Ministry of Defence

Synopsis of Causation

HIV Infection and AIDS

Author: Dr Adrian Roberts, Medical Author, Medical Text, Edinburgh
Validator: Dr Michael Waugh, Nuffield Hospital, Leeds

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

1.1. Acquired Immune Deficiency Syndrome (AIDS) was first reported in 1981 in the USA. The disease is caused by infection with a retrovirus known as human immunodeficiency virus (HIV).

1.2. HIV has a high affinity for a subset of cells called $CD4^+$ T-cells or $CD4^+$ T-lymphocytes, which play a major role in the body's cellular immunity. The virus binds to the CD4 molecule and penetrates these cells. Within the cell, a viral enzyme (reverse transcriptase) transcribes viral RNA into double-stranded DNA, which is then integrated into the host cell's DNA, enabling further replication to take place.

1.3. The destruction of $CD4^+$ T-cells results in progressive impairment of the host's immune response, leading eventually to AIDS and death. Studies have shown a strong association between the development of life-threatening opportunistic illnesses and the absolute number or percentage of $CD4^+$ T- cells. As the number of $CD4^+$ T-cells decreases, the risk and severity of opportunistic illnesses increase.

1.4. An **AIDS** diagnosis is made by reference to criteria specified in one of a number of case definitions that have been drawn up for the purposes of AIDS surveillance. The definition drawn up in 1993 by the Centers for Disease Control and Prevention (CDC) in the USA specified the following criteria:

- Laboratory evidence of HIV infection: **and**
- $CD4^+$ T cell count below 200 cells/mm^3 (normal range 500-1500 cells/mm^3) or $CD4^+$ T cells account for fewer than 14% of all lymphocytes: **or**
- Presence of one or more indicator conditions (full list at Appendix A)

The European case definition relies on just the first and last of the above criteria.

1.5. There are two strains of HIV, designated HIV-1 (with multiple groups and sub-types) and HIV-2 respectively. The routes of transmission and risk factors for the two strains are similar, as are the resulting opportunistic infections. However, HIV-2 is far less common, occurs predominantly in West Africa, and is associated with immunodeficiency that develops more slowly than is the case with HIV-1.[1,2] As the prevalence of HIV-2 is very low compared to HIV-1, the information in this synopsis focuses on HIV-1 and, unless stated otherwise, use of the term "HIV" refers to HIV-1.

1.6. HIV infection has developed into a worldwide pandemic. By the end of 2003, an estimated 34.6 to 42.3 million people throughout the world were living with HIV infection and, over the course of the entire epidemic, over 20 million deaths had been caused by AIDS. Almost 5 million people acquired the virus in 2003, the greatest number in any one year. Worldwide, 1.1% of all people aged between 15 and 49 are now infected with HIV.[3] The epidemic is most rampant in the developing world, principally striking geographic regions where the infrastructure is least well equipped to prevent and treat infection. Two-thirds of infected people are in Africa and one-fifth in Asia. The impact of the epidemic is illustrated by figures from South Africa, where 5.3 million people are currently living with HIV, and from Botswana, a country of less than 2 million people, where the HIV prevalence rate amongst adults is 37.3%. 2.2 million

people died of AIDS in sub-Saharan Africa during 2003. In contrast, in Western Europe where effective treatment is available, around 6000 people died of AIDS in 2003.

1.7. HIV remains a major health issue in the United Kingdom. By the end of 2003, there were an estimated 53,000 adults over the age of 15 living with HIV in the UK, of whom 14,300 (27%) were unaware of their infection. The number of new diagnoses made in the UK in 2003 was 6606, more than double the figure for 1998.[4]

1.8. Markedly different patterns of transmission are seen in different regions of the world. Globally, unprotected heterosexual intercourse is now the predominant mode of transmission, accounting for more than 85% of cases of HIV infection that occur in developing countries. In parts of Asia, eastern Europe, and Latin America the HIV epidemic is currently being driven by injecting drug use.[5]

1.9. In 2003 in the UK, 58% of new HIV infections *diagnosed* were attributable to heterosexual intercourse. It is considered that three-quarters of these infections were probably acquired in sub-Saharan Africa, although the acquisition of HIV-infection through heterosexual intercourse taking place within the UK is also rising. With regard to cases of infection *acquired* within the UK, the group at highest risk is men who have sex with men. In contrast, it is probable that just 6.5% of all HIV diagnoses made in the UK since the early 1980s have been acquired through injecting drug use. Marked regional differences exist in the distribution of HIV infections in the UK.[4]

1.10. The number of AIDS diagnoses and deaths in HIV-infected individuals in the UK has fallen since more effective treatment regimes were introduced in the mid-1990s. The UK's Health Protection Agency reported 766 cases of AIDS and 475 deaths during 2003.[4]

2. Clinical Features

2.1. HIV infection has a multitude of different clinical presentations and, in addition can alter the presentation of many other disease processes. Clinically, the disease proceeds through a number of stages:

2.1.1. After initial infection, there is an acute phase of viraemia in which plasma viral loads reach very high levels of several million copies/mL. In 40% to 90% of recently infected people, this initial phase is accompanied by symptoms of **seroconversion illness** (also known as acute retroviral syndrome). This presents as a glandular fever-like illness that typically commences 2-6 weeks after exposure, with a duration of around 14 days. Symptoms may include fever, night sweats, malaise, swollen glands, weight loss, muscle pains, diarrhoea, rash, buccal ulceration, and pharyngitis. Neurological involvement including aseptic meningitis may also be evident. Although subjects are highly infectious during the acute stage, laboratory tests that rely of the detection of anti-HIV antibodies (e.g. HIV ELISA and Western blot assays) yield negative results. The appearance of markers in the blood i.e. seroconversion usually takes place between 3-12 weeks, but may be delayed for up to 12 months.[1,6]

2.1.2. The body's immune responses to HIV infection produce a fall in viral load. The acute stage is superseded by mild immune suppression that lasts for a variable period, typically 4-7 years. Patients are generally **asymptomatic** during this time but may experience an increase in episodes of recurrent viral upper respiratory infection, mucocutaneous candida infection, allergic disease, lymphadenopathy, splenomegaly, and some other rare diseases.

2.1.3. Progression to **symptomatic** HIV infection ensues which, in the absence of treatment, typically lasts 1-3 years. This stage is characterised by persistent generalised lymphadenopathy, localised fungal infections, vaginal yeast infections, oral hairy leukoplakia, cutaneous manifestations, herpes zoster, herpes simplex, and constitutional symptoms.

2.1.4. **AIDS** represents a state of severe immunodeficiency that leads to life-threatening opportunistic infections and cancers. The list of **AIDS indicator conditions** is extensive (see Appendix A). The range of manifestations of AIDS includes:

- **Opportunistic infections** affecting the lungs, brain, eyes, and other organs, caused by specific organisms including *Mycobacterium tuberculosis* (TB) and *Pneumocystis carinii* (pneumonia)
- **Malignancies**, particularly those linked with viral co-infection such as Kaposi's sarcoma, which is associated with human herpesvirus 8
- A direct effect on the **central nervous system** resulting in HIV-related encephalopathy (also called "HIV dementia" or "AIDS dementia"), characterised by disabling cognitive or motor dysfunction
- A direct effect on the **gastrointestinal tract** resulting in HIV wasting syndrome associated with profound involuntary weight loss, chronic diarrhoea, chronic weakness, and fever

- Direct effects of the virus may also be associated with cardiomyopathy, neuropathy and chronic dysfunction within other organ systems

2.1.5. Prior to the advent of combination antiretroviral therapy, most patients would not survive more than 1-2 years following a diagnosis of AIDS. **Death** usually occurs because of wasting, opportunistic infection, or malignancies.

2.2. The diagnosis of HIV infection in adults is usually based on the serological detection of specific anti-HIV antibodies using the combination of enzyme-linked immunoabsorbent assay (ELISA) and Western blot assay. Effective pre-test counselling is vital. Anti-HIV antibodies remain detectable throughout the course of the disease. Following diagnosis, analyses of **HIV viral load** and **$CD4^+$ T-cell counts** are used to monitor progress, as these tests provide the most accurate measure available for predicting the development of HIV-associated conditions and progression to AIDS.

2.3. HIV shares common transmission pathways with other blood-borne virus infections, notably hepatitis B (HBV) and hepatitis C (HCV). HIV and HBV co-infection is common, particularly in men who have sex with men. Co-infection with HCV affects an estimated 30% of HIV-infected individuals in Europe and the USA.[7] HCV is more efficiently transmitted through blood than by sexual exposure. Therefore HIV and HCV co-infection is particularly common in people who have a history of injecting drug use or receipt of blood and/or blood products.[8]

3. Aetiology

3.1. HIV is a bloodborne and sexually transmitted disease. HIV may be found in varying concentrations in blood, semen, vaginal fluid, breast milk, saliva, and tears. Transmission occurs through:

- insertive or receptive sexual intercourse
- exposure to contaminated blood or blood products
- vertical transmission from mother to child

The risk of HIV transmission is affected by numerous **behavioural**, **viral**, and **biological factors**, which are detailed in the following paragraphs.

3.2. **Sexual transmission**

3.2.1. Sexual transmission constitutes the most common route of infection. The efficiency of male-to-female transmission of HIV during heterosexual intercourse has been estimated as twice that of female-to-male transmission, although some studies have found no significant difference. Certain forms of sexual behaviour have a higher average per-act risk of transmission than do others. The relative frequency of performance of higher- and lower-risk sex acts will affect the overall risk of transmission. The estimated risk of HIV transmission *per exposure* from a *known HIV positive source* is summarised in the following table, ranked in ascending order of risk:[9]

Receptive oral sex (fellatio)	0 - 0.04%
Insertive vaginal intercourse	0.03% - 0.09%
Insertive anal intercourse	0.06%
Receptive vaginal intercourse	0.1% - 0.2%
Receptive anal intercourse	0.1% - 3.0%

3.2.2. The consistent and proper use of latex or polyurethane condoms during sexual intercourse (vaginal, anal, or oral) provides a high degree of protection against the risk of acquiring or transmitting HIV. The risk of transmission for each of the activities listed above is decreased 20-fold by condom usage.[10]

3.2.3. Genital inflammatory conditions increase shedding of HIV in seminal fluid and in vaginal and cervical secretions. Sexually transmitted diseases (STDs) have a synergistic effect on both HIV **infectivity** and **susceptibility**, and infection with ulcerative (e.g. herpes simplex) and non-ulcerative STDs is associated with an increased risk of HIV transmission and acquisition.[11] Inflammation and ulceration in the rectum and mouth increase the risks associated with anal and oral intercourse respectively.

3.2.4. Other factors known to increase the risk of sexual transmission are intercourse during menstruation and trauma e.g. from sexual assault. In a number of studies, lack of male circumcision has been associated with an increased risk of HIV acquisition. However, the question remains as to whether this observation may be explained by differences in behavioural practices.

3.3. **Exposure to contaminated blood or blood products**

3.3.1. **Sharing of needles and/or syringes.** This factor relates primarily to injecting drug users. The estimated risk of HIV transmission per exposure from a known HIV positive source is 0.67%.[9] In the UK, HIV prevalence was 1% in injecting drug users attending specialist agencies.[4]

3.3.2. Other **procedures that breach the skin** pose a potential risk if sterilisation procedures are inadequate or technique poor. Instances are very rare with the CDC in the USA reporting in 1999 that it knew of no cases of HIV transmission through tattooing or body piercing, and of just one case of transmission through acupuncture. In theory at least, household spread of HIV is possible via the sharing of blood-contaminated razors and toothbrushes.[12]

3.3.3. **Transfusion** of a unit of blood from an HIV-infected donor is associated with a virtually 100% risk for transmission of infection. Fortunately, measures are available that make the blood supply exceedingly safe. In the UK, screening of all donated blood for HIV antibodies commenced in 1985, and the risks have decreased even further since that time as more sensitive screening tests have become available. In addition, potential donors are excluded if they self-report on situations that place them at higher risk of HIV infection. Nevertheless, there remains a residual risk of transfusion-transmitted HIV infection because it is possible for an infected donation to escape detection. This can occur because of the time lag or "window period" that exists between the initial infection and the capacity to detect the virus by means of laboratory antibody tests. In the USA, the risk for HIV is now estimated to be one in 1 million units transfused.[13] In the UK, five incidents of transfusion associated transmission have occurred since 1985, involving three donors. However, in many developing countries, exclusion and screening procedures are less stringent and consequently the receipt of blood transfusions carries a higher level of risk.

3.3.4. **Blood products.** Over 1300 people, many of them suffering from haemophilia, have been diagnosed in the UK as having acquired HIV infection through blood product treatment. In some of these cases treatment was administered abroad. No cases of HIV transmission through blood products have arisen in the UK since viricidal heat treatment was introduced in 1985.

3.3.5. **Transmission from health care workers.** No case of HIV transmission from an infected health care worker to a patient has ever been recorded in the UK. There have only been two confirmed sources worldwide, one involving a dentist in the USA and the other an orthopaedic surgeon in France.[14]

3.3.6. **Occupational exposure.** The risk of transmission of HIV from infected patients to healthcare workers is greater than that from infected workers to patients. Up to June 1999, there were 102 cases worldwide of definite occupational transmission and a further 217 documented cases of infection that had possibly been acquired occupationally. Monitoring and surveillance systems are poorly developed in many countries with a high prevalence of HIV, and so the true worldwide incidence of occupationally acquired HIV infection is likely to be higher.[15] In the UK between 1984 and 2003, five cases of occupationally

acquired HIV infection were documented in healthcare workers. A further 14 healthcare workers with probable occupational acquisition of HIV have been diagnosed in the UK, all of whom had previously worked overseas in countries with high HIV prevalence.[4,16]

3.3.7. Exposures may be percutaneous (e.g. needlestick) or mucocutaneous (e.g. blood splash to the inside of the eyes, nose or mouth). The risk of acquiring HIV infection following occupational exposure is low. The average risk for HIV transmission after percutaneous exposure to HIV-infected blood is around 1 per 300 injuries. The average risk for a mucocutanous injury is less than 1 per 1000 injuries.[17] In contrast, the average risk of transmission of HBV following percutaneous exposure to an infected patient is 1 in 3, whilst that for HCV is 1 in 30.[18]

3.3.8. Prevention of avoidable exposure is of prime importance. The risk of occupational transmission for all bloodborne diseases including HIV can be reduced to a minimum by scrupulous adherence to universal precautions whereby all blood and tissues, as well as certain body fluids, are regarded as potentially infectious.[18] Many exposures result from a failure to adhere to recommended procedures, including the safe handling and disposal of sharps. Factors that are associated with an above average risk of occupational transmission include:

- greater depth of a percutaneous exposure
- presence of visible blood on the device producing the injury
- injury caused by instruments that had been placed in a source patient's vascular channels
- injury with hollow-bore (i.e. injection) needles. As yet, no cases of occupational transmission have been reported following injury with a solid surgical (e.g. suturing) needle

3.3.9. In addition to blood, several other types of body fluid, including amniotic fluid, cerebrospinal fluid, and breast milk are considered high risk for HIV transmission if significant occupational exposure occurs. Urine, vomit, saliva, and faeces are considered low-risk unless visibly blood stained. There is no risk of HIV transmission where **intact** skin is exposed to HIV-infected blood.[17]

3.4. **Mother-to-child transmission.** In the absence of treatment targeted to interrupt vertical transmission, approximately 20-30% of children born to HIV-infected women become infected. Three separate mechanisms are involved in mother-to-child transmission:

- **Transplacental transmission** to the foetus. Approximately 20% of HIV-infected infants acquire the infection in utero through this route. The clinical course of the condition tends to be aggressive and most of these infants progress to AIDS within the first 2 years of life
- **Perinatal infection** is the most common route, accounting for around 60-70% of infected infants. Transmission is thought to occur by exposure to the virus within maternal blood or by aspiration of infected maternal secretions. The estimated rate of progression to AIDS is 8% per year
- **Breastfeeding**, which exposes the infant to virus-laden breast milk, accounts overall for around 15% of HIV-infected infants. It is a particular problem in

developing regions, where the availability of infant formula as an alternative to breast-feeding is limited. The risk of HIV transmission increases with the duration of breastfeeding

- Mechanisms that increase the risk of mother-to-child transmission are incompletely understood and probably involve multiple factors. These are thought to include high maternal viral load, advanced maternal disease, maternal vitamin A deficiency, maternal co-infection with other sexually transmitted diseases, prolonged rupture of the membranes, maternal bleeding during pregnancy, prematurity, and infant genetic factors. Elective caesarian section reduces perinatal transmission[19]

3.5. Several popular myths have arisen regarding HIV transmission. The virus cannot maintain infectiousness outside its host and does **not** spread environmentally e.g. via air, water, insects, or contact with environmental surfaces. HIV is not transmitted through intact skin or by normal domestic contact e.g. holding hands, hugging, sharing bathrooms and toilets, and sharing crockery and kitchen utensils. There is no known risk of transmission from HIV-infected workers in food-service establishments. Similarly there is no evidence of transmission from a personal-service worker (e.g. hairdresser, barber, or massage therapist) to a client or vice versa, although routine precautions should be followed in dealing with instruments that may become contaminated with blood (e.g. razors). HIV concentration in saliva and tears is very low and contact with these body fluids has never been shown to result in HIV transmission. Closed-mouth or social kissing carries no risk of HIV transmission. The CDC has investigated just a single case of HIV infection that may be ascribed to open-mouth kissing, believed to be attributable to contact with blood rather than saliva. There have been very rare reports of HIV transmission through a human bite, on each occasion associated with severe trauma, extensive tissue damage and the presence of blood.[12]

3.6. **Viral factors**

3.6.1. The efficiency of HIV transmission for any form of exposure correlates to the viral load of the infected person. Viral load is highest in the first 1-3 months following infection, falling thereafter during the period of chronic HIV infection, only to rise again when the infected person progresses to advanced AIDS. Recently infected individuals who may be unaware of their infection and continue to practise high-risk behaviours are thus particularly liable to transmit the infection. In contrast, low or undetectable plasma viral loads reduce the risk, although transmission may still be possible.

3.6.2. When considering sexual transmission, it should be noted that viral loads in the genital tract normally correlate with plasma viral loads, although it is possible to have a detectable genital viral load with an undetectable plasma viral load.

3.6.3. Mutations in the viral genes of HIV carried by an infected individual may prevent transmission to an uninfected person.

3.7. **Resistance to HIV infection.** Some individuals appear to exhibit relative resistance to HIV infection despite multiple high-risk exposures. Natural resistance appears to be mediated by multiple mechanisms, both genetic and immunological. Thus both innate and acquired host factors have been identified that lower susceptibility to HIV infection or, once acquired, slow disease progression to AIDS.

3.7.1. **Innate host factors**[20]

- **Chemokine receptor mutations:** There is strong evidence for an association between chemokine receptor gene mutations and resistance to HIV transmission. Genetic polymorphisms or deletions within the CCR5 gene (notably CCR5Δ32 deletions) have been linked to resistance to HIV transmission, as have polymorphisms of the SDF-1 and CCR2 genes. However, the overall prevalence of these mutations appears to be low
- **Human leukocyte antigen (HLA) haplotypes:** Certain HLA haplotypes reduce susceptibility to a number of infectious agents, and there are indications of a possible protective effect against HIV infection. HLA-B27, which has a strong association with ankylosing spondylitis, is one of a number of haplotypes that may slow progression to AIDS.[21] The association with HLA haplotypes is less well established than that for chemokine receptor mutations
- Natural resistance to HIV may also be influenced by **autoantibodies and alloantibodies**, and by **enhanced production of chemokines** such as RANTES. These associations are also less well established

3.7.2. **Acquired host factors**

- $CD8^+$ T-cells with **cytotoxic T lymphocyte (CTL)** activity play a pivotal role in controlling viral infections. During the clinical course of HIV infection, the host's HIV-specific $CD8^+$ T-cell immune response is unable to control viral replication successfully. **Resistance to infection** has been linked to CTL activity against multiple HIV epitopes that are different to those epitopes that are recognised by subjects who have become infected.[22] On the other hand, **slow disease progression** has been linked to the maintenance of a strong HIV-specific CTL response[23]
- Protection against transmission may also be linked to **helper T-cell responses**, **HIV-specific antibodies**, and **soluble suppressive factors**. The evidence for these associations is weaker than that for CTL activity[20]

3.8. **Progression to AIDS.** Without treatment, it typically takes 7-11 years for HIV infection to progress to AIDS. Younger age at seroconversion has been linked to slower progression.[24] However there is substantial variability in the length of time to AIDS diagnosis and death. This variability appears to be determined multifactorially.

3.8.1. After the initial infection and peak viraemia, a steady-state level of plasma virus is established. Higher steady-state values generally reflect poorer immune control of viral replication, and predict a faster rate of $CD4^+$ T-cell depletion and disease progression to AIDS. People with a steady-state level of viral replication >35,000 copies/mL have a greater than 60% risk for the development of AIDS within 5 years of infection. This compares with an 8% risk of developing AIDS within the same time frame for people with steady-state viral loads of <5000 copies/mL.[1]

3.8.2. Slow progressors and long-term non-progressors have been recognised. Innate and acquired host factors as listed in section 3.7 have been implicated. Viral phenotype is another factor that contributes to the rate of disease progression,

with non-syncytium-inducing strains being associated with prolonged AIDS-free survival.[25]

3.8.3. Individuals who have HIV and HBV co-infection are at increased risk for liver-related mortality, especially in cases where the $CD4^+$ count is low.[26] Similarly, HIV co-infection increases HCV replication rate, and accelerates the course of hepatitis C towards cirrhosis and hepatocellular carcinoma, especially when immunodeficiency progresses. However, evidence to suggest that HCV may hasten HIV disease progression to AIDS has been conflicting. The most recent studies suggest that there are no major differences in HIV-related mortality between HCV-co-infected individuals and patients infected with HIV alone, especially if antiretroviral treatment is given.[7]

3.8.4. Some co-existing infections such as GB virus C (GBV-C), *Orientia tsutsugamushi* (scrub typhus agent), and human herpesvirus 6 (HHV-6) may exert a protective effect on HIV progression.[20] Conversely, in cases of herpes simplex virus (HSV) co-infection, there is evidence of an increased rate of HIV replication during episodes of HSV reactivation.[27]

3.9. **Mental health issues.** Despite conflicting findings in the literature and continuing debate in the scientific community, there is a growing body of opinion that would suggest that chronic depression and stressful events may adversely affect HIV disease progression.

3.9.1. **Depression.** It is estimated that approximately 60% of HIV-infected individuals will suffer from at least one depressive episode during the course of their illness.[28] Studies that have analysed the chronic effects of depression over periods of 5 years and longer have reported a relationship between depression and HIV disease progression. This finding raises the question as to whether depression increases the risk of disease progression or, alternatively, whether changes associated with the disease increase the risk of depression. Support for the former alternative is lent by a study which reported that depression develops more frequently in those individuals who have a past history of depressive episodes before HIV diagnosis.[29] It should be noted that a small proportion of individuals who take certain standard anti-retroviral drugs experience severe neuropsychiatric complications ranging from symptoms of anxiety or depression to manic depression.[28]

3.9.2. **Stress.** It is postulated that cell-mediated immunity is enhanced by acute stress but suppressed by chronic stress. Research published by the Coping in Illness and Health Project (CHIP) in 1997 marked the first occasion on which evidence from a *prospective* study had linked severe life event stress to HIV disease progression.[30] Since then, further reports from CHIP have been issued after 5.5, 7.5, and 9 years of data collection. In this research, the assessment of stress did not rely upon the subjects' perception. An objective approach was adopted whereby raters assessed the severity of stress, based on the degree of threat that most people would experience given particular set of circumstances. Discrete incidents (e.g. bereavement) and chronic stresses occurring over a 1-month period or more (e.g. financial difficulties) were considered. The study design aimed to exclude stresses that could be attributable to disease progression. The limitations of the CHIP study include the relatively small number of subjects

involved, drawn from a restricted population (men who have sex with men from a localised geographical area in the USA). The study found that the risk of progression to AIDS was approximately doubled for each severe stressful event or equivalent cumulative average stress. Examples of severe stressful events include death, life-threatening illness, or deteriorating health of a close family member or close friend, serious assault, rejection after disclosure of HIV-status, and break-up of a relationship with a long-term partner.[29, 31,32]

3.9.3. The CHIP research also linked HIV disease progression with decreased satisfaction with social support, higher anger scores, and passive coping strategies i.e. denial.[32] It may be the case that psychosocial factors exert most influence on disease progression in subgroups of vulnerable patients, such as the elderly, chronically depressed individuals, or those who consistently demonstrate poor coping strategies.[28]

3.9.4. A suggested mechanism is that depression and stress are associated with alterations in the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, and that these changes may affect immunological cells and processes, thus influencing HIV disease progression.

4. Prognosis

4.1. Prevention remains a mainstay of the response to the HIV epidemic. Widespread public health education campaigns about sexual and drug injecting practices have been mounted in the UK and elsewhere, largely aimed at people who are not HIV infected to help them to avoid infection. New strategies include an increased emphasis on communicating prevention messages to HIV-infected persons to encourage them to adopt and sustain behavioural changes that reduce risk-associated activities.[10]

4.2. An estimated 1 million people throughout the world are now using antiretroviral medications for HIV infection.[33] The best treatment for HIV infection is combination antiretroviral therapy that targets multiple steps in the viral life cycle. This approach to treatment is known as highly active antiretroviral therapy (HAART) and was first introduced in 1996. HAART has been shown to have a significant impact on delaying disease progression and preventing or reversing immune deficiency. As a result, death rates in Europe and North America have fallen 80% since the introduction of these drugs.[5]

4.2.1. The main goal of antiretroviral therapy is to suppress plasma viraemia as much as possible for as long as possible. Maximum virus suppression is achieved in approximately 50% of treated patients. However, despite its success in controlling viral replication, treatment with HAART cannot eliminate infection. Therefore, it should be assumed that all patients who are receiving therapy, even those with undetectable plasma HIV levels, can still transmit HIV.

4.2.2. HAART regimens typically consist of daily administration of a combination of at least three drugs, these being a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two or more nucleoside reverse transcriptase inhibitors (NRTIs). Drug-related toxicity can adversely affect adherence to antiretroviral treatment, and different drug combinations may have markedly different toxicity profiles.[34] The emergence of drug-resistant viral variants can occur. Other classes of antiretroviral drugs are available or undergoing development. For patients with HIV and HCV co-infection, HAART can be administered with HCV-specific therapy.[7]

4.2.3. The optimum time to commence HAART has yet to be established. It appears that patients who have the lowest $CD4^+$ cell counts when they begin HAART are at the highest risk of progression to AIDS or death and do not experience the same clinical benefit as do patients who begin therapy earlier.[35] Although there is a consensus that all patients with a $CD4^+$ T-cell count below 200 cells/mm^3 should receive antiretroviral therapy, the precise level above 200 cells/mm^3 at which it should be initiated remains the subject of considerable debate.

4.2.4. Although older patients (>50 years of age) respond to HAART, reconstitution of $CD4^+$ T-cells is slower than in younger patients, a factor that may explain their higher risk of clinical progression.[36]

4.2.5. The advent of HAART has impacted on the relationship between exposure category and progression. During the period 1999-2001, men infected through having sex with men had a lower risk of progression to AIDS than did injecting drug users, a reversal of the trend found before 1997. Although competing non-

HIV related mortality such as liver disease is likely to be partly responsible for the high number of deaths in injecting drug users, HIV-related causes are also thought likely to have contributed.[37]

4.2.6. The administration of antiretroviral drugs to mothers and infants has proved highly effective in preventing mother-to-child transmission, and may reduce the rate of perinatal infection by more than two-thirds. In 2003 in London, 5% of children exposed to vertical transmission became HIV infected, compared to 16% in 1998.[4] In developing countries with scarce resources, short-course treatment is used to interrupt vertical transmission, being administered to the mother in labour and to the infant at birth. Even so, lack of access to treatment contributes largely to the figure of around 630,000 infants who contract HIV from their mothers each year, mainly in sub-Saharan Africa.[3]

4.3. The key approach to **occupational exposure** to HIV is avoidance, with a focus on adherence to safer working practices. The Department of Health has published guidelines that contain recommendations on the circumstances in which **post-exposure prophylaxis (PEP)** with antiretroviral drugs should be prescribed. Advice on appropriate treatment regimens and follow-up arrangements is also given. The rationale for PEP relies on a limited window of opportunity following HIV exposure during which infection may be aborted by inhibiting viral replication. Triple therapy is currently recommended, whilst an earlier study demonstrated an 80% reduction in HIV transmission using zidovudine monotherapy, prescribed after percutaneous exposure to an infected source.[17] Although PEP has proved effective following occupational exposure, it does not always prevent HIV infection,[38] and in the UK, one case of occupationally acquired HIV infection has been documented despite the administration of PEP.[16]

4.4. Limited observational data only is available to suggest that prophylaxis is effective for non-occupational exposure. Physicians may be confronted with requests for post-exposure prophylaxis following sexual exposure (PEPSE) in various situations including rape, unprotected sexual intercourse, and condom breakage. The British Association of Sexual Health and HIV (BASHH) has recently published guidelines on the circumstances in which PEPSE may be recommended, accompanied by advice on appropriate treatment regimens.[9]

4.5. The health provisions available to people living with HIV and AIDS in developing countries compare most unfavourably with the services available to people in the developed world. The WHO is spearheading the "3 by 5" initiative which, by the end of 2005, aims to deliver antiretroviral treatment to three million people living with HIV/AIDS in low and middle income countries. This is just a step towards the eventual goal of providing universal access to HIV/AIDS prevention and treatment services to all who need them.[3]

4.6. Research into the development of vaccines against HIV is ongoing. The task has proved complicated for a variety of reasons, including the fact that each HIV subtype is epidemiologically and antigenically distinct. Nevertheless, several candidate vaccines have reached an advanced stage of clinical development. Ultimately, it may prove more feasible to adopt a vaccine approach directed towards the attenuation of disease rather than one that aims to prevent infection.[1]

5. Summary

5.1. HIV infection is responsible for a pandemic that is particularly intense in sub-Saharan Africa and parts of Asia. It remains a major health issue in the UK.

5.2. Infection with HIV leads to a progressive impairment of the host's immune response, with accompanying progression over a variable timeframe towards AIDS and death.

5.3. HIV is transmitted through sexual intercourse, exposure to contaminated blood or blood products, and from mother to child. The efficiency of transmission is affected by numerous behavioural, viral, and biological factors, including patterns of risk behaviour and host genetics.

5.4. Prevention is a key strategy in the fight against HIV and AIDS. Combination antiretroviral therapy known as HAART has been shown to have a significant impact on delaying disease progression and preventing or reversing immune deficiency.

6. Related synopses

Hepatitis and Liver Injury

Appendix A – AIDS indicator conditions

Indicator conditions for adolescents and adults as specified in the CDC's 1993 AIDS Surveillance Case Definition are as follows:[39]

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, oesophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex; chronic ulcer(s) (>1 month duration); or bronchitis, pneumonitis, or oesophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, any site (pulmonary or extrapulmonary)
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis carinii* pneumonia (PCP)
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicaemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome of HIV infection

7. Glossary

ankylosing spondylitis	An inflammatory disease of the spine that causes the vertebrae to form a solid inflexible column.
chemokine	A type of cytokine (protein produced by a cell to control reactions between other cells) that specifically alters the behaviour of white blood cells.
encephalopathy	A degenerative condition affecting the brain.
epitope	The part of the antigenic molecule to which a T-cell receptor will bind.
haplotype	A set of closely linked genetic markers present on one chromosome that tend to be inherited together.
hypothalamic-pituitary-adrenal axis	A major part of the neuroendocrine system that controls reactions to stress. It involves the interactions of the hypothalamus, the pituitary gland and the adrenal glands.
Kaposi's sarcoma	A malignant skin tumour seen most commonly in patients who suffer from AIDS. Tumours may also occur within the intestines and lungs.
lymphadenopathy	Swelling of the lymph nodes.
mucocutaneous	Pertaining to the skin and mucous membranes, i.e. inner lining of body cavities/passages that communicate with the exterior e.g. mouth, vagina, and urethra.
percutaneous	Penetrating through the skin.
perinatal	Pertaining to the period shortly before and after birth.
phenotype	What an organism looks like as a consequence of the interaction between its genetic constitution and the environment.
polymorphism	The presence of several distinct forms of a gene or phenotypic trait within a population with frequencies greater than 1%.
prophylaxis	Preventative treatment.
seroconversion	The appearance of antibodies (in this case to HIV) after an earlier negative test.
splenomegaly	Enlargement of the spleen.
sympathetic nervous system	Division of the autonomic nervous system that promotes "flight or fight" response; i.e. raises rate of heart and breathing, dilates pupils, etc.

syncytium	A mass of cytoplasm (cell contents) containing several nuclei and enclosed in a membrane but with no internal cell boundaries.
viraemia	The existence of viruses or viral particles in the bloodstream.

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