Our knowledge of HIV has grown since the virus’s discovery in the 1980s. Globally, 33 million people are now infected.

HIV infection
pathology and disease progression

By Rosy Weston, MRPharmS, and Brett Marett, DipClinPharm, MRPharmS

Some 33 million people are living with HIV/AIDS worldwide, with 67% believed to be in sub-Saharan Africa. In the UK, an estimated 77,400 people were living with HIV at the end of 2007, over a quarter (28%) of whom were unaware of their infection. According to the Health Protection Agency, almost a third (31%) of all newly diagnosed individuals have advanced infection with CD4 cell count lower than 200 cells/µl of blood. These patients fall under the current recommended treatment threshold of around 350 cells/µl.

Late diagnosis of HIV is the most significant factor associated with HIV-related morbidity and mortality in the UK. Since the advent of combination antiretroviral therapy (CART) in the mid 1990s, patients have been receiving effective treatment and are living longer. Cohort studies in the developed world report that individuals infected at 20 years of age have an average life expectancy that is around two-thirds that of the general population.1 The number of older people living with HIV and those with co-infections such as hepatitis B and C is also increasing.

The treatment of HIV-positive patients is not just limited to specialist clinics in secondary care: most patients are currently treated as hospital outpatients but also access primary care providers such as GPs and community pharmacists. This article covers HIV infection, transmission, testing and disease progression.

The history

The first cases of what is now known as acquired immune deficiency syndrome (AIDS) were described in 1981 in the US. Increasing numbers of a rare pneumonia, caused by Pneumocystis jiroveci, were reported in homosexual men. The common feature in these reports appeared to be profound immune suppression.

Two years later the cause was identified as an infectious pathogen, human immunodeficiency virus type 1 (HIV-1). Worldwide HIV-1 is the predominant type, with another form HIV-2 concentrated in populations from Western Africa. In this article we will discuss HIV-1 infection and will refer to the virus as HIV.

What is HIV?

HIV belongs to a subgroup within the retrovirus family known as lentiviruses or “slow” viruses. Lentiviruses are known for having a long period between initial exposure and the beginning of long-term symptoms leading to disease.

The retrovirus stores its genetic information as RNA rather than DNA. On gaining entry into a human cell, HIV uses an enzyme, reverse transcriptase, to convert its RNA into viral DNA. It then proceeds to integrate itself into the host genome and replicate using the cell’s own processes.

HIV continually replicates using host cell infrastructure and viral enzymes. The replication cycle involves many steps and it is important to understand because antiretroviral medicines target different stages of the process (see Figure 1, p388). Currently there is no cure for HIV.

SUMMARY

UK HIV infection rates continue to increase and the proportion of undiagnosed infection remains a problem. Undiagnosed individuals are at risk of developing advanced disease and infecting others. Transmission can occur sexually, parenterally or from mother to child and current prevention strategies target these routes.

HIV infection can be characterised into distinct stages from time of infection to advanced disease or AIDS. Many patients are asymptomatic for long periods before they develop HIV symptoms. Antiretroviral therapy is necessary to prevent disease progression in patients with declining immune function.
Entry of HIV into cells The external proteins on the HIV virion (Figure 2, p391) play an important role in attachment and fusion to the target cell. Viral glycopeptide 120 (gp120) binds tightly to the CD4 receptor expressed on the surface of the host cell. A conformational change in the gp120 protein allows it to bind to a second protein on the cell surface known as a chemokine co-receptor. Drugs that target this step of viral replication are called entry inhibitors.

Fusion The viral surface protein glycopeptide (gp41) interacts with the target cell to complete the fusion process and allow subsequent entry of the viral RNA and enzymes into the cell. Fusion inhibitors target this step.

Reverse transcription The viral enzyme reverse transcriptase converts RNA into viral DNA in the cytoplasm of the host cell. This process is error-prone and contributes to the development of mutations and different strains of virus. Nucleoside and non-nucleoside reverse transcriptase inhibitors target this process.

Integration The newly made HIV DNA moves to the cell nucleus, where it is spliced into the host cell DNA using an enzyme called integrase. Integrase inhibitors target this step in viral replication.

Transcription and translation Messenger RNA is produced and transported to the cytoplasm. The virus then co-opts the cell’s protein-making machinery to use the mRNA template to produce long chains of viral proteins and enzymes. This process is called translation.

Assembly and budding HIV proteins and genomic RNA gather inside the cell. The precursor proteins that make up the immature viral core are now cut into smaller functional proteins by a viral protease enzyme. A viral particle then forms and buds off from the cell. This is the final step in the replication cycle and results in infectious virions being released into the blood. ARVs that target the protease enzyme are called protease inhibitors.
What is AIDS?
AIDS is caused by HIV, which attacks the immune system by destroying CD4-positive T cells (CD4 cells). These are a type of T-helper white cell and are important in co-ordinating the immune response. The destruction of CD4 cells leaves people infected with HIV vulnerable to infection, disease and other complications.

A CD4 cell count from the blood is used as a surrogate marker for how well an individual’s immune system is functioning. An uninfected adult will have a CD4 cell count between 800 and 1,500 cells/µl. People infected with HIV are at risk of developing opportunistic infections (OIs) due to pathogens that can cause life-threatening infection or malignancy in those who are immunosuppressed.

An AIDS diagnosis is made when a HIV-infected individual develops one or more OIs in the presence of underlying immune deficiency. Such infections are known as AIDS-defining illnesses and will be discussed further in the “Advanced disease” section below.

Transmission
HIV is present in the blood, cerebrospinal fluid, semen, vaginal fluid, saliva, tears and other body fluids of an infected individual (see Box 1). HIV cannot be acquired through routine contact with household items such as drinking glasses, cutlery and lavatory seats, or through activities such as shaking hands or social kissing. There is no evidence that HIV can be transmitted through insect bites or stings.

Prevention of transmission
Currently there is no vaccine to prevent HIV infection. In the UK, post-exposure prophylaxis (PEP) is recommended depending on risk following sexual or occupational exposure. Current PEP is a month’s course of Truvada (tenofovir disoproxil/emtricitabine) and Kaletra (lopinavir/ritonavir).

Antenatal screening for HIV has allowed the treatment of women during pregnancy, which lowers the risk of transmission from mother to child (vertical transmission); this has dramatically reduced the number of HIV-positive newborns. Preventing mothers from breastfeeding has also reduced transmission since HIV is expressed in breast milk.

The role of CART in reducing the risk of onward sexual transmission is unclear. Many studies have investigated different interventions to reduce the risk of transmission in populations where HIV is highly prevalent. Studies have looked at the impact of circumcision in sub-Saharan Africa where access to antiretroviral therapy is limited. Antiretroviral therapy is also being investigated as “pre-exposure prophylaxis” (PrEP) to protect uninfected individuals in some high-risk populations.

Various prevention strategies are listed in Box 2.

Testing
HIV testing is recommended for all at-risk individuals — this includes those at risk following sexual exposure and blood-to-blood exposure (eg, needle-stick injury), as well as children born to women with HIV.

The British HIV Association, in conjunction with the British Association of Sexual Health and HIV and the British Infection Society, produced UK national guidelines for HIV testing in 2008. A list of “clinical indicator diseases” has been produced where HIV could be a differential diagnosis. These guidelines cover all care settings and implementation of these is critical to reducing the undiagnosed population in the UK. It is important that HIV tests are offered as those unaware of their HIV status are at risk of contributing to onward transmission. In the UK almost all antenatal units offer opt-out testing to women during pregnancy. Many sexual health centres are now moving towards this for all patients.

**Box 1: Routes of HIV transmission**

<table>
<thead>
<tr>
<th>ROUTE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual</td>
<td>Vaginal, anal or oral (lower risk)</td>
</tr>
<tr>
<td>Mother to child</td>
<td>In utero, childbirth or breast feeding</td>
</tr>
<tr>
<td>Parenteral or percutaneous</td>
<td>Exposure via inoculation with contaminated needles, instruments, blood or blood products (non-screened) Direct exposure of body fluids (eg, saliva, semen, vaginal fluid, tears) to mucous membranes or exposed/open wounds</td>
</tr>
</tbody>
</table>

**Box 2: HIV prevention**

- Use of condoms for all forms of sexual intercourse
- Use of clean needles and syringes
- Testing of individuals in high-risk groups
- Antiretroviral treatment for HIV-positive women during pregnancy
- Offering HIV-positive pregnant women Caesarean section deliveries
- Advising all HIV-positive women not to breastfeed
The recommended test involves a venous sample for both HIV antibody and viral protein p24 antigen. All new HIV diagnoses should be made following confirmatory testing of a second sample.

Point-of-care testing (POCT), which involves using a pin prick or a mouth swab, allows rapid initial diagnosis. Positive POCT results must be confirmed with a venous blood sample since these rapid tests have a low specificity and can give false positives. POCT has the added advantage of being able to be undertaken outside conventional healthcare settings.

**Typical progression of HIV infection**

HIV has a high replication rate with several billion new viruses made every day. In the early stages of infection, while the immune system is intact, there is dynamic equilibrium between virus replication and destruction. The level of HIV in a person’s blood can be measured — this is called the HIV viral load (VL). The VL increases rapidly in the first few months of infection and then returns to a level known as the set point.

An individual’s viral population may consist of many different strains. This viral diversity is predominantly due to the error-prone nature of reverse transcriptase (the viral enzyme that makes DNA copies of the HIV RNA). Some strains are fitter than others and occupy a larger proportion of the viral population. Others may be less fit and occupy a smaller proportion. Some strains may harbour mutations that are associated with drug resistance. However, this is uncommon in patients who have never had antiretroviral treatment. Drug resistance testing and antiretroviral treatment will be discussed further in the accompanying article (p.393).

Over time, the VL increases and the number of CD4 cells decline, eventually depleting the immune system’s capacity to regenerate or fight other infections (Figure 3).

**Acute phase** In the initial stages of HIV infection most people will have few, if any, symptoms. Some individuals may experience a seroconversion illness usually within a month or two after infection. This is when the body has identified the presence of HIV and starts to generate antibodies. Symptoms are typically influenza-like and can include fever, headache, tiredness and enlarged lymph nodes in the neck and groin area. These symptoms usually disappear within a week to a month and are often mistaken for another viral infection, such as flu. During the period before seroconversion people are highly infectious because HIV is present in large quantities.

**Chronic phase** Some chronically infected individuals may remain asymptomatic for a long period, whereas others experience disease progression and develop symptoms related to HIV infection.

**Asymptomatic HIV** Following diagnosis, individuals are monitored closely for any changes in symptoms, viral load and CD4 cell count. Changes can indicate that the immune system is becoming overwhelmed and CART may need to be started.

**Symptomatic HIV** Some people may experience non-specific symptoms as their CD4 cell count drops. These include:

- Rapid weight loss or weight loss of unknown cause
- Recurring fever
- Profuse night sweats
- Profound fatigue
- Prolonged swelling of the lymph glands in the armpits, groin or neck
- New presentations of conditions associated with immunosuppression

**Advanced disease/AIDS** During the late stages of HIV infection, the virus severely weakens the immune system, CD4 cell count drops below 200 cells/µl and the individual is susceptible to AIDS-defining illnesses such as OIs and malignancies (see Box 3).

### References