THE NATURAL HISTORY OF HIV INFECTION

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HIV produces a relentless, progressive and ultimately fatal immunodeficiency syndrome in the vast majority of infected untreated patients.

The immunodeficiency that develops during HIV infection is a continuum, but the disease conveniently falls into several discrete clinical phases. Adding the results of simple blood tests to a clinical assessment allows the treating clinician to make a remarkably accurate assessment of the immediate risk of opportunistic disease, and initiate preventive and antiviral therapy accordingly.

Understanding the natural history of HIV-infected people allows a clinician to delay therapy when the risk of disease is low, and initiate prevention and antiviral therapy when that risk starts to rise.

Despite limited African prospective evidence, it seems that the progression of immunodeficiency is very similar here to developed countries. The range of opportunistic illnesses is significantly different, though, probably reflecting the difference in profiles of diseases in different regions.

EVENTS DURING ACUTE HIV INFECTION

The acute antiretroviral syndrome, or 'seroconversion', is usually but not always symptomatic. Symptoms vary from minor 'flu-like' symptoms to severe illness requiring hospitalisation. The infected person or his or her health care practitioner often dismisses the symptoms, especially in pressured, resource-poor environments like South Africa. Prolonged persistence or severity of the seroconversion illness is an independent risk factor for more rapid progression to AIDS, as is a short incubation period (less than 21 days between exposure and symptom development), but most illnesses last less than 2 weeks. Classic symptoms include malaise, fever, myalgias,
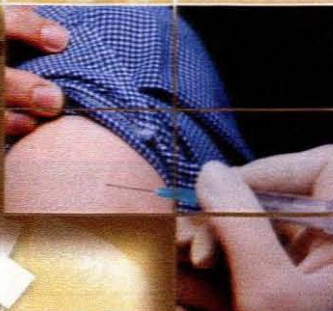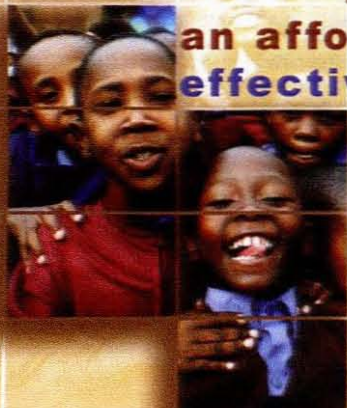
headaches and retro-orbital pain, mucocutaneous inflammation and ulcers, lymphadenopathy, splenomegaly, skin rashes, and gastrointestinal symptoms. The presence of a morbilliform rash on the trunk is a classic sign, but may be less apparent in dark skins. Cases of opportunistic diseases usually associated with advanced HIV have been described, suggesting that immune damage during seroconversion occurs. In a high HIV prevalence area such as South Africa, any probable viral illness should warrant questioning about risk factors, specifically possible recent sexual exposure.

During seroconversion, virus-specific cellular immunity and antibodies are generated in the face of a very high viral load. Mucosal surfaces are protected by dendritic cells, which efficiently transport the virus to lymphoid tissue after sexual or other mucosal exposure. Within days of exposure and infection of these lymphocytes, viral replication begins, and infected cells enter the bloodstream. Massive amounts of virus, often numbering tens of millions of copies, can be found in the bloodstream within a week after infection, with seeding of lymphoid and other tissue. The viral RNA and p24 levels are high, with a negative enzyme-linked immunosorbent assay (ELISA) and Western blot, which become positive later. The host responds with a strong cellular immune reaction, in an effort to contain the virus, with full antibody response following, typically within 21 to 28 days. Isolated incidences of seroconversion up to a year later have been documented. Blood testing during seroconversion will almost always show very high viral loads. Low viral loads (less than 50 000 copies/ml) with a negative ELISA usually indicate a false positive viral load. Viral load testing should therefore be interpreted with care.

Clinical guidelines, including the Southern African guidelines published in this edition, support the use of antiretrovirals in the acute seroconversion phase. These recommendations are not yet backed by clinical trials showing morbidity or mortality benefit, although some work has shown significantly better CD4 rises in treated patients immediately after seroconversion. The theory around treating seroconversion illness is that the viral set point (discussed later) may be set at a lower level, as the body has less virus to fight during seroconversion, prolonging the plateau phase. Treating aggressively with antiretrovirals during this critical period may preserve key HIV-specific T-helper cell responses. Enticing anecdotal evidence exists of patients able to rely entirely on their own immune system to control the virus, after a relatively brief exposure to antiretrovirals during seroconversion, and animal models suggest that treatment prolongs the plateau phase. However, equally theoretical risks exist of the archiving of drug-resistant virus, and there are the usual concerns regarding toxicity with use of long-term antiretrovirals. If one is to treat, it is not clear yet for how long, at how high a viral load, or with which drugs. Many experts recommend treating with conventional three-drug regimens for a year, and then withdrawing, with close monitoring subsequently. Clinical trials are currently looking at this issue, but the results of these may be some time away.

THE 'SET POINT'

As HIV-specific cytotoxic T cells appear, the plasma viral load drops dramatically. Neutralising antibodies only appear after the viraemia has already started to decrease. Resolution of symptoms usually corresponds with the drop in viraemia.

The viral set point is established once the plasma viral load has stopped falling. There is a large degree of individual variation of the set point, but this tends to change fairly slowly over the years following infection. People with high set point viral loads tend to progress more rapidly to AIDS. The set point appears to be associated with a large number of interactive factors, including genetic differences in co-receptors and qualitative differences in immune responses. The HIV immune system model is one of an incompletely effective antiviral immune response. The continued interaction between host and virus may explain the wasting syndrome seen in these patients – up to a billion virions are released into the plasma and then subsequently cleared by the immune system, every day, with loss of 5% of the total CD4 population daily, creating a constant regenerative stress.

Despite constant viral proliferation, and a persistent immune reponse, HIV-infected people usually remain asymptomatic during the time after seroconversion. During this time the viral load remains relatively stable and the CD4 count declines slowly, and the disease is often mistakenly referred to as 'latent'. Gradual destruction of lymph node architecture occurs, and anergy to skin testing develops. The onset of a more rapid drop of CD4 cells is associated with accelerated disease, and is known as the inflection point. The triggering events for this change in viral and immune kinetics are poorly understood.

The CD4 cell count is widely used as a reflection of the steady damage incurred by the immune system. There is wide variability in the rate of decline of the CD4 count, with some patients falling into 'fast' and 'slow' or even 'non'-progressors, but the average time from seroconversion to AIDS is about 10 years. CD4 cells are lost at an average of 40 - 80 cells/μl per year. A high viral load predicts more rapid progression. The progression rate is determined by a complex interaction between host, virus and environment.
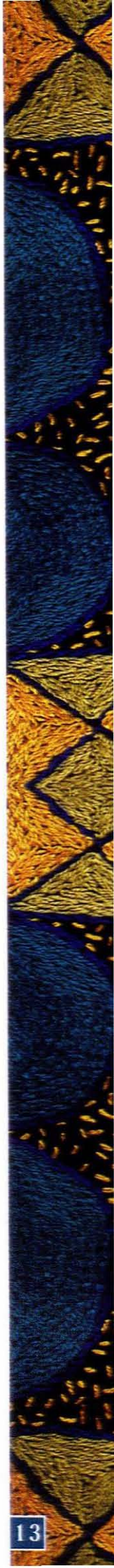
The model often used is a 'train-on-a-track' heading for a broken bridge (Fig. 1). The train represents the HIV-infected person, and the broken bridge serious disease or death. The length of track represents the CD4 count, and the speed of the train the viral load. A person with a high CD4 (lots of track) may still have a viral load that is high (the train is travelling fast) and be expected to run into trouble sooner, and therefore more frequent monitoring may be needed. The analogy can be extended further – successful antiretroviral therapy reduces the viral load (stops the train), and allows the immune system and CD4 count to recover (pushes the train backwards on the track).

Fig. 2. Host-virus dynamics. The drop in CD4 during acute infection occurs in the face of high viral loads; the plateau phase reflects viral-host homeostasis; finally, immune control is lost, with a drop in CD4 count and a rise in viral load.
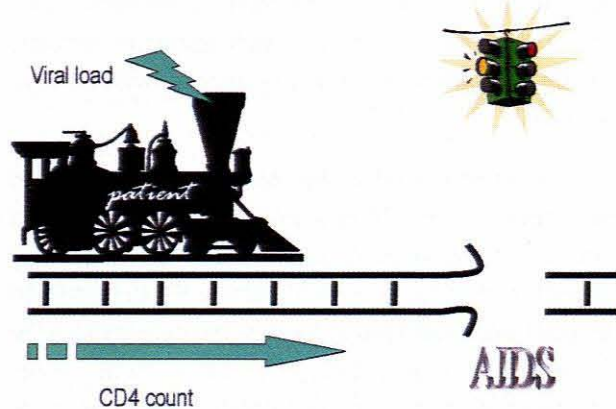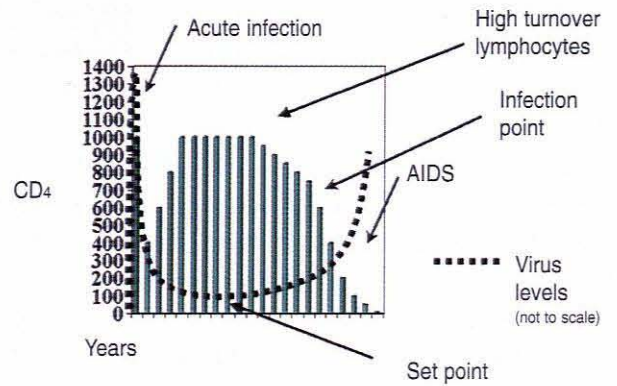

Fig. 1. The train-on-a-track model. The train is moving at a certain speed (viral load) along a defined amount of track (CD4 count), towards disaster (AIDS).

During the 'plateau phase' HIV-positive persons are usually asymptomatic, despite often having nonspecific laboratory abnormalities. Mild cytopenia and raised liver transaminase values are common. Occasionally patients will have flares of immunological-related diseases, particularly dermatological conditions, and have an increased risk of drug idiosyncratic conditions. Persistent generalised lymphadenopathy has no prognostic significance.

As the disease progresses, headaches, night sweats, anorexia, malaise and weight loss may occur, even in the absence of opportunistic disease. Sinusitis is a common and under-recognised syndrome. Mucocutaneous manifestations and tuberculosis occur, even in the face of relatively high CD4 counts, reflecting the limitations of this surrogate measure of overall immune function. Plasma CD4 counts reflect only 2% of the total body's T-cell population. The immune dysfunction is not simply a quantitative loss of CD4 and CD8 cells, but also of altered diversity and strength of cellular immune response. Hypergammaglobulinaemia is due to uncontrolled B-cell replication, commonly seen as a raised total protein, and auto-antibodies often test positive, despite the absence of clinical manifestations associated with these antibodies. Recurrent vaginal candidiasis is one of the commonest early symptoms of HIV disease in women, often occurring at CD4 counts of over 400 cells/μl.

LATE DISEASE

As the CD4 count approaches 200 cells/μl, the risk of opportunistic disease rises dramatically. The spectrum of disease changes steadily, and the presentation of other diseases becomes more atypical. This sudden loss of immune-virus homeostasis signifies an exhaustion of lymphocyte proliferative capacity, as well as possible irreversible architectural damage to the lymph node system.

The commoner HIV-related diseases in South Africa are herpes zoster, oral candidiasis and tuberculosis. As the CD4 count drops, the clinical presentation of tuberculosis changes, from the classic fibrocavitatory pulmonary changes, to atypical lung changes including mediastinal lymphadenopathy, and extrapulmonary TB. Responses to treatment of opportunistic infections are also more atypical, with incomplete responses, prolonged treatment course requirements, and repeated relapses. With the CD4 count below 200 cells/μl other common diseases start becoming apparent, including cryptococcal meningitis, pneumocystis, bacterial pneumonia, and oesophageal candidiasis. Some diseases, such as cytomegalovirus and non-tuberculous mycobacteria, appear to be less common in our setting than in the developed world. These diseases, in addition to other diseases such as progressive multifocal leucoencephalopathy, radiculitis and central nervous system lymphomas, are difficult and expensive to treat, and are usually associated with a CD4 count below 50 cells/μl, with a very poor prognosis.

Effective prophylaxis against specific infections is available, and is covered in the current guidelines, published in the March of the *Journal*.

The term 'AIDS' is used to describe profound immunosuppression, and is most commonly used in association with Centers for Disease Control (CDC)

definitions, using CD4 counts and clinical criteria. Terms like AIDS-related complex (ARC), referring to symptoms pre-dating strict definitions of AIDS, have been abandoned.

All current treatment guidelines recommend starting antiretrovirals if the CD4 count is found to be less than 200 cells/µl.

What is not clear is how soon before the '200 level' antiretrovirals should be started, before the patient's risk becomes great enough to warrant the cost, adherence and toxicity challenges of lifelong antiretroviral treatment. Most cohorts in the developed world show minimal disease and minimal benefit of antiretrovirals above 350 cells/µl, and the new guidelines specifically recommend not starting antiretrovirals at this level unless the patient has significant HIV-related symptoms or AIDS-related disease, or is in the seroconversion phase. The Southern African guidelines, along with other guidelines, recommend stratifying the 200 - 350 cells/µl into a high-risk group

(viral load greater than 55 000 copies), where treatment should be started, versus a low-risk group (less than 55 000), where closer monitoring is warranted.

CONCLUSION

The disease is predictable, and patients can be 'staged' into broad risk categories according to clinical and immunological criteria. These risk categories can be correlated to the risk of disease progression, as well as giving a good prediction of opportunistic illness risk. As new, safer treatments and strategies or more accurate predictors of risk become available, we may need to re-evaluate the 'when-to-start' criteria we use, especially as the risk of tuberculosis increases even with relatively well preserved CD4 counts. However, understanding the natural history of the disease allows an accurate and sober assessment of the individual patient's risk, with rational initiation of treatment.