CHAPTER 6

NATURAL HISTORY OF HIV INFECTION

Abstract

In the first stage of infection, individuals are highly infectious. Antibodies are not detectable by serological tests during the "window period". The infection is clinically silent for 10 years or more. In about 70 per cent of cases, seroconversion illness is seen. The second stage lasts 3–5 years or longer. Antibodies are detectable by serological tests. The patient is less infective to others, as compared to stage 1, and is prone to small range of clinical problems and diseases. In stage 3, which lasts about 3–5 years, the patient becomes vulnerable to a select group of common infections as a result of immune suppression. The CD4 count is 200–500 cells per μL. There may be common symptoms like chronic diarrhoea, loss of body weight, pyrexia of unknown origin, and manifestations of AIDS-related complex (ARC). The fourth or terminal stage is characterised by signs and symptoms of AIDS, including opportunistic infections; the CD4 count falls below 200 cells per μL; and the patients are highly infectious. Wasting (or "slim disease") and tuberculosis are mainly seen in this stage in developing countries.

Key Words

Long-term non-progressors, Opportunistic infections, Oral hairy leukoplakia, Persistent generalised lymphadenopathy, Rapid progressors, Slim disease, Typical progressors, Window period.

6.1 – PROGRESSION OF HIV INFECTION

The range of incubation period is 1–14 years, with an average of 6 years. There are three patterns in the progression of HIV infection. *Typical progressors* comprise about 50–70 per cent of the HIV positive persons. The disease may progress over 8–10 years. *Rapid progressors* constitute about 5–10 per cent and may develop AIDS in 2–3 years. A small number of persons first infected with HIV 10 or more years ago have not developed symptoms of AIDS (NIAID, 2005). Such persons (called "long-term non-progressors") have stable CD4 counts for long periods and comprise about 5 per cent of the HIV positive persons. In *typical progressors*, there are four stages in progression of the disease.

6.2 – WHO CLINICAL STAGING CLASSIFICATION

Stage 1: Only a small number of infected persons have a clinically apparent illness. The symptoms of seroconversion illness are often mistaken for those of other viral infections. Most of the infected individuals are *highly infectious* to others in this stage and may not be aware that they have become infected. HIV is present in large quantities in their blood and genital secretions (NIAID, 2005). Antibodies are not detectable in the *window period*. The infection is clinically silent for 10 years or more. Though the CD4 count may be near normal (the normal CD4 cell count is 950–1700 cells per μL) and the infection may be clinically silent or asymptomatic, and the HIV replication and CD4 cell reversal goes on. There is a selective damage to the immune system and the patient gets progressively immunocompromised (Panteleo *et al*., 1993).

Stage 2: This stage lasts 3–5 years or longer. The antibodies are detectable by serological tests. The CD4 cell count falls (but is more than 500 cells per μL) and the viral load increases with simultaneous development of immune suppression. Usually, there are no symptoms, but persistent generalised lymphadenopathy (PGL) may be present (NACO, Training Manual for Doctors).

The patient is less infective to others, as compared to stage 1, and is prone to small range of clinical problems and diseases, that include weight loss, minor skin and oral problems, recurrent sinusitis, and herpes zoster (or "shingles"). These clinical manifestations do not affect the normal activities of an individual and require minimal clinical intervention (NACO, Training Manual for Doctors; Panteleo *et al*., 1993; WHO, 1990).

Stage 3: With further immune suppression, the patient becomes vulnerable to a select group of common and more virulent infections like bacterial pneumonia. These pathogens also cause diseases in individuals with normal and intact immune systems. But in case of HIV positive persons, they occur at much higher rates and with higher mortality. This stage lasts about 3–5 years. The CD4 count is 200–500 cells per μL. This stage is characterised by common symptoms such as chronic diarrhoea, loss of body weight, and pyrexia of unknown origin. Patients may need hospitalisation, specific treatment, and extra follow-up visits to the health centre (NACO, Training Manual for Doctors; Panteleo *et al*., 1993; WHO, 1990). The signs and symptoms of immune deficiency, seen in ARC include opportunistic infections such as oral thrush, PGL, enlarged spleen, fatigue, acute weight loss (more than 10 per cent of body weight lost in one month), fever, night sweats, and malaise. Oral hairy leukoplakia seems to be unique to HIV-infected individuals. The margins of the tongue show white ridges of fronds on the epithelium. An association with EBV and papilloma viruses has been proposed (Simmonds & Peutherer, 2006).

Stage 4: With more profound immune suppression, the CD4 cell count falls below 200 cells per μL and the individual becomes an easy victim for various opportunistic infections. The individual is considered to have advanced

disease – AIDS. Patients are *highly infectious* in this stage. In the absence of specific therapy, AIDS patients present with multiple clinical problems and death may occur. This is the terminal stage, characterised by signs and symptoms of AIDS. In the developing countries, wasting due to HIV infection (also called "slim disease"), and tuberculosis are the most important health problems at the fourth stage of the disease. As a result of human exposure to environmental pathogens, the clinical spectrum of the disease that is seen in poor countries is different and diseases like tuberculosis, pneumonia, and salmonellosis are significantly more common as compared to other opportunistic infections seen in the developed world (Morgan *et al*., 1998).

The opportunistic infections in this stage are tuberculosis, herpes zoster, fungal, and parasitic infections. Kaposi's sarcoma, non-Hodgkin's lymphoma, and carcinoma of cervix are considered "AIDS-defining malignancies". These diseases are disseminated throughout the body. AIDS encephalopathy and AIDS dementia are rare. AIDS dementia is probably due to direct action of HIV on the central nervous system, since HIV can cross the blood-brain barrier (NACO, Training Manual for Doctors; Panteleo *et al*., 1993; WHO, 1990).

6.3 – CDC CLASSIFICATION

6.3.1 – Group I: Acute HIV Infection

Seroconversion illness resembles glandular fever with lymphadenopathy and symptoms such as acute onset of fever, malaise, sore throat, myalgia, arthralgia, and skin rash. Only 5–10 per cent of individuals may experience this stage in its entirety though few individuals may experience few symptoms. Encephalitic presentations are rare (Simmonds & Peutherer, 2006). Peripheral blood shows lymphocytosis. Serological test for antibodies are usually negative at the onset of acute stage, but may become positive during its course. The virus itself, viral nucleic acid, or viral p24 antigen may be detected.

6.3.2 – Group II: Asymptomatic Infection

HIV-infected persons are symptomatic but test positive for HIV antibody tests and are *infectious* to others.

6.3.3 – Group III: Persistent Generalised Lymphadenopathy (PGL)

The lymph nodes are symmetrical, painless, and enlarged (Simmonds & Peutherer, 2006). They are more than 1 cm in size and present at *two or more extra-genital sites* for at least 3 months. Other causes of lymph node enlargement such as lymphomas need to be ruled out. PGL is present in 25–30 per cent of HIV-infected individuals, who may be otherwise asymptomatic (Simmonds & Peutherer, 2006).

6.3.4 – Group IV: Symptomatic HIV Infection

SUB-GROUP A = Constitutional disease (ARC)
SUB-GROUP B = Neurological disease
SUB-GROUPS C_1 & C_2 = Secondary infectious diseases
SUB-GROUP D = Secondary cancers
SUB-GROUP E = Other conditions
The infections are based on CD4 counts. When the CD4 count is *less than* 400 cells per mm^3, signs and symptoms of immune deficiency are manifested. When the CD4 count drops below 200 cells per mm^3, titre of virus increases markedly with an irreversible breakdown of immune mechanism. Most patients die of opportunistic infections and malignancies. AIDS is the terminal stage of HIV infection.

6.4 – DISEASE PROGRESSION

At the individual level, the progression of the disease and survival are both variable. Either the disease rapidly progresses over about 2 years or hardly progresses at all, for a longer period of 10 or 15 years (Morgan *et al*., 1997). Once the life-threatening severe diseases of clinical AIDS have developed, the life span of the patients is reduced due to scarcity of resources in the developing countries. The *mean survival* may be in the range of 6–7 years especially among patients belonging to the poorer communities (Morgan *et al*., 1998). The available data suggest that the progression of the disease is independent of race, ethnicity, or gender. Old age and low socio-economic status adversely affect the survival (Chaisson *et al*., 1995). Very few natural history studies have been conducted in developing countries. Individuals progress through various stages of HIV infection at a variable rate. In rich communities, deaths usually occur after clinical AIDS has developed. But, in poorer communities, HIV positive persons may die in early stages of the natural history of the disease due to higher exposure to virulent and opportunistic infections, and inadequate resources for clinical care at stages 1 and 2 (Morgan *et al*., 1997; Morgan *et al*., 1998; Chaisson *et al*., 1995; Gilks *et al*., 1996).

6.5 – LONG-TERM NON-PROGRESSORS

Since the onset of the HIV/AIDS epidemic, it has been observed that some HIV-infected individuals (called *long-term non-progressors*) took a long time to progress to AIDS, while some individuals did not get infected at all, in spite of repeated exposures to HIV. These individuals have very low levels of detectable virus in their blood or in the peripheral blood mononuclear cells. On the other hand, they have high levels of active HIV-specific cytotoxic T-cells and CAF, the antiviral factor produced by CD8 T-cells (Barker *et al*., 1995). It is not known how some HIV-affected individuals have remained asymptomatic for long periods of time. Factors responsible for their non-progression to AIDS could include

particular features of their immune system or possible past infection with a less virulent strain of the virus. It is possible that these individuals have received a low dose of infection (equivalent to low-dose vaccination) leading to protective immunity. This has been seen in primates infected with SIV. National Institute for Allergy and Infectious Diseases (NIAID) supported researchers continue to trace how the disease progresses in different people (NIAID, 2005). Genetic factors may have a role since the presence of human leukocyte antigen (HLA) types B-8 and DR-3 are associated with faster progression of HIV infection. If a blood donor has slowly progressing HIV infection, then the recipient also gets the same type of infection (Learmont *et al*., 1992; Ashton *et al*., 1994).

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