to fuse the HIV envelope with the cell wall. This process of fusion allows the HIV capsid to enter the CD4 cell.

Several types of antiretroviral drug have been developed to block different stages of the processes of attachment and entry:

- CCR5 inhibitor
- Attachment inhibitor
- Fusion inhibitor

The gp41 and gp120 proteins on the surface of the virus are also targets for vaccines that are designed to produce antibody responses.
2. Reverse transcription

When HIV RNA enters the cell it must be `reverse transcribed` into proviral DNA before it can be integrated into the DNA of the host cell. HIV uses its reverse transcriptase enzyme to convert RNA into proviral DNA inside the cell.

Two types of antiretroviral drug have been developed to stop the action of reverse transcriptase and the creation of proviral DNA:

- Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs and NtRTIs) block HIV production by inserting a nucleoside or nucleotide into the chain of HIV DNA as it is created, terminating the chain.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) block HIV production by binding directly to the reverse transcriptase enzyme. 9
3. Integration

After HIV RNA is converted into DNA, HIV’s integrase enzyme attaches itself to the end of the proviral DNA strands and it is passed through the wall of the cell nucleus. Once the proviral DNA enters the cell nucleus, it binds to the host DNA and then the HIV DNA strand is inserted into the host cell DNA.

HIV integrase inhibitors have been developed to block the transfer of the HIV DNA strand into the host cell DNA.

After the proviral DNA is integrated into the DNA of the host cell, HIV remains dormant within the cellular DNA. This stage is called latency and the cell is described as ‘latently infected’. It can be difficult to detect these latently infected cells even when using the most sensitive tests.
4. Transcription and Translation

The cell will produce HIV RNA if it receives a signal to become active. CD4 cells become activated if they encounter an infectious agent.

When the cell becomes active, HIV uses the host enzyme RNA polymerase to make messenger RNA. This messenger RNA provides the instructions for making new viral proteins in long chains.

The long chains of HIV proteins are cut into smaller chains by HIV’s protease enzyme. 11
5. Assembly and budding

These protein chains begin to assemble into new viruses at the cell wall.

- HIV protease inhibitors are designed to block the activity of HIV’s protease enzyme. 12

As the virus buds from the cell wall, its genome becomes enclosed in a capsid produced from HIV’s gag protein. After the new virus is assembled, it must leave the cell by pushing through the cell wall. To leave the cell completely and become infectious, the virus must take lipids (fats) from the cell wall to make the surface glycoproteins.

- Maturation inhibitors are being developed to block the cutting of the gag protein that is needed to produce a mature virus. 13
Clinical stages of infection

1. Primary (acute) HIV infection

HIV enters the body by infecting CD4 cells in the mucous membranes of the vagina or the rectum, or by direct infection of CD4 t-cells in the bloodstream.

At this stage pre-exposure prophylaxis using antiretroviral drugs can prevent HIV infection if it is taken consistently. Post-exposure prophylaxis with a three-drug antiretroviral combination can prevent HIV infection at this stage and for up to 72 hours after exposure.

Dendritic cells are among the first to encounter HIV, their job is to transport infectious agents to the lymph nodes. When HIV arrives in the lymph nodes - around 24 to 48 hours after exposure - they activate other immune cells, such as CD4 t-cells, HIV’s primary target.
It is here in the lymph nodes that HIV begins to replicate. At this stage, HIV is not detectable in the blood by viral load (HIV RNA) testing or antibody testing. This stage may last for between 7 and 21 days and during this period HIV can only be detected by taking samples directly from the lymph node tissue (biopsy). Three-drug antiretroviral therapy begun at this stage of HIV infection may greatly restrict the spread of HIV to long-lived cells of the immune system that form a ‘reservoir’ of HIV infection in the body. Several weeks after infection HIV becomes detectable in the blood by viral load testing. At this point people may begin to experience symptoms of acute HIV infection as levels of HIV in the blood rise very high. Common symptoms of acute HIV infection include fever, body rash, swollen glands, among others. While fever and rash are the most common symptoms of acute HIV infection, not everyone will experience these.

Symptoms of acute infection may last for up to 2 weeks. Viral load reaches its peak at this time and may measure above 1 million copies per ml of blood. CD4 cell levels will fall at this time too. The likelihood of transmitting HIV is highest during the first few months after infection when HIV levels in blood, semen and vaginal fluid are very high. Around three to four weeks after infection, HIV antigen (p24) will also become detectable. ‘Fourth-generation’ antibody/antigen tests which combine the detection of HIV antibodies and HIV p24 antigen will show a positive result at this stage. Within a further 4 to 8 days HIV antibody-only tests using blood will show a positive result. HIV levels begin to fall in the blood and CD4 levels begin to rise again, although not to the level prior to infection. After around 6 months viral load and CD4 levels will stabilise at a level known as the `set point`.

2. Chronic infection

HIV infection will not cause further illness for some years. This period is known as the asymptomatic phase. HIV gradually reduces the number of CD4 cells in the body until the CD4 cell count falls below 200 cells/mm3. After the CD4 cell count falls below this level, the risk of developing AIDS-related infections (opportunistic infections) greatly increases.

The asymptomatic phase lasts for around ten years on average. The length of the asymptomatic phase depends on how quickly the CD4 cell count declines. If a person has a very high viral load (above 100,000 copies/ml), they will lose CD4 cells more quickly.

Antiretroviral treatment suppresses HIV to undetectable levels, restores the CD4 cell count to normal levels and prevents disease if started at any time during the asymptomatic phase and taken every day. All treatment guidelines recommend that people start treatment as soon as they are ready after HIV diagnosis.

During the asymptomatic phase, CD4 cell counts and viral load tests can monitor the progression of HIV disease.

Why is HIV so evasive? What is the ‘HIV reservoir’?

Although HIV can be controlled by antiretroviral therapy, it cannot be eliminated from the body. This is because HIV evades the normal immune system mechanisms for getting rid of cells infected by viruses.

HIV integrates itself into the DNA of human immune system cells and only replicates when the cell is stimulated to respond to an infection. These cells are called latently-infected cells. These cells are not recognised as infected by the immune system and killed off, allowing them to persist for as long as
the cell lives.\textsuperscript{17}

Some of the cells infected by HIV are very long-lasting memory T-cells. Reservoirs of latently-infected cells become established in the lymph nodes, the spleen and the gut. HIV also infects cells in the brain, but it is unclear if HIV can pass from the brain to other parts of the body. HIV may also persist for many years in macrophages - immune cells found largely in tissues - and in dendritic cells, which recognise infectious agents and alert other immune cells to remove them.

Latently-infected cells can proliferate without being activated and HIV may also pass from cell to cell within tissues in the gut and other reservoirs. \textsuperscript{18} This means they evade the immune system and are not suppressed by antiretroviral drugs before infecting other cells.

It’s unclear how quickly a reservoir of HIV-infected cells becomes established in the body. Observations in small numbers of people who have started antiretroviral treatment within a few days or weeks of infection show that they have fewer HIV-infected cells and if they stop antiretroviral treatment, some can control HIV for long periods without resuming treatment.\textsuperscript{19}

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\textsuperscript{1} German Advisory Committee Blood (Arbeitskreis Blut) (2016) \textit{‘Human Immunodeficiency Virus (HIV)’} Transfusion medicine and hemotherapy: offizielles Organ der Deutschen Gesellschaft fur Transfusionsmedizin und Immunhamatologie, vol 43, issue 3, 203–222.
\textsuperscript{5} Protein Data Bank (2014) HIV Envelope Glycoprotein (accessed 7 November 2018)
\textsuperscript{6} Protein Data Bank (2014) HIV Capsid (accessed 7 November 2018)
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Last full review: 30 November 2018
Next full review: 29 November 2021