INVITED ARTICLE

UNDERSTANDING HIV DISEASE

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ABSTRACT

The world is now facing the second decade of global epidemic of HIV infection. Most of the Asian countries including Singapore are seeing a trend of rapid increase of HIV infected cases each year. It is now known that the HIV disease has a prolonged asymptomatic period of several years before the onset of AIDS defining illness. A HIV-infected person may present to a physician at any point of the entire course of HIV infection. Hence, this article aims to give an overview of HIV disease and to provide information for doctors today to equip themselves with adequate knowledge to deal with this deadly infection.

Keywords: *HIV, AIDS, epidemiology, clinical features, treatment*

SINGAPORE MED J 1995; Vol 36: 545-548

INTRODUCTION

Human immunodeficiency virus type 1 (HIV-1) has been clearly identified as the primary agent for the Acquired Immunodeficiency Syndrome (AIDS). The understanding of the clinical manifestation of HIV disease has broaden significantly since the first description of AIDS in 1981. It is known that this viral disease is a long-term condition with a prolonged asymptomatic clinical state before the onset of AIDS defining illnesses. The diagnosis of HIV infection can be made at any point of its course after the silent window period. But to be able to detect the infection early when the patients are relatively asymptomatic presents a great challenge to the physicians. As the number of HIV infected patients continue to rise each year, it is not surprising that most of the practising physicians today will in his or her life time encounter at least one HIV patient. Therefore it is important to have an adequate knowledge of this viral disease to facilitate early diagnosis. The advantages of early diagnosis are many, these include initiation of antiviral treatment and prophylaxis for certain opportunistic infections. In addition, a more personal counselling and education may help to reduce the rate of viral transmission.

EPIDEMIOLOGY

The HIV infection is now in its second decade of global epidemic. The number of HIV infected cases continue to rise each year. The WHO estimated that by now there are approximately 17 million HIV infected cases. The majority of the symptomatic cases are from Sub-Saharan Africa. By year 2000, there will be at least 30 million HIV infected cases and at least 40% of these cases will be from Asia. Recently, Thailand has documented the spread of this virus in the general population. In Chiang Mai, the antenatal clinic detected 8% HIV sero-prevalence rate among asymptomatic pregnant women and hence a foreseeable number of paediatric HIV cases[1].

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In Singapore, although the number of reported HIV sero-positive cases remained relatively small, a definite increase in number each year is noted. By end of October 1994 there were a total of 278 HIV sero-positive cases reported in Singapore. The majority of these cases were detected late with AIDS defining illnesses indicating a severely depressed immunity. The number of female HIV sero-positive cases has risen sharply in recent years. A total of 26 cases of female HIV sero-positive cases was reported by end of October 1994. Of these, 9 cases were detected in the first 10 months of 1994.

MODE OF TRANSMISSION

The HIV infection is transmitted via sexual intercourse, intravenous drug use, transfusion of contaminated blood or blood products, transplantation of contaminated organs, perinatal transmission and breast feeding. The rate of viral transmission is facilitated by compromise of the integrity of mucosal surfaces and the presence of other sexually transmitted disease such as syphilis, chancroid etc[2]. In the local setting, the majority of the patients acquired the virus via unprotected sexual activities. There is a clear switch from predominantly homosexual transmission to heterosexual transmission in the past few years. There is one confirmed case of perinatal transmission.

The perinatal transmission rate is about 25% and a variety of factors may influence the rate of transmission. An increased rate of perinatal transmission is noted in those pregnant women with a more advance disease as evidenced by a high maternal p24 antigen level, a low CD4 counts. Other factors affecting rate of transmission include placenta membrane inflammation, maternal fever, etc[2]. To date, there is no conclusive evidence to suggest that Caesarean section may reducc the rate of perinatal transmission.

NATURAL COURSE OF HIV DISEASE

The clinical events secondary to HIV infection tend to follow a fairly predictable chronological order starting from the time of exposure to the virus to the occurrence of AIDS defining illnesses and eventual death. An acute clinical illness usually become apparent 3-6 weeks after the acquisition of the virus. After that patients recover concurrently with the appearance of HIV antibodies[3]. The majority of the patients then remained asymptomatic for years before the onset of AIDS defining illnesses. The average survival from the onset of

first AIDS illness to death is approximately 2 years.

a) Primary HIV infection

After exposure to the virus, there is typically a 3 to 6-week period of intensive virus replication before the onset of an acute clinical illness. The incidence of this acute illness was noted to be around 53-93% in some study, although the range and severity of the illness vary considerably[3]. The common clinical features of symptomatic primary HIV infection include general ill health, a mononucleosis-like syndrome and other multisystemic involvement. (Table I) The illness can be associated with an appreciable degree of morbidity and patients may require hospitalisation. Most of the clinical manifestations of primary HIV infection are self-limited, lasting about 1 to 2 weeks. After that the majority of the patients remained asymptomatic for years in the clinically latent phase. (Fig 1)

Table I - Clinical Features of Primary HIV infection

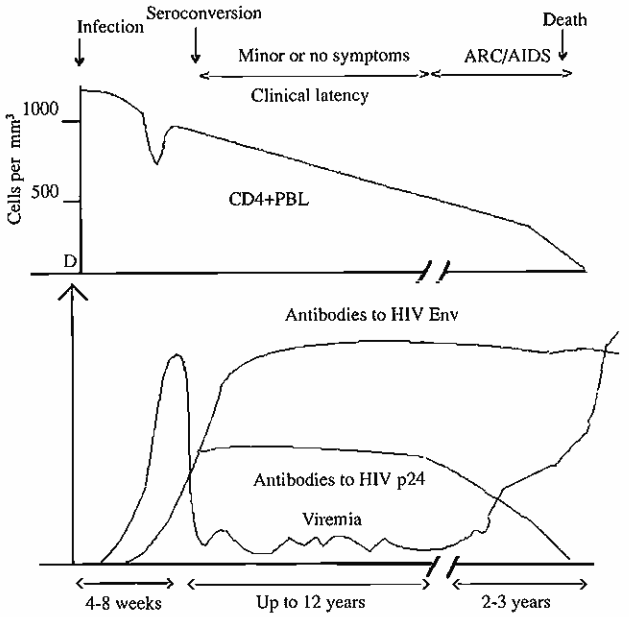
General
Fever
Pharyngitis
Lymphadenopathy
Arthralgia / myalgia
Lethargy / malaise
Anorexia / weight loss
Neuropathic
Headache, retro-orbital pain
Meningoencephalitis
Radiculopathy, peripheral neuropathy
Brachial neuritis
Guillain-Barré syndrome
Cognitive / affective impairment
Dermatopathic
Erythematous maculo-papular rash
Diffuse urticaria
Roseola-like rash
Desquamation
Gastrointestinal
Mucocutaneous ulceration
Oropharyngeal candidiasis
Nausea, vomiting, diarrhoea

b) Clinical latency phase

Once the symptoms of primary infection subside and an antiviral immune response appears, the patient becomes seroconverted with a detectable serum anti-HIV antibodies. After that most patients became asymptomatic or mildly affected in the clinical latency phase. The duration of the asymptomatic period varies, some patients progress rapidly to AIDS in 1-2 years after exposure to HIV. But for the majority of the patients it typically lasts for 7-10 years. Although patients remain clinically asymptomatic, there are clear evidence to show that the virus continue to replicate and progressively destroy the host immune system[4]. During this period, only a small fraction of infected CD4 T cells are circulating in the peripheral blood and a low level of plasma viraemia. But many patients do have a significant amount of viral RNA detectable in the plasma. Quantitative PCR for HIV RNA may be a better marker for monitoring disease progression during this asymptomatic phase.

The average time from primary HIV infection to death is about 10 years. However, it is estimated that about 5% of HIV infected individual may experience a prolonged symptom-free period. The studies of this so-called long-term non-progressers (LTNP) showed that the majority of them had evidence of HIV infection more than 10 years ago. They are able to maintain a normal and a stable CD4 cell count without antiviral treatment. Their lymph node retained an architecture indicative of healthy response to infection in contrast to those with progressive disease who have eroded lymph node and a poor immune response. A lower level of plasma viraemia is also noted in the non-progressers. The ultimate fate of this group of LTNP is still uncertain. Some of them may finally develop symptoms after a much prolonged asymptomatic period and it is also possible that some may remain asymptomatic for life. Studies are underway to identify possible factors responsible for the delay of the disease progression. The role of CD8 seems to be an important link in this aspect. Nonetheless, much more need to be learned from these patients and hopefully such knowledge can be applied to improve treatment in the future[5].

Fig 1 - Schematic course of HIV disease (modified from Silvijia et al[2])



c) Conditions associated with early or intermediate HIV infection

There are a few clinical conditions that are recognised to be highly associated with early HIV infection. These may serve as indicators for the initiation of HIV serology testing. Conditions thought to be immune-mediated include Guillain-Barré syndrome, chronic demyelinating neuropathy, idiopathic thrombocytopenia, Reiter's syndrome, polymyositis, Bell's palsy and Sjögren syndrome. Certain infections may appear with minimal immunosuppression, eg aggressive warts, molluscum contagiosum, tinea, herpes zoster (particularly recurrent or multi-dermatome involvement), sinusitis, mucocutaneous candidiasis, hairy leucoplakia, etc. Finally, skin manifestations such as seborrhoeic dermatitis, non specific papular dermatosis or Kaposi's sarcoma are also highly associated with HIV disease.

d) Acquired Immunodeficiency Syndrome (AIDS)

AIDS is an arbitrary classification for case surveillance purposes. It denotes an advance stage of HIV disease when

host immunity is severely depressed. Conditions defining AIDS may be infective, neoplastic in nature or illnesses secondary to HIV itself such as HIV encephalopathy. In Singapore, we adopt the AIDS surveillance definition (Table II) from the Centres for Disease Control and Prevention except the CD4 counts below 200 cells/μl. There were 112 AIDS cases notified in Singapore by the end of October 1994 (out of 278 sero-positive cases). The common AIDS defining opportunistic infections seen locally include *Pneumocystis carinii pneumonia, Mycobacterium tuberculosis,* cerebral toxoplasmosis, cryptococcal meningitis, CMV retinitis and diarrhoeal disease secondary to *Cryptosporidia, Isosporia,* etc. Malignancies like Kaposi's sarcoma and lymphoma are occasionally seen in local HIV sero-positive population. AIDS defining conditions and its management will be further discussed in a future article.

Table II - CDC AIDS Surveillance Case Definitions

Oesophageal, tracheal or bronchial candidiasis
Extrapulmonary coccidioidomycosis
Extrapulmonary cryptococcosis
Chronic intestinal (>1 month) cryptosporidiosis
Chronic isosporiasis (>1 month)
CMV retinitis, or CMV in other than liver, spleen, nodes
Herpes simplex bronchitis/ pneumonia or mucocutaneous ulcer > 1 month,
Disseminated / extrapulmonary histoplasmosis
Extrapulmonary *M. avium* or *M. kansasii*
Pulmonary or extrapulmonary *M. tuberculosis*
Recurrent pneumonia (≥2 episodes in 1 year)
Recurrent *Salmonella* bacteraemia
Cerebral toxoplasmosis
HIV encephalopathy
Invasive cervical cancer
Kaposi's sarcoma
Burkitt's lymphoma, immunoblastic lymphoma or primary lymphoma of the brain
Wasting syndrome due to HIV

HIV TESTS INTERPRETATION

In order to interpret HIV testing appropriately, the natural history of HIV infection and host immune response must be understood. The anti-HIV antibodies became detectable in the serum generally within 14 to 21 days after the onset of symptoms secondary to primary HIV infection. The median time of the silent window period after acquisition of HIV is around 2 months. Most individuals should have detectable antibodies by 6 months after HIV exposure[3]. High level of plasma viraemia and P24 antigen are well documented during primary HIV infection. As the immunity gather pace, the level of plasma viraemia and P24 antigen drop to undetectable level in the serum during the asymptomatic phase. However, PCR of viral RNA and DNA will remain positive. The CD4 counts drop sharply during the seroconversion period but usually bound back to normal level. Thereafter, the CD4 counts decline gradually which allow its use as a surrogate marker for disease progression. (Fig 1)

Once a patient develops a mature antibody response to HIV infection, it usually will remain detectable for life. As the patient approaches advance phase of disease, the plasma viraemia and P24 antigens return to detectable level again.

The current tests available locally for the detection of HIV infection include enzyme immunoassay (EIA), particle agglutination and the Western Blot for confirmation. A false positive EIA may be seen as a result of crossreacting antibodies such as a HLA class II antigens or the presence of other autoantibodies[6]. In general, the positive predictive value of a positive HIV test is dependent on the prevalence of HIV infection in the population tested.

MANAGEMENT OF HIV DISEASE

HIV disease is a continuum of clinical events and an early detection provides multiple advantages to the patients as well as the community. An early detection of the disease provides ample time for the physicians to monitor patients' progression and to start appropriate treatment and prophylaxis when indicated. Such measures are useful for prolonging the asymptomatic period, delay disease progression and also prevention of opportunistic infections. For the community, a more personal counselling and education may help reduce the rate of viral transmission.

a) Anti-retroviral therapy

The development of drugs for anti-HIV therapies is based on the knowledge of the replication cycle of the HIV. A number of compounds that are under evaluation or available interfere with HIV replication at different stages. The most promising class of agents include the nucleoside analog and the protease inhibitor. Zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC) are the currently available nucleoside analogs which inhibit the reverse transcriptase. Newer nucleoside analogs which are not yet available for clinical use include stavudine (D4T) and 3TC[7].

Zidovudine is beneficial in the treatment of patients with advanced HIV disease and is the initial drug of choice for the treatment of patients who have not received any prior anti-HIV therapy. AZT monotherapy has proven useful in prolonging survival among patients with symptomatic HIV disease, delaying the onset of AIDS defining illness, improving cognitive function in patients with AIDS related dementia, improving idiopathic thrombocytopenic purpura, etc[7]. The most recent discovery is its capability to reduce perinatal transmission from 25% to 8.3%[8]. The dose of AZT used locally is 400mg per day in 4 divided doses. Its main toxicity is marrow suppression leading to anaemia, neutropenia and less commonly thrombocytopenia.

The ddI and ddC are the other two nucleoside analogs available here. Their clinical efficacy as a monotherapy lacks behind AZT in patients who had no prior exposure to AZT. Either ddI or ddC can be used in patients who are intolerant or had prolonged exposure to AZT. The major side effects encountered are peripheral neuropathy, pancreatitis, gastro-intestinal intolerance, etc.

Other newer agents showing favourable results include 3TC, protease inhibitors, interleukin 2, etc[9]. The majority of these agents are now being studied as part of a combination drug regimens. The possible advantages of combination therapy are many; these include enhanced HIV suppression, improved CD4 cell count responses, improved clinical benefit, prolongation of the duration of treatment effect, delayed emergence of resistance and the potential to reduce toxicity through reduced drug doses[10]. There is as yet no universal consensus on the best time to start treatment and the drug/s to start with. But from the data available and the understanding of the disease thus far, it seems more rational to start treatment early using multiple drugs in combination when the viral load is low.

b) Prophylaxis of opportunistic infections (OI)

Opportunistic infections occur as the HIV disease progresses, resulting in a severely impaired immunity. *Pneumocystis cariini* pneumonia and cerebral toxoplasmosis are the two major life threatening OIs commonly occurring when CD4 count falls below 200 cell/μl. Several prophylactic regimens which had proven effective in the primary prevention of these infections will be discussed further in a future article.

c) Vaccines

The principal aims of the development of a HIV vaccine are firstly, to prevent infection in people who have not yet been infected; and secondly, to delay or prevent disease progression in those already infected. The development of preventive vaccine has been disappointing so far because of the unique behaviour of HIV. The therapeutic vaccine appears safe, but its long-term clinical efficacy is yet to be seen.

Several other vaccines may be used to prevent some of the common bacterial or viral diseases in HIV infected patients[11]. The available vaccines include the pneumococcal vaccine, H.influenzae vaccine and hepatitis B vaccine. In general, a higher response to most vaccines is found in those individuals with early HIV disease and higher CD4 counts. The antibodies may decline more rapidly in HIV infected cohort, but the need for booster dose has not been evaluated.

CONCLUSION

The continuous increase of HIV cases globally and particularly in Asia is a problem that cannot be overlooked. Although no cure can be provided at this point of time, the pace of research into improving treatment has progressed significantly. The current trend of management is toward early diagnosis and early intervention. Doctors today need to equip themselves with adequate knowledge to be able to recognise the disease at its early course.

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