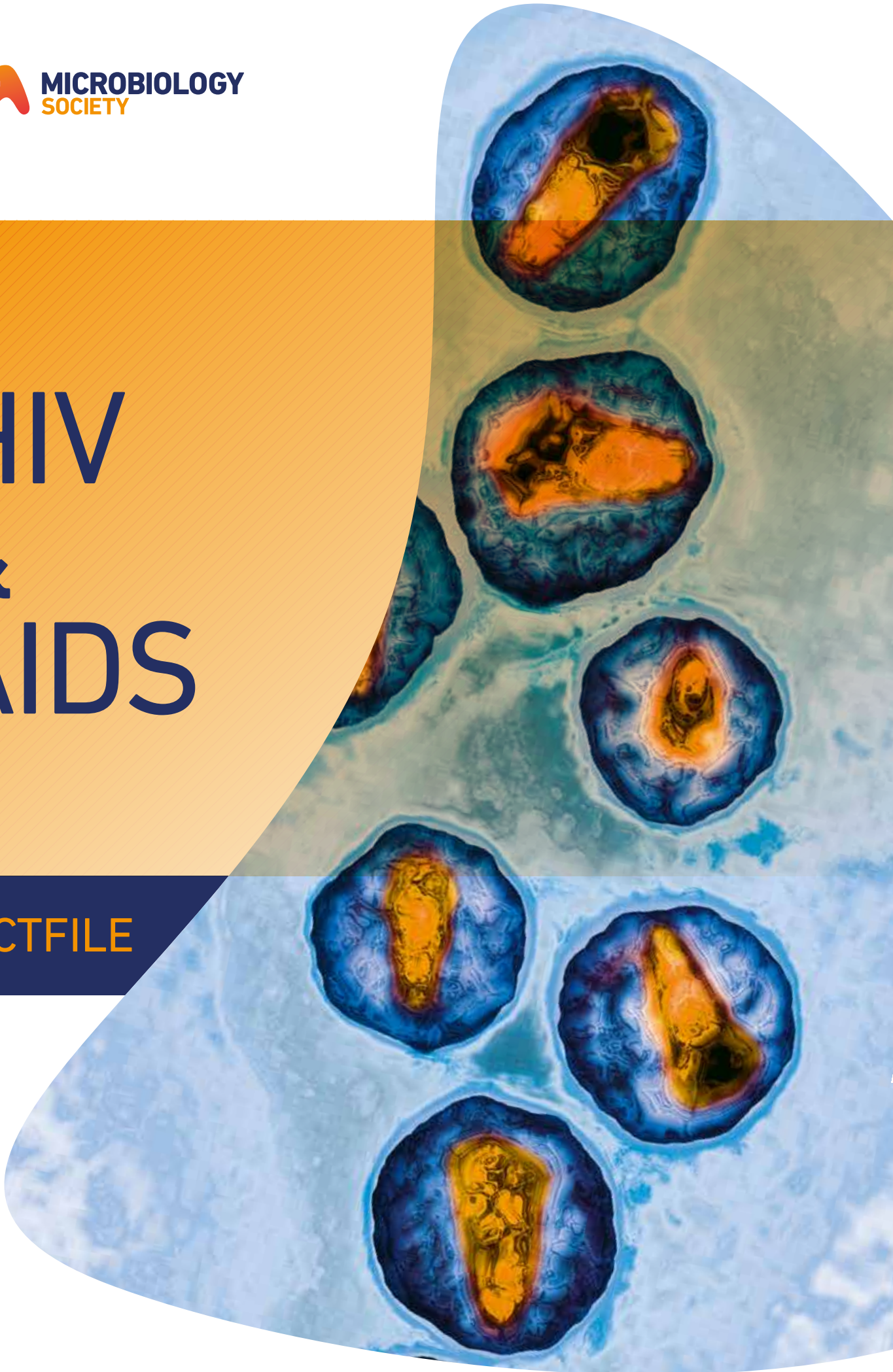


# HIV & AIDS

FACTFILE







# HIV & AIDS

Coloured scanning electron micrograph of HIV particles (yellow) budding from the membrane of a host cell (red).

## HIV

The human immunodeficiency virus (HIV) is the cause of one of the most destructive human pandemics in recorded history. Since it was first recognised in 1981 it has killed more than 39 million people. Estimates suggest that 37 million people are currently infected: 71% of these live in sub-Saharan Africa. In the UK, in 2013, there were 107,800

HIV-positive people and the rates of new HIV diagnoses have continued to rise in each of the last 25 years.

## What is HIV?

HIV is an RNA virus known as a retrovirus. The HIV virion has a central core containing two identical positive strand RNA genomes and the enzymes reverse transcriptase, protease and integrase. There is a



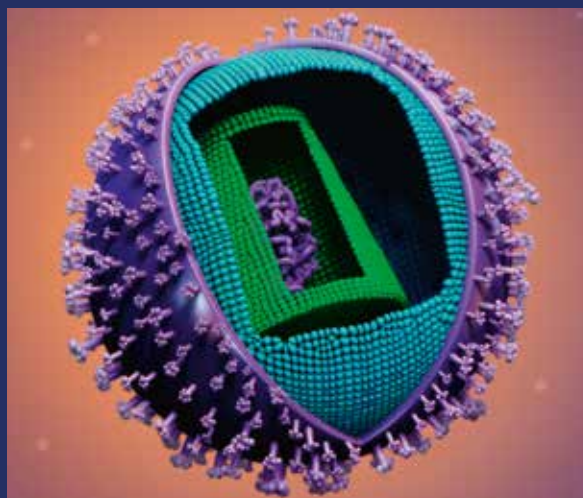


## What is a retrovirus?

When cells make proteins they use their DNA as a template to make another nucleic acid called RNA. This is the process of transcription. The information on the RNA is then used to assemble the sequence of polypeptides that make up a particular protein. This process is called translation.

### Reverse transcription

Retroviruses are capable of carrying out transcription in reverse. They contain an enzyme called reverse transcriptase which transcribes the viral RNA into DNA. This DNA can then be inserted into the genome of the host cell, where it stays for the lifetime of the cell. The cell synthesises viral RNA and proteins, allowing the virus to multiply inside the host cell.



Computer artwork of an HIV particle. The virus consists of an RNA genome, surrounded by an icosahedral (20-sided) protein nucleocapsid. The whole virus is enclosed in an envelope derived from the host cell's plasma membrane. The envelope has viral proteins integrated into it, including glycoprotein spikes that aid its attachment to host cells.

protein capsid covered by a lipid bilayer envelope, which contains virally encoded glycoprotein spikes.

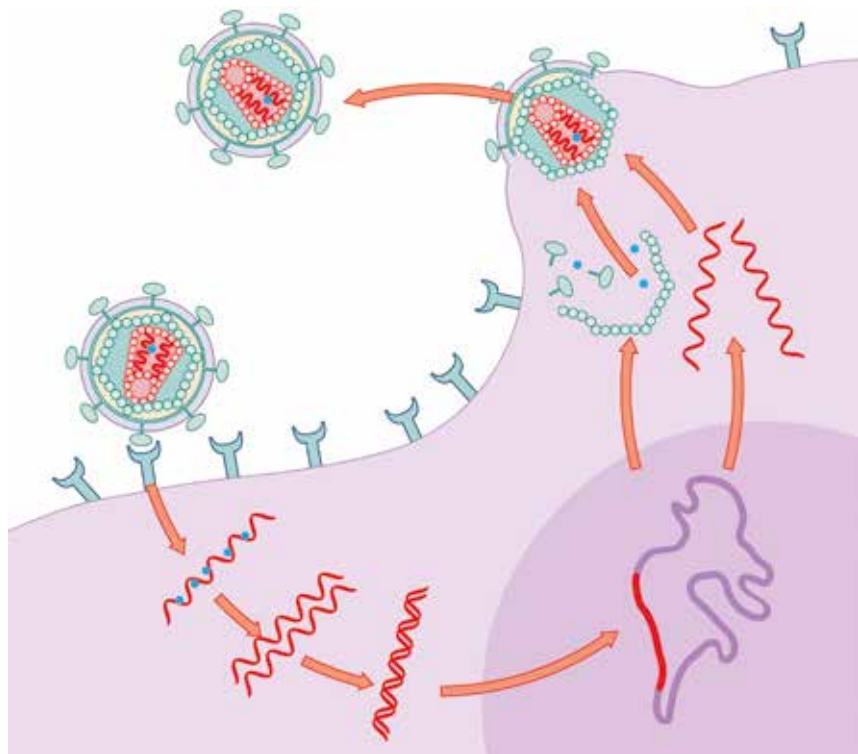
There are two major strains of HIV, termed HIV-1 and HIV-2. HIV-1 causes the majority of the infections worldwide and is more easily transmitted than the other strain, HIV-2. HIV-2 is restricted to West Africa, although there are imported cases in the UK.

AIDS occurs when the virus has destroyed the immune system, leaving the patient highly susceptible to other life-threatening infections. People who are infected with HIV are referred to as being 'HIV-positive', but they do not necessarily have any symptoms of disease. With the advent of new drug regimes it is now hoped that many HIV-positive people may never reach the AIDS stage.

### HIV infection and replication

HIV only infects white blood cells which have specific receptor proteins on their surface. The primary receptor is called CD4 and is found on lymphocytes called T-helper cells (CD4+ cells) and certain other cells such as dendritic cells and macrophages. The CD4 receptor is normally involved in antigen recognition but HIV 'hijacks' it, along with a second 'co-receptor' in order to get into the cell.

- HIV binds to the CD4 receptor and the co-receptor, either CXCR4 or CCR5, on the cell surface using its envelope glycoproteins. Once the receptors are engaged, the viral envelope glycoproteins trigger fusion between the virus and host cell membranes, allowing virus entry into the cell cytoplasm. The nucleocapsid containing RNA and reverse transcriptase is inserted into the cell;
- Complementary single-stranded DNA (cDNA) molecules are made using the RNA as a template;
- The cDNA hybridises to make double-stranded DNA;
- The viral DNA integrates into the host genome;
- Viral RNA and proteins are synthesised;
- New HIV particles are assembled;
- HIV leaves the cell by budding (acquiring its envelope in the process)



**HIV replication cycle.** Glycoprotein spikes on the virus envelope attach to surface proteins on a T cell (left). The RNA genome (red) and reverse transcriptase (RT) enzyme (blue dots) are injected into the cell. RT transcribes the RNA to DNA (bottom), which then integrates into a host cell chromosome (bottom right). The virus hijacks the cell's nuclear machinery, causing it to produce viral RNA molecules and proteins. The proteins assemble around the RNA, forming the viral cores, which then bud from the cell, taking part of the membrane as an envelope.

### How does HIV cause disease?

The specific (or adaptive) immune system recognises and remembers antigens on specific pathogens and is vital in defending us from infectious disease. The white blood cells responsible for specific immunity

are lymphocytes. HIV causes AIDS because it infects and destroys lymphocytes called T-helper (CD4+) cells. These help to regulate the functions of other cells involved in immunity, for example B lymphocytes. B cells secrete antibodies that attack pathogens, but they cannot do this unless they receive a signal from an activated T-helper cell. So when T-helper cells are destroyed by HIV infection, B cells cannot function correctly either. This causes the patient to become severely immunocompromised and they cannot fight infections properly.

### How is HIV transmitted?

The three main routes for HIV transmission are:

- Sex: vaginal, anal (and very rarely, oral)
- Contaminated blood (for example between injecting drug users)
- From mother to child (either in pregnancy, during birth or via breast milk)

## Fighting back – a natural resistance?

Some people are naturally resistant to HIV infection due to a mutation in the gene coding for a protein called CCR5. This is found on the cell surface of some white blood cells and is a receptor for chemicals called cytokines that help regulate the immune system. It is the primary co-receptor that, along with the CD4 receptor, HIV requires to enter a host cell. Homozygous individuals do not express the receptor on their cells and are completely resistant to HIV infection. Heterozygous individuals show partial resistance and if they do become infected the disease progresses more slowly. The mutation could help scientists in their quest for new HIV treatments, for example the development of drugs that block the CCR5 receptor.

The mutation is thought to exist in 10% of people of European origin, but is not found in people with African, Asian, Middle Eastern or Native American roots. It is still not known why the mutation exists in such a high frequency in Europeans, but its absence in other populations suggests that it occurred relatively recently (within the past 2000 years). It is possible that the mutation could have provided protection from diseases once common in Europe, for example smallpox or bubonic plague.

## Worldwide trends

Globally, half of the people who acquire HIV become infected before they turn 25 and typically die of AIDS before their 35th birthday. In Africa, women are 1.4 times more likely to be infected with HIV than men. In the UK, sex between men accounts for 45% of transmission and sex between men and women 41%.

Worldwide, approximately 60% of new HIV infections are contracted through sex between men and women. The other cases are usually due to:

- Babies who acquire the virus from their mothers (10%)
- Drug users sharing used needles (10%)
- Sex between men (5–10%)

In the early stages of the epidemic, some transmission occurred in healthcare settings, for example via infected blood for transfusion. This is now rare due to better screening techniques and increased awareness.

### How does the disease progress?

Infection with HIV-1 is associated with a progressive decrease of the CD4+ T cell count and an increase in viral load (the concentration of viral particles in the blood plasma). The disease progresses in three stages:

#### Acute or Primary Stage:

This stage occurs soon after initial infection and is characterised by rapid viral replication and a fall in the number of CD4+ cells. Early symptoms include fever, headache, lymph node enlargement and muscle pain. Because the symptoms are non-specific the patient will not necessarily associate

them with HIV and they can be easily mistaken for glandular fever or flu. The symptoms usually subside after one month and CD4+ cells levels return to normal.

#### Chronic or Asymptomatic Stage

This is an asymptomatic period lasting approximately 7–11 years (but which varies considerably between individuals). During this time the CD4+ count remains normal but the number of infected CD4+ cells increases. Many patients will not know they are infected so will continue to carry out risky behaviour that increases the chance of spreading HIV to others.

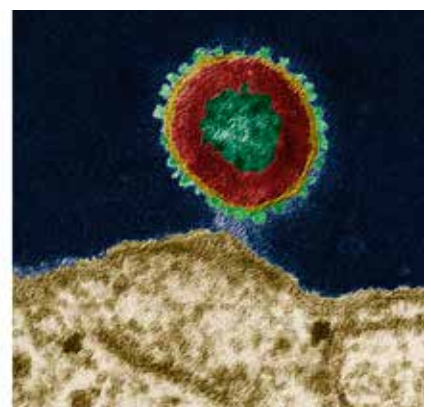
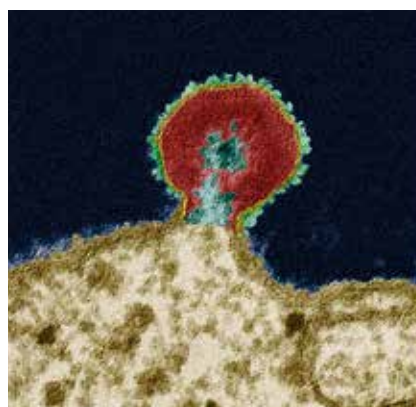
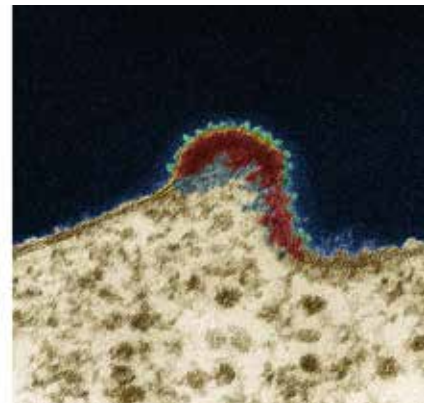
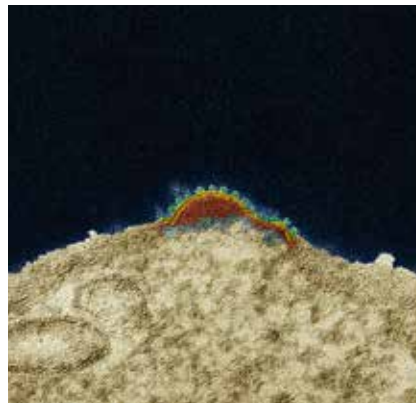
During this time there is an intense immune response but eventually the immune system is overwhelmed and

begins to deteriorate, leading to the final stage of the disease.

#### Crisis Stage or AIDS

By this point patients have a very low CD4+ count and their immune system is severely compromised. Without a functioning immune system patients suffer from opportunistic infections from a whole range of microbes such as:

- Candidiasis or 'thrush': a fungal infection in the mouth, oesophagus, bronchi or lungs
- Kaposi's sarcoma: a tumour that often forms blood-filled lesions on the skin
- Pneumonia caused by the fungus *Pneumocystis jirovecii*
- Tuberculosis caused by the bacterium *Mycobacterium*



Coloured transmission electron micrograph of an HIV particle (red/green) budding from the surface of a T cell.



*tuberculosis* or *Mycobacterium avium*

- Toxoplasmosis caused by the parasitic protozoan *Toxoplasma gondii*
- Infection by cytomegalovirus (with complications like liver failure and inflammation of the colon and retina)
- Infection by the Herpes simplex virus that can cause outbreaks of painful blisters on the skin, mouth and genital regions.

Other symptoms can be rapid weight loss (hence the name 'slim disease' in Africa) and AIDS

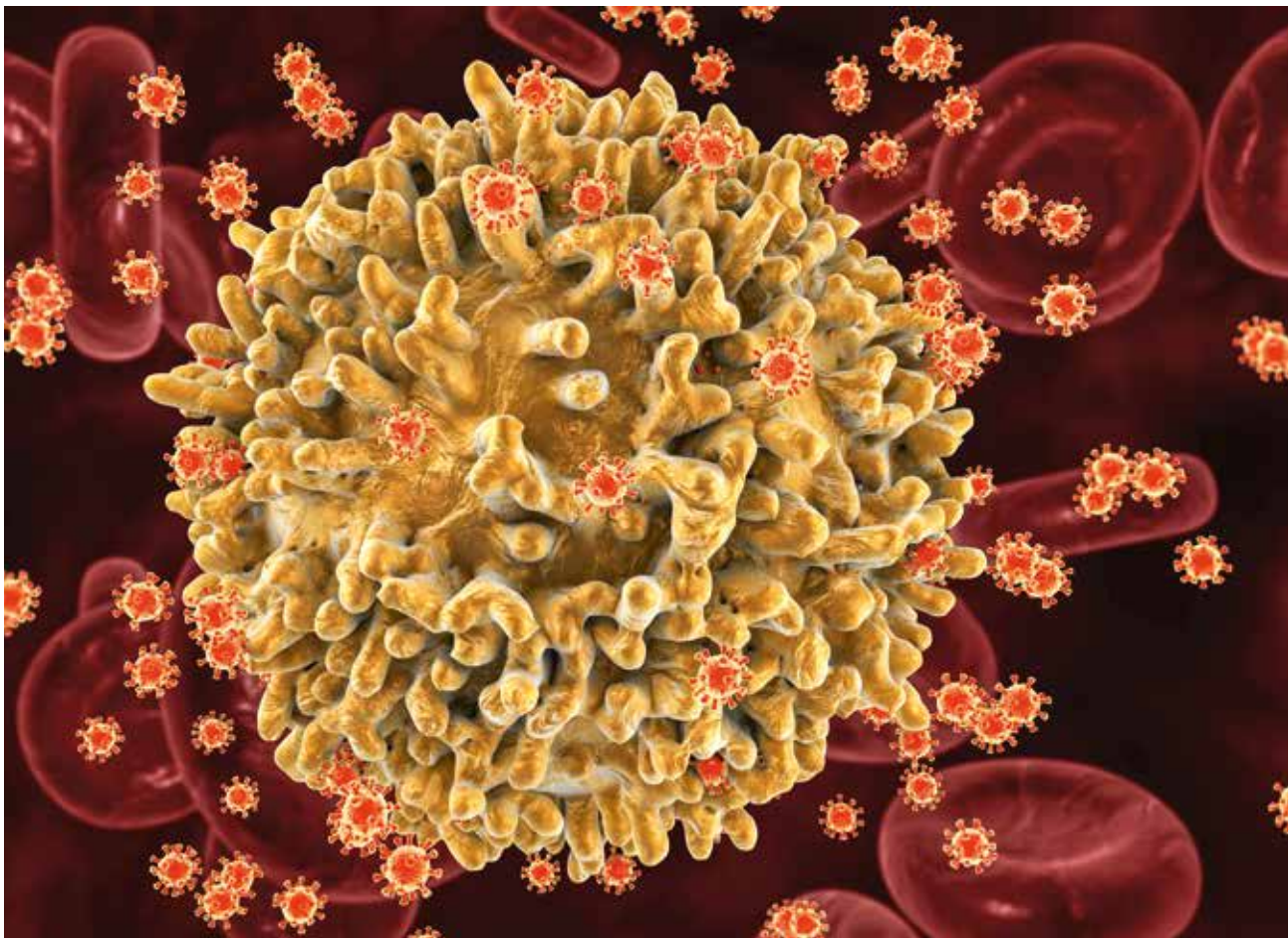
dementia complex (the virus-infected macrophages can cross the blood–brain barrier). Further complications arise from the fact that patients are often co-infected with other viruses such as hepatitis B and C.

### HIV tests

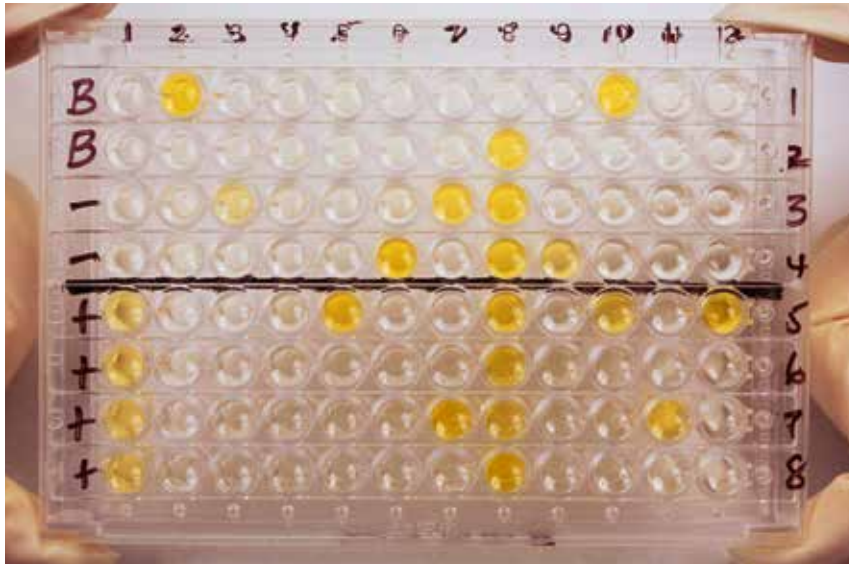
There are different screening methods which can test for HIV infection. One type detects antibodies against HIV and not the virus itself. It can take three months after initial infection for antibodies to be present, so this type of test taken immediately after possible exposure will not give a conclusive

result. This rapid test is most commonly used in community settings such as Fastest clinics. Most labs, however, now use 'combination assays' that detect the presence of both antibodies and HIV antigens. HIV antigens are present in the blood before antibodies are produced so this helps to close the 'window' between infection and possible detection.

HIV tests can be carried out at a GP's surgery, sexual health (genito-urinary medicine) clinic, private clinic or anonymously at a Fastest clinic (run by the Terrence Higgins Trust). The test begins with pre-test counselling after which a sample of blood is taken. The



Computer illustration of HIV particles infecting T cells. The surface of the T cell has a lumpy appearance with large irregular surface protrusions. The smaller, spherical structures on the cell surface are HIV particles budding away from the cell membrane. This viral budding causes the T cell to die.



Positive (yellow) and negative (clear) results for presence of antibodies to HIV, displayed on an ELISA (enzyme-linked immunosorbent assay) test plate.



The OraQuick Rapid HIV-1/2 Antibody Test is a rapid test designed to detect antibodies to HIV in saliva within 20 minutes.

results are available within a week (but can take as little as 15 minutes) and post-test counselling is provided. A positive result means that the patient is infected with HIV. This may be a frightening diagnosis but it allows anti-retroviral treatment to be started immediately. This will enable the patient to lead a normal, healthy life for considerably longer than without treatment.

### Treating HIV

There is currently still no cure for HIV infection, or a vaccine to prevent it. Infection does not have to be seen as a death sentence. Doctors now have an arsenal of drugs to control the infection and increase the average life expectancy of HIV-positive people. The drug regime that infected people require is called combination therapy and uses three or more anti-retroviral drugs (ARVs). It is also known as HAART (Highly Active Anti-Retroviral Therapy). There are currently five kinds of HIV drugs available, all of which have a different mode of action:

#### Reverse transcriptase inhibitors (RTIs)

block reverse transcriptase and prevent the virus replicating. There are two different types categorised as nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs).

**Protease inhibitors (PIs)** inhibit the action of the viral protease enzyme involved in the production of new viruses.

**Entry inhibitors (EIs)** prevent HIV from binding to a co-receptor on the host cell.

**Fusion inhibitors (FIs)** prevent fusion of the viral envelope with the cell surface.





Production of tablets containing AZT.

**Integrase inhibitors** (IIs) prevent the integration of the viral genome into the host genome.

Combination therapy usually involves two NRTIs plus either a NNRTI, a protease inhibitor or an integrase inhibitor. Other types of drugs (for example antibiotics) are also used to treat the opportunistic infections associated with the Phase Three or Crisis Stage of AIDS.

Many patients find it extremely difficult to stick to complex drug regimes but 'treatment adherence' is vitally important to reduce the chances of drug resistance and keep the infection under control.

#### **Why is a 'cocktail' of drugs required?**

HIV has a high degree of genetic variability and a very fast replication cycle. As HIV is an RNA virus and reverse transcription has a very high error rate, the virus mutates very rapidly. Many of the mutations make the virus resistant to anti-retroviral drugs. It is possible for an individual patient to

be infected with one or more different drug-resistant HIV strains, either due to mutations that have occurred post-infection or because they were initially infected with a resistant strain. As many as 28 different strains of HIV have been found in one infected individual and some patients are infected with strains that are resistant to all 30 currently available ARVs. It is therefore important that patients have resistance tests

before and during their treatment so that the correct combination of drugs can be used.

#### **Side effects**

All anti-retroviral drugs cause side effects, but the severity and effects can differ. Any drug that is licensed for use has undergone extensive research to try and minimise its toxicity, but common side effects include:



AIDS vaccine research. Petri dishes are shown containing a liquid culture of genetically engineered cells carrying a gene for an HIV protein. The protein is manufactured by incubation of the cell culture.



- diarrhoea
- nausea and vomiting
- fatigue
- damage to peripheral nerves
- liver and kidney damage
- problems with fat and cholesterol metabolism

### Vaccines

A vaccine would be the best way to prevent HIV infection and halt the pandemic, but this goal has been elusive. There are many possible types of experimental HIV vaccines, although none have successfully passed a phase three clinical trial.

**Subunit vaccine:** vaccines based on the use of soluble or particulate forms of the envelope glycoproteins are currently being tested in an attempt to elicit neutralising antibodies. Neutralising antibodies have been shown to completely prevent HIV

## Prophylactic treatment

### Immediate post-exposure prophylactic treatment (PEP)

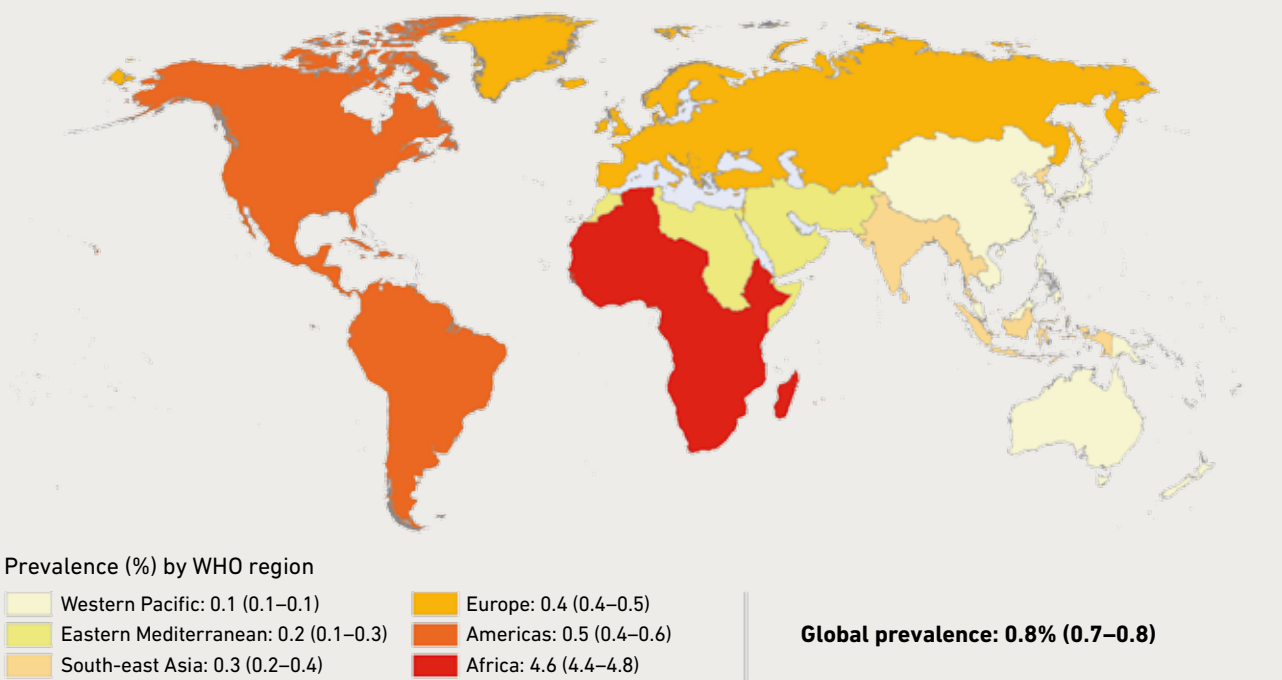
PEP is short-term anti-retroviral treatment to reduce the likelihood of HIV infection after potential exposure. This is used by health workers who have had 'needle-stick' injuries and for people who think they may have been infected during sex (although the prescribing guidelines in this circumstance are strict). The treatment is available from sexual health clinics and accident and emergency departments. It is most effective when started within one hour of possible exposure (or at least within 3 days) and continues for 4 weeks. It is not always effective, has side effects and is NOT an alternative to safe sex!

### Pre-exposure prophylactic treatment (PrEP)

Pre-exposure prophylactic treatment (PrEP) is where people who are at very high risk of exposure to HIV take daily antiretrovirals to reduce their likelihood of becoming infected. Truvada (a combination of two NRTIs, tenofovir and emtricitabine) is currently approved for daily use as PrEP in the USA. PrEP is currently not available on the NHS, however it can be purchased privately with a prescription. If taken consistently, PrEP can reduce the risk of sexual transmission of HIV by more than 90% and intravenous transmission by more than 70%.

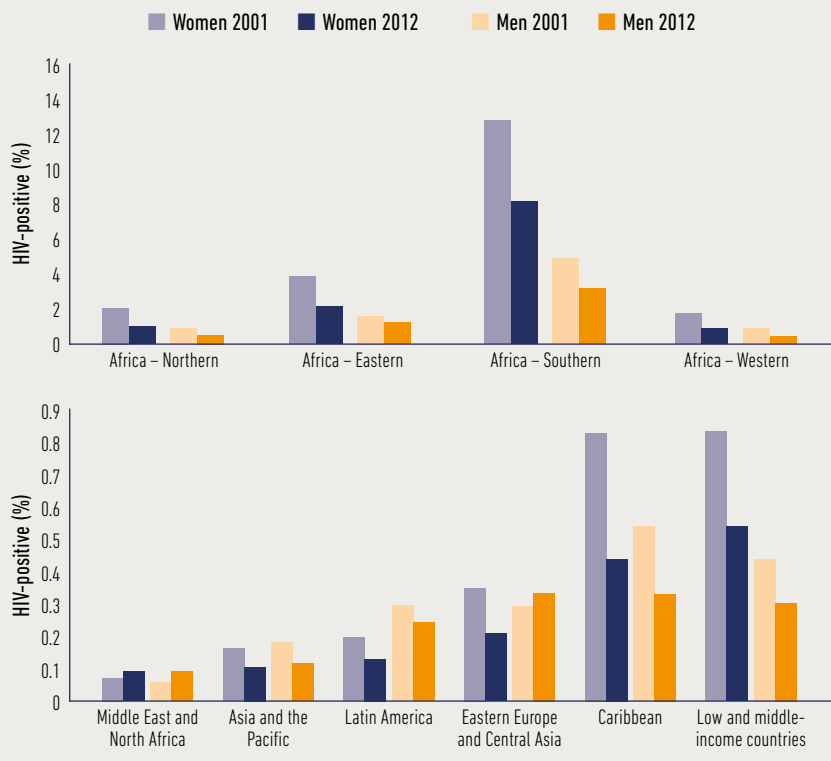
**A global view of HIV infection. Adult HIV Prevalence (15–49 years) by WHO region (2011).** ©WHO 2013

In 2014, 36.9 million people (34.3–41.1 million) were living with HIV.



### Prevalence of HIV among young women and men (15–24 years) by region (2001 and 2012)

Data from the Joint United Nations Programme on HIV/AIDS (UNAIDS) report on the global AIDS epidemic (2013)



### HIV – its origins and future...

The Hunter Theory provides the most plausible origin of the current HIV pandemic. A virus called Simian Immunodeficiency Virus (SIVcpz) has been found in chimpanzees in the Cameroon, Africa. It is extremely similar to HIV-1 and it is thought that people hunting wild chimpanzees contracted the virus either through consumption of the meat or via cuts when they killed and butchered the animals. Over time the virus mutated into a form transmissible between humans. HIV has probably been in the human population since the 1930s and spread from the Cameroon to the Democratic Republic of Congo (DRC). The increased ease of international travel allowed its global spread: first to Haiti in the 1960s (with people returning from work in DRC) and then from Haiti to the US in the 1970s.

infection in animal models, and so this is considered a promising approach.

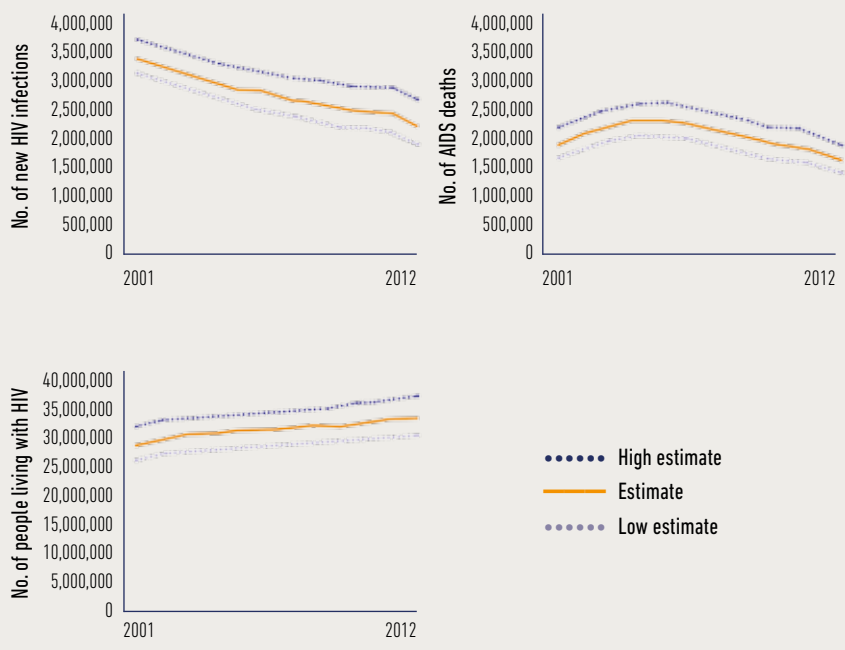
**Live vector vaccine:** non-HIV viruses that are genetically engineered to carry genes for HIV proteins. The genetically engineered virus will have proteins normally found on the surface of HIV.

**DNA vaccine:** uses copies of a small number of HIV genes which are inserted into pieces of DNA called plasmids. The HIV genes will produce proteins very similar to the ones from real HIV.

**Virus-like particle vaccine (pseudovirion vaccine):** a non-infectious HIV 'look-alike' that has one or more, but not all, HIV proteins.

### Numbers of people living with HIV, new HIV infections, and AIDS deaths, 2001–2012, globally

From the Joint United Nations Programme on HIV/AIDS (UNAIDS) report on the global AIDS epidemic (2013)





By 1980 it had reached Asia, Europe and Australia, although it wasn't detected as a new disease until 1981. The first cases in the USA were among homosexual men; doctors were confused as to why young men were succumbing to infections usually only seen in severely immunocompromised people. The disease was attributed to their lifestyles and high rates of sexually transmitted infections and given names like: 'gay compromise syndrome', and 'gay cancer'.

But then the disease turned up in injecting drug users and female prostitutes. It seemed more likely that an infectious agent was responsible

and the name AIDS was finally coined in 1982. The infectious agent had not been identified however and unfortunately blood infected with HIV was used by the transfusion service, resulting in many haemophiliacs contracting the disease. It was terrifying: no-one knew what caused it, how to cure it or why it caused such hideous destruction of the immune system. In 1984 HIV was eventually identified as being the cause of AIDS and by 1985 clinical trials showed a drug called AZT to be active against the virus. At last there was hope, but the lives of those infected with HIV were still dogged by prejudice, discrimination and the fear of death.

More than 30 years later there is now a huge wealth of HIV research and a concerted global effort to stem the pandemic. There are currently 30 anti-retroviral drugs licensed for use and due to its modes of transmission it is easy to prevent. There is still no sign of an effective vaccine.

The situation in the UK is also a cause for concern. Recent research suggests that there is a high level of ignorance in young people and a quarter of infected people do not know that they are HIV-positive. One third of UK diagnoses occur in people whose infection is at such a late stage that it is often untreatable.



The red ribbon symbolises AIDS awareness and a male condom symbolises safe sex.

## HIV conspiracies

There have been many ideas about the origins of HIV, some of which have been quite outrageous! For example, the Vaccine 'Theory' that claimed HIV was accidentally introduced to Africa in the 1950s via an oral polio vaccine produced using monkey tissue. Another conspiracy theory claimed that HIV was manufactured as part of a biological warfare programme designed to wipe out large numbers of black and homosexual people. These ideas are now completely discredited and considerable evidence suggests that the *Hunter Theory* is the most probable.

## Taking it further

AVERT is an international AIDS charity [www.avert.org](http://www.avert.org)

The Terrence Higgins Trust is the largest HIV and sexual health charity in the UK [www.tht.org.uk](http://www.tht.org.uk)

The World Health Organization is the directing and coordinating authority on international health [www.who.int/hiv/en](http://www.who.int/hiv/en)

## Factfile: HIV & AIDS

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**Front cover and right** Coloured transmission electron micrograph of HIV particles.

