Natural history of HIV and AIDS

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Abstract

Medical knowledge of HIV is rapidly evolving, leading to increased understanding of the disease, its immunology and clinical manifestations. Antiretroviral therapy (ART) has provided a means of controlling but not curing the disease, and patients now live longer, healthier lives with the disease. However, new challenges are emerging, including those of treating a population ageing on ART and continuing to prevent viral transmission. Worldwide, strategies including universal testing and the roll-out of ART have reduced transmission, and the number of new diagnoses is falling. In the UK, however, approximately 1 in 4 individuals with HIV are unaware of their diagnosis, and nearly half present with a CD4 count <350 cells/microlitre. It remains essential that all healthcare providers are alert to at the risk of HIV, and those who display the signs of early infection, to ensure these patients are tested and treatment is put in place before the development of HIV-related infections, cancers and complications.

Keywords Antiretroviral therapy; CD4; HIV-1; HIV-2; MRCP; seroconversion

Key points

- Globally, the number of new cases of HIV is falling
- The greatest burden of disease is in Africa
- Early diagnosis and treatment gives people living with HIV a near-normal life expectancy

Introduction

Human immunodeficiency virus (HIV) is a lentivirus, part of the family *Retroviridae*, transmissible through blood and other body fluids. Continuous high-level HIV replication in the human body leads to both virus- and immune-mediated destruction of the key immune effector cell, the CD4 lymphocyte. Over time, the decline in CD4 lymphocytes leads to opportunistic infection, which defines the acquired immune deficiency syndrome (AIDS).

AIDS was first recognized in 1981, and HIV was identified as its cause in 1983. The oldest proven HIV infection was found in plasma collected from an adult man in Kinshasa, Democratic Republic of Congo in 1959. Subsequent molecular sequencing has indicated that the HIV epidemic probably originated in central Africa in the early 20th century, when there were multiple cross-species transmission events of a similar lentivirus from primates to humans, most likely through hunting practices.

Early treatments for HIV were limited and most patients died. However, over three decades of study have provided a wealth of information about the natural history of HIV, allowing the development of effective antiretroviral therapy (ART). ART has radically improved the prognosis for patients living with HIV, meaning a normal or near-normal life expectancy, particularly when the diagnosis is made before HIV-related complications occur.

HIV-1 and HIV-2

Two HIV subtypes are recognized: HIV-1, whose primate reservoir is chimpanzees, and HIV-2, originating from sooty mangabey monkeys. HIV-1 is found worldwide and if untreated almost always progresses to AIDS. HIV-1 can be divided genetically into groups M, N, O and P. Group M is responsible for the global pandemic and is further divided into subtypes or clades. Each subtype is associated with a particular geographical area: for example, subtype B dominates in the Americas, Australia and western Europe, while subtype C — responsible for nearly 50% of all HIV infections — predominates in southern Africa and India.

HIV-2 causes a similar illness to HIV-1 but is less aggressive and its distribution is restricted mainly to Western Africa. Patients have lower viral loads, slower CD4 decline and lower rates of vertical transmission, and only 20–30% develop AIDS. From a treatment perspective, HIV-2 is inherently resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Epidemiology

It is estimated that, in 2016, there were 36.7 million people living with HIV worldwide, of whom 53% were in eastern and southern Africa. Around 19.5 million people with HIV had access to ART, an increase from 7.7 million in 2010. The number of people newly infected with HIV worldwide is falling. In 2016, there were 1.8 million new infections, representing an estimated decline of 11% since 2010. As might be expected with fewer new infections and increasing access to ART, AIDS-related deaths are also reducing. One million people died from AIDS-related illnesses in 2016, compared with a peak of 1.9 million in 2005, overall a 48% reduction in 11 years.[1]

However, this declining trend is not consistent worldwide. For example, while the eastern and southern Africa region had a 29% decline in new HIV infections between 2010 and 2016, in the same period Latin America showed no change in rates of new infection, while eastern Europe and central Asia experienced a 60% rise.[1]

In the UK, there was an 18% decrease in people newly diagnosed with HIV between 2015 and 2016. The decline was most significant among men who have sex with men (MSM). This

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change can be accounted for by large increases in HIV testing, repeat testing of higher risk men and increased uptake of ART among patients known to have HIV. The recent internet availability of pre-exposure prophylaxis is also contributing to this decline. Among men and women who were probably infected through heterosexual contact, there has been a 52% decline in diagnoses between 2007 and 2016; however, this is largely to the result of changes in migration patterns, as the largest proportion of heterosexual diagnoses were previously among African-born men and women. The number of diagnoses made at a late stage, when CD4 count is <350 cells/microlitre, remains high, especially among heterosexuals: 60% of heterosexual men and 47% of heterosexual women were diagnosed at a late stage in 2016, compared with 32% of MSM. Late diagnosis is associated with a higher risk of short-term mortality and increased risk of onward transmission.[2]

Worldwide, the major route of HIV transmission remains heterosexual contact. MSM account for 12% of new infections worldwide, and 22% outside sub-Saharan Africa. About 9% of new HIV infections annually are in children, the vast majority of whom are infected in utero, at birth or through breastfeeding.[1] The prevalence of HIV among injecting drug users varies widely between countries. In the UK, approximately 1% of people who inject drugs have HIV; in other areas of the world, including Romania, Estonia and the Philippines, >40% of people who inject drugs have HIV.

Natural history of HIV-1

HIV is present in the blood and bodily fluids of an infected individual, so can be transmitted through sexual contact, parenterally, perinatally or through breastfeeding. Shortly after infection, individuals become viraemic, and at this stage HIV is detectable in the plasma by nucleic acid amplification of viral RNA or detection of the viral core protein p24. About 4–6 weeks after infection, antibodies to HIV become detectable. Most infected individuals seroconvert by 3 months and become HIV antibody-positive; rarely, this takes up to 6 months.

Initially, there are high levels of circulating HIV virus, the result of rapid replication in infected cells. During this period, patients can be symptomatic with features of primary HIV infection. After specific antibody has developed, viral levels decline to reach a steady state, and patients generally remain asymptomatic for several years. Over time, CD4 lymphocyte numbers gradually decline because of viral killing, apoptosis and activation of CD8 lymphocytes. CD4 cell levels eventually decline to a point where cell-mediated immunity is affected, and the individual becomes susceptible to opportunistic infections, HIV-associated nephropathy, dementia and cancers.[3]

Clinical manifestations

Primary HIV infection/seroconversion illness

Symptomatic primary HIV or seroconversion illness occurs in approximately half of infected individuals because of high levels of circulating HIV-1 and the acute immune response (Figure 1). Evidence suggests that seroconversion illness is more likely to occur with higher viral loads, and individuals with more severe symptoms are more likely to undergo rapid disease progression.

Seroconversion illness typically begins 2–4 weeks after exposure and can resemble influenza, infectious mononucleosis or aseptic meningitis. The most commonly reported symptoms at seroconversion include fever, malaise, myalgia and arthralgia, lymphadenopathy, rash, pharyngitis and diarrhoea. Rarely, the illness is more severe and can be associated with an opportunistic infection, most commonly oesophageal candidiasis, as the CD4 count transiently declines to <200 cells/microlitre.

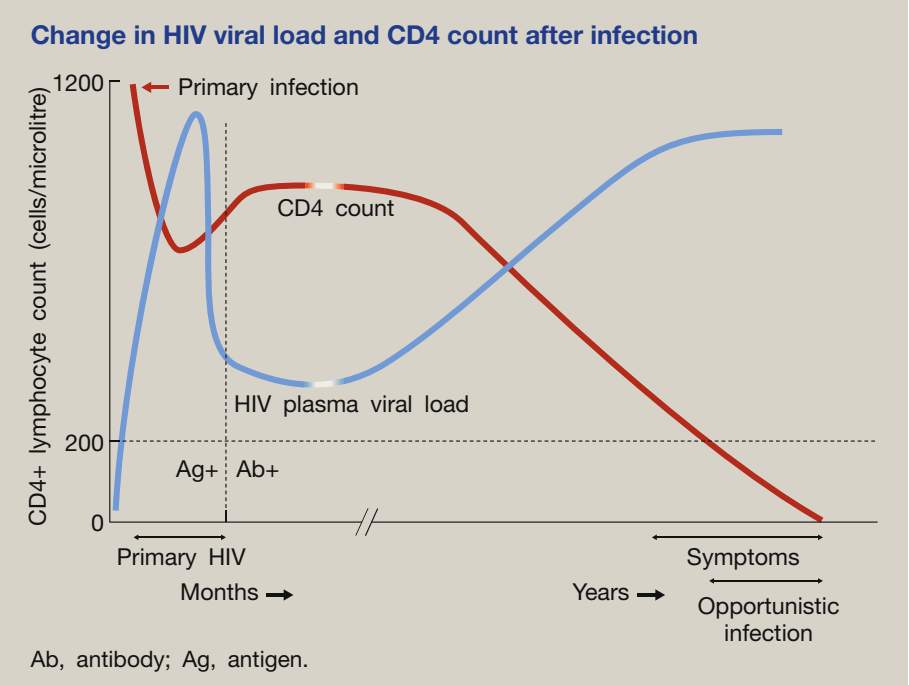

Figure 1