

Aetiology and pathology of hiv and AIDS

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HIV disease is now considered to be pandemic. The first part of this special feature discusses the origins, transmission and diagnosis of HIV, as well as its progression to AIDS

The HIV pandemic has far exceeded projections over the past decade. The World Health Organization estimates that, all over the world, the number of people living with the human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS) at the end of 2000 was 36.1 million. During that year, there were 5.3 million new cases of HIV infection and three million AIDS deaths. A total of 21.8 million people with AIDS have died since the start of the pandemic.¹ The major burden of the pandemic and deaths has been in the developing world.

In the UK, there have been approximately 43,000 cases of HIV infection, with 17,400 AIDS diagnoses and 13,780 deaths attributable to HIV.² In 1999, for the first time, the number of new infections acquired through heterosexual intercourse exceeded those acquired through homosexual intercourse. This trend continued into 2000 (1,315 in

heterosexuals, compared with 1,096 in homosexuals), when the number of people who acquired HIV in the UK was the highest for any year since 1985.³

■ ORIGINS

In 1981, several clusters of a distinct immunodeficiency syndrome were reported in homosexual men in the US.^{4,5} Two years later, a retrovirus, subsequently named HIV-1, was isolated by independent researchers from a number of individuals with this acquired immunodeficiency syndrome.^{6,7} Antibodies to HIV can be identified in all individuals with AIDS.⁷ Subsequent reviews of medical literature have discovered reports of AIDS-like illnesses as far back as the 1940s. However, some of these, such as the case of the Manchester sailor reported to have died from AIDS in 1959, are doubtful.⁸ The exact origins of HIV are unknown, but HIV-1 is a descendant of the simian immune deficiency virus (SIV), which has been isolated from central African chimpanzees.⁹ HIV-2 is closely related to SIV and is isolated from macaques

and sooty mangabeys.¹⁰ It is possible that these viruses somehow crossed over into human populations. Theories as to how this happened include inadvertent introduction using contaminated oral polio vaccines in the late 1950s,¹¹ and malaria experiments with blood transfusions.¹² However, more recent studies suggest that the time of this crossover to humans was much earlier (nearer to the 1930s) and that the virus then mutated, leading to the modern day HIV.¹³

■ TRANSMISSION

HIV can be found in many body fluids, although in some of these fluids it is present in such low concentrations as not to constitute a risk. The predominant fluids of transmission are semen, cervical and vaginal secretions, breast milk and blood. HIV can also be transmitted by the transfusion of blood or blood products, and by the sharing of injecting equipment among drug users. In other words, transmission can occur via sexual intercourse, injectable drug use, transfusion of infected blood and from mother to child. HIV can be transmitted as

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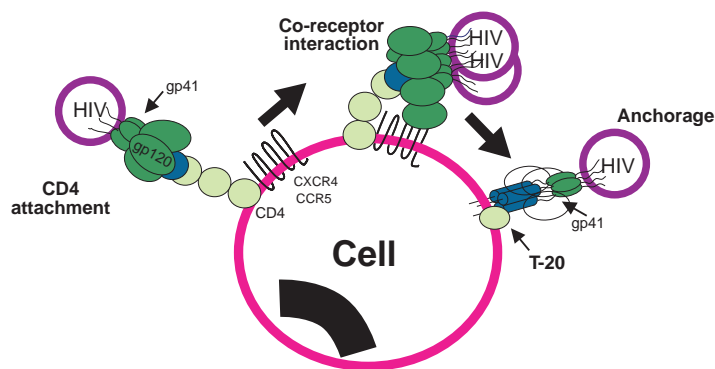


Figure 1: HIV interaction with CD4 cell

the free virus or as virus-infected cells, and several factors determine the likelihood of transmission. HIV ribonucleic acid (RNA) has been isolated from blood,¹⁴ and measurements of HIV RNA levels, known as viral load, are now used in monitoring those infected with HIV. Viral load is higher during primary HIV infection and in late stage disease, and loads have been shown to correlate with HIV transmission.¹⁵ Concurrent illnesses, such as tuberculosis (TB) may also increase the viral load.¹⁶

Many studies have shown the presence of HIV in the semen, particularly in patients with lower CD4 counts and symptomatic disease.^{17,18} However, in one study, HIV was isolated in 43 per cent of a group of asymptomatic men on at least one occasion over six months.¹⁹ In women, HIV can be isolated from the cervix and the vagina, although swabs from the former yield HIV more readily.²⁰ Levels of HIV RNA in the plasma and vaginal fluid have been shown to correlate very closely.²¹ It is logical that levels of HIV in the vagina also increase at the time of menstruation.²² The presence of other sexually transmitted infections (STIs) has been shown to increase the amount of HIV in genital secretions, therefore increasing transmission. A study in Malawi of 86 HIV positive men with urethritis showed a significant reduction in concentration of HIV in semen, following treatment for urethritis.²³ A more recent study in HIV positive women in Kenya showed that treatment for cervicitis reduced HIV shedding in cervical secretions.²⁴

Some individuals remain HIV negative despite repeated exposure to the virus. There have now been several studies in such people, suggesting possible mechanisms of HIV resistance. A study in Gambia found HIV specific cytotoxic T cells in three HIV-exposed but uninfected women.²⁵

Some studies have found genetic defects for the HIV receptors required for viral entry into cells. There are several studies suggesting that mucosal immunity might play a role in protecting individuals from HIV. These include studies of sero-discordant couples showing HIV-specific mucosal and cellular immunity in the HIV negative female partners and studies of seronegative

Kenyan and Thai sex workers, which demonstrate the presence of HIV-specific immunoglobulin A (IgA) antibody in the genital tract.²⁶⁻²⁸

Mother-to-child HIV transmission can occur at three stages:

- During pregnancy, when HIV crosses the placenta
- During delivery, when infection is from HIV in vaginal secretions or blood
- During breast-feeding, via breast milk

The rates of transmission from mother to child vary from 13 to 45 per cent,²⁹ with the highest rates being seen in developing countries. This variation may be due to several factors, such as the stage of maternal HIV infection and adequacy of obstetric care. Indeed, maternal viral load has been shown to correlate with transmission rates.³⁰ Most transmission seems to occur during labour and delivery, and population studies have been used to estimate that the additional risk of transmission through breast-feeding is 14 per cent. HIV has been found in breast milk, and the risk of transmission via this route increases with the viral load in breast milk, the presence of mastitis and nipple disease.³¹ A study in Malawi showed a high risk of early breast milk transmission, with a lower but continued risk afterwards. A Kenyan study also showed that 75 per cent of breast milk transmission occurred during the first six months of life.^{32,33} Other studies, for example, by Cout-soudis *et al*, have suggested that mixed infant feeding (breast milk plus other liquids) is associated with higher transmission rates.³⁴

REPLICATION

The replication cycle of HIV begins with the attachment of the virus envelope protein gp120 to CD4 recep-

tors on certain cells. These cells include T helper cells (lymphocytes), monocytes, macrophages and dendritic cells. For attachment to happen, there also needs to be a second receptor present, the main two of which are CCR-5 and CXCR-4³⁵ (Figure 1). Following attachment, there is fusion of the lipid coating of HIV with the target cell membrane. Once HIV has entered the cell, it is uncoated and the reverse transcriptase enzyme converts viral genomic RNA into double-stranded DNA, which can then enter the nucleus and be integrated into the host cell DNA as pro-viral DNA. This pro-viral DNA is then controlled as a cellular gene, and HIV gene expression is stimulated initially by the action of host transcription factors. This leads to the production of viral proteins, which then regulate the subsequent production of the viral structural proteins. The structural proteins are initially produced in the form of precursors, which must be split to enable assembly of the whole virus. This is achieved by the action of the protease enzyme (Figure 2).

IMMUNOLOGICAL EFFECTS

HIV infection causes a progressive loss of CD4 T cells and immune deterioration. The reduction in CD4 T cells is most likely due to a combination of decreased production of cells and increased cell death. It now seems that decreased cell production plays a much larger role than has been previously appreciated.³⁶ Cell death can occur via several mechanisms, including apoptosis (programmed cell death), which may be initiated by sensitised T cells, and cell fusion (syncytia formation), where a few HIV infected cells might fuse with and eliminate many uninfected cells. Indeed, it is known that syncytium-inducing (SI) strains of HIV are found in late infection.²⁹ After entry into the CD4 cell, HIV may establish a latent form of infection.³⁷ The pattern of latency may be determined by cellular activity, as HIV does not replicate in resting T cells and



Figure 2: Life cycle of HIV-1

Table 1: Clinical categories of HIV infection

CD4 count (cells per mm ³)	A Asymptomatic, lymphadenopathy or primary HIV	B Symptomatic disease	C AIDS-defining condition
>500	A1	B1	C1
200-500	A2	B2	C2
<200	A3	B3	C3

activation of these T cells by factors such as co-infection with other viruses and vaccination promotes HIV replication.²⁹ Despite some cells containing latent virus, studies suggest a dynamic pattern of HIV replication and CD4 cell turnover. Approximately one billion new virions (elementary virus particles) are produced on a daily basis. This is initially countered by the daily production of one to two billion new CD4 cells.³⁸ As there is no proofreading gene within the HIV genome, replication of HIV is prone to error, particularly at the reverse transcription stage. This leads to a high frequency of HIV variants (mutations). Many of these mutations are deadly to the virus, but some confer benefits on it. For example, the virus may escape immune control or develop resistance to antiretroviral drugs.

DIAGNOSIS

The diagnosis of HIV infection is made by detecting antibodies to the virus or by detecting the virus itself (using p24 antigen tests) or by estimating the viral load (virus amplification, using polymerase chain reaction [PCR]). Antibodies to HIV are detectable from three to 12 weeks following infection, and the standard screening test is an antibody test using an enzyme linked immunosorbent assay (ELISA). This is then usually confirmed using a Western blot test (immunoblot) which detects HIV antibodies and determines their specific antigens, using electrophoresis. ELISA antibody tests were in widespread use by mid-1985, although they have evolved since then. With improvements in ELISA tests, results are now more often confirmed with a second ELISA. The newer fourth generation assays are more sensitive and combine ELISA with p24 antigen detection.³⁹ The use of p24 antigen or PCR testing alone is not an adequate screening test for HIV, as during the course of infection, there are times when HIV antigens or RNA may be undetectable and false positive results are not uncommon.

The Centers for Disease Control and Prevention in the US divide HIV disease into three categories according to a patient's clinical condition. These are then subdivided by CD4 counts. In the US, in addition to category C, all patients with CD4 counts less than 200 (categories A3 and B3) are report-

ed as AIDS patients (see Table 1). Here in the UK, a CD4 count of less than 200 is not AIDS defining, only category C.

PRIMARY HIV INFECTION

A glandular fever-like illness may occur within three months of exposure to HIV, most commonly by about eight weeks. From 50 to 90 per cent of people present with some degree of symptoms, ranging from a mild non-specific influenza-like illness to life-threatening disease, such as meningoencephalitis.

In one study of 46 patients, the five most common symptoms were fever, sore throat, fatigue, myalgia and weight loss (average 5kg).⁴⁰ Seventeen per cent were admitted to hospital and 24 per cent had signs of aseptic meningitis.⁴⁰ At this stage, the viral load is usually high, often greater than one million, and the CD4 count drops, sometimes to such a low level that presentation is with an AIDS-defining illness. The antibody test is most often negative to begin with, but HIV can be detected using p24 or viral load tests and an evolving antibody response can be documented if samples are repeated two to seven days later.

An initial cellular immune response precedes antibody production and this is thought to play the major role in controlling the massive viraemia. However, at this stage there has already been widespread dissemination of the virus around the body. Studies in macaques show that the virus can be found in regional lymph nodes within 36 hours and systemic lymph nodes within four to five days of infection or transmission.⁴¹ Lymphoid tissue serves as the major reservoir of HIV burden and replication.³⁷ So, there is an increase in the CD4 count and a decrease in the viral load to reach a plateau. Symptoms then settle and there is a period of clinical latency, the length of which is variable, but is usually several years.

LONG-TERM NON-PROGRESSORS

Between two and five per cent of HIV-positive individuals are termed long-term non-progressors (LTNPs), that is, they have had asymptomatic infection for 13 or more years, have CD4 counts that remain normal or stable without antiviral therapy

and have viral loads less than 5,000 copies per ml. This is thought to be due to either viral or host factors. The virus might be less pathogenic in these individuals, and there are several studies showing that the presence of virus with gene deletions, such as nef gene deletions, is associated with non-progression.^{42,43} There is also evidence to suggest the presence of genetic protection factors in some of these people. Genes have been discovered that code for the co-receptors on immune cells required for the entry of HIV into these cells. Defects in these genes may protect against the acquisition of HIV or slow the progression of HIV once infected. Variants in the CCR-5 co-receptor gene were the first to be reported.⁴⁴ Initial infection with HIV is usually via this co-receptor on macrophages. Defects in this receptor do not afford complete protection against HIV, as SI strains use the CXCR-4 co-receptor, mainly found on T lymphocytes.³⁵ Gene mutations for the CCR-2 receptor, which slow progression by two to four years, have also been reported and about 30 per cent of LTNPs have at least one CCR-5 or CCR-2 mutant gene.⁴⁵ Other genetic factors may possibly affect disease progression. However, their role is less clear.^{46,47} Unfortunately, these genetic differences do not account for all LTNPs; for example, about 60 per cent of LTNPs have a normal CCR-5 receptor.

The initial control of HIV viraemia is achieved by an HIV-specific CD8 cytotoxic T lymphocyte (CTL) response and indeed these CTL responses have been shown to coincide with the decrease in viral load seen in primary infection.⁴⁸ Antibodies are not detected until there has already been a substantial drop in the viral titres. This initial CTL immune response is critical in determining the subsequent course of HIV infection, in that a good response means a greater reduction in viral load. LTNPs have been shown to have very strong HIV-specific CTL responses⁴⁹ and one of the arguments for early therapy at the stage of primary HIV

Table 2: Opportunistic infections

Symptomatic disease CD4 200-500 cells per mm ³	AIDS-defining disease CD4<200 cells per mm ³	AIDS-defining disease CD4<50 cells per mm ³
Oral candida	<i>Pneumocystis carinii</i> pneumonia	Disseminated cytomeg- alovirus infection
Oral hairy leukoplakia	Recurrent herpes sim- plex or herpes zoster	<i>Mycobacterium avium</i> infection
Herpes zoster	Oesophageal candida	
Fatigue/weight loss	Toxoplasmosis	
Anaemia	Kaposi's sarcoma*	
Thrombocytopenia	Cryptococcal meningitis	
	Non-Hodgkin's lymphoma*	
	Cryptosporidiosis	
	Microsporidiosis	
	Progressive multifocal encephalopathy	
	Tuberculosis*	
	Cervical carcinoma*	

*Can occur at higher CD4 counts

infection is that this may maintain strong CTL responses capable of controlling viraemia.

■ DISEASE PROGRESSION

Without treatment for HIV, the average time from seroconversion to death is approximately 10 to 12 years (Figure 4). In a study carried out in San Francisco, US, 54 per cent of patients progressed to AIDS in 11 years and 19 per cent had no symptoms at 11 years.⁴⁰ Rates of progression appear similar by gender, race and risk category if adjusted for quality of care. However, older age is associated with higher rates of progression.⁵⁰ Patients with symptomatic primary HIV infection have also been shown to progress to AIDS more rapidly.⁵¹ Those with long-lasting symptoms have a higher viral load at six to 24 months following seroconversion than those with milder symptoms,⁵² and clinical progression has been shown to correlate with the viral load and CD4 counts,^{52,53} the prognosis being worse with a steeper CD4 decline and a higher viral burden.

There is a gradual decline in CD4 cells, leading to a reduction in cell-mediated immunity. Cell-mediated immunity plays an important role in the body's response to many types of infection and such a reduction leads to an increased risk of infection and of tumours, such as non-Hodgkin's lymphoma. Many of these infections would be innocuous in the immunocompetent and as such they are considered to be opportunistic. Many opportunistic infections (OIs) are AIDS-defining and occur with CD4 counts less than 200. However, other OIs, such as oral candida, are indicative of symptomatic infection only and can occur at higher CD4 counts. Symptomatic disease usually occurs

when the CD4 count drops below 500, as shown in Table 2.

Once the CD4 count drops below 200, there is a much higher risk of the development of serious opportunistic infections, such as *Pneumocystis carinii* pneumonia (PCP). With decreasing CD4 counts, there is a risk of many other OIs, including cryptococcal meningitis, toxoplasmosis and cytomegalovirus (CMV) infection (Figure 4). The median time between the CD4 count reaching 200 and the development of an AIDS-defining illness is 12 to 18 months. Prior to the introduction of highly active antiretroviral therapy (HAART), the most common initial AIDS-defining illness was PCP, seen in 28 per cent of those who had received PCP prophylaxis and 61 per cent of those who had not.⁴⁰ Some tumours associated with HIV are AIDS-defining, including Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma. It is not common for AIDS-defining illnesses to occur with CD4 counts above 200. Instances where they can occur

include cases of TB and Kaposi's sarcoma, but they can also happen with OIs such as PCP. Once the CD4 count drops to 50 or less, the median life expectancy without HAART is 12 to 18 months.⁴⁰

Since the advent of HAART in 1996, disease progression has changed. There has been a dramatic reduction in the number of AIDS diagnoses and in the number of deaths due to HIV infection.^{54,55} The pattern of OIs has changed, with previously untreatable conditions, such as cryptosporidiosis, now responding to HAART. Other OIs, which were difficult to treat or relapsed (sometimes despite secondary prophylaxis) respond better to treatment in conjunction with HAART. In addition, it is now possible to stop primary or secondary prophylaxis for OIs, following improvement in immune function with HAART.⁵⁶ On the downside, some patients are now presenting with acute illnesses during immune reconstitution (improvement of the immune system). This is caused by an enhanced immune response to infection and has been documented for infections such as *Mycobacterium avium-intracellulare* and CMV.^{57,58} The full extent of the changes in the natural history of HIV infection is yet to be revealed. However, the reduction in morbidity and mortality following the introduction of HAART means that quality of life is now much improved. Unfortunately, therapy for HIV is not without problems, with long-term drug toxicities, for example lypodystrophy, becoming more apparent with time.

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