

## HIV infection and AIDS

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### SUMMARY

Many of the clinical features of HIV/AIDS can be ascribed to the profound immune deficiency which develops in infected patients. The destruction of the immune system by the virus results in opportunistic infection, as well as an increased risk of autoimmune disease and malignancy. In addition, disease manifestations related to the virus itself may occur. For example, during the primary illness which occurs within weeks after first exposure to HIV, clinical symptoms occur in at least 50% of cases, typically as a mononucleosis syndrome. HIV-related complications are rarely encountered in patients with preserved immunity (i.e. CD4 T-cell counts greater than 500 cells/mm<sup>3</sup>). Recurrent mucocutaneous herpes simplex (HSV), herpes zoster (VZV), oral candidiasis and oral hairy leukoplakia occur with increasing frequency as the CD4 count drops below this level. Immune thrombocytopenia (ITP) occurs in association with HIV and often presents early in the clinical course. The risk of developing opportunistic infections and malignancies typical of AIDS increases progressively as CD4 counts fall below 200 cells/mm<sup>3</sup>. The clinical manifestations of infections associated with AIDS tend to fall into well-recognized patterns of presentation, including pneumonia, dysphagia/odynophagia, diarrhoea, neurological symptoms, fever, wasting, anaemia and visual loss. The commonest pathogens include *Candida albicans*, *Pneumocystis carinii*, *Mycobacterium tuberculosis*, *Toxoplasma gondii*, *Cryptococcus neoformans*, *Mycobacterium avium intracellulare* and cytomegalovirus. Malignant disease in patients with HIV infection also occurs in a characteristic pattern. Only two tumours are prevalent: Kaposi's sarcoma, a multifocal tumour of vascular endothelium which typically involves skin and mucosal surfaces; and non-Hodgkin's lymphoma, which is typically high grade in phenotype, often arising within the central nervous system. The principles of therapy include reduction of HIV replication by antiretroviral agents, prophylaxis against the common opportunistic infections and treatment followed by subsequent lifelong maintenance therapy for infections when they do occur.

It is estimated that approximately 20 million people worldwide will have been infected with the human immunodeficiency virus (HIV) by the turn of the century. Unfortunately, almost every country in the globe, including Papua New Guinea, now has growing numbers of cases of HIV/AIDS. Undoubtedly the paramount issue for Papua New Guinea in relation to the HIV epidemic is rapid, widespread and effective public education about HIV and other sexually transmitted diseases. This review focuses on the clinical features of the illnesses associated with HIV infection. For further information see Stewart (1) and Gold et al. (2).

### The virus and the immune system

The human immunodeficiency virus is the cause of the acquired immune deficiency syndrome (AIDS). The virus belongs to a recently discovered family of small RNA viruses, the retroviruses, whose unique feature is the mechanism of replication (RNA to DNA, rather than the converse) via a virally encoded enzyme, reverse transcriptase. The retroviruses, including HIV, are transmitted 'vertically' from mother to infant, and 'horizontally' via sexual intercourse and blood-to-blood contact (Table 1). Although HIV has been isolated from saliva, tears, urine and cerebrospinal

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**TABLE 1**

## TRANSMISSION OF HIV

Sexual intercourse	Vaginal intercourse Anal intercourse
Contaminated needle or syringe	Reused needles or syringes Needlestick injuries Shared injecting apparatus
Blood, organ or tissue donation (if not screened)	Blood products Semen Kidneys Skin, bone marrow, cornea, heart valves, tendons etc
Mother to child	In utero At birth Breastmilk

**TABLE 2**

## CLINICAL CLUES TO HIV INFECTION

Common disorders which are increased in prevalence with HIV infection	Herpes zoster Molluscum contagiosum Seborrhoeic dermatitis Recurrent herpes simplex infection Gingivitis Cervical intraepithelial neoplasia (CIN)
Uncommon disorders suggestive of HIV infection	Oral candidiasis Immune thrombocytopenia Guillain-Barré syndrome Tuberculosis Cryptococcal meningitis Dementia Non-Hodgkin's lymphoma
Uncommon disorders highly suggestive of HIV infection	Oral hairy leukoplakia Kaposi's sarcoma <i>Pneumocystis carinii</i> pneumonia (PCP) Cerebral toxoplasmosis Oesophageal candidiasis <i>Mycobacterium avium</i> complex (MAC) Cytomegalovirus (CMV) infection

fluid, the concentration is very low. Hence, transmission from these fluids is extremely unlikely.

Many of the clinical features of HIV infection can be ascribed to the profound immune deficiency which develops in infected patients. The cellular target for HIV is the surface protein called CD4, found on peripheral blood T lymphocytes (and to a lesser extent other cells in the skin, gut, brain etc). Thus progressive depletion of CD4<sup>+</sup> T lymphocytes is the characteristic feature of the advancing immune deficiency in patients with HIV and AIDS. CD4 T cells are a critical component of the immune system. These cells regulate the synthesis of antibodies, orchestrate the killing of intracellular microorganisms and tumour cells by regulating the activity of cytotoxic T cells, and control the function of nonspecific effector cells of the immune system, including macrophages and neutrophils. Thus it is the complications of immune deficiency (infection, tumour development and autoimmunity), rather than the direct effects of HIV itself, which predominate in the clinical manifestations of AIDS.

### **Diagnosis of HIV infection**

The diagnosis of HIV-related illnesses in the patient presenting to general practice relies heavily on the history of risk factors for HIV transmission (Table 1), on the lifestyle history, and on the detection of clinical clues suggestive of HIV infection (Table 2).

The HIV antibody test is the key to confirmation of HIV infection. If the patient is aware of HIV/AIDS and has some understanding of its significance then it is important that, before an antibody test is ordered, the physician allows time to explain the testing process and the implications of a positive result. However, in Papua New Guinea very few patients (especially in the village setting) currently have enough prior knowledge to allow truly informed consent for an HIV antibody test. The physician and the patient should be aware that confirmatory tests in a reference laboratory are necessary if an initial positive result is obtained, and hence definitive results may take several weeks to become available.

Laboratory testing for HIV is primarily based upon detection of antibodies directed against the virus. In Papua New Guinea, the most commonly used screening test is a gel particle agglutination assay (Serodia Fujirebio). If the initial test is positive then it is first confirmed by a repeat in the same assay, followed by confirmatory testing, which is usually done by enzyme-linked immunoassay in the National Reference Laboratory.

### **Primary HIV infection**

After first exposure to HIV there is a period of two to four weeks in which viral replication is high, there is little evidence of immune response, and the virus becomes established within lymph nodes and other sites including the central nervous system. This primary illness is associated with clinical symptoms in at least 50% of cases, typically as a mononucleosis syndrome (Table 3). The differential diagnosis of the primary HIV illness includes viral hepatitis, Epstein-Barr virus or cytomegalovirus (CMV) infection, rubella, other viral infections, secondary syphilis and toxoplasmosis.

### **Ongoing management of the patient with HIV**

After initial exposure to the virus, the course of HIV infection thereafter varies significantly between patients. Over 10 years, approximately 50% of patients will develop significant immune deficiency and associated opportunistic infections or tumour, marking the onset of AIDS. This interval from infection to the advent of AIDS may be as short as months, or perhaps as long as 20 years or more.

A patient who has a positive HIV diagnosis should have baseline investigations seeking to define relevant co-morbidity including a blood count and differential, and renal and liver function tests. Where appropriate, evidence for other blood-borne or sexually transmitted infections should be sought, such as hepatitis B and C, and syphilis. Assays for IgG antibodies against toxoplasmosis and CMV may be helpful (as these infections may reactivate and produce disease later in the clinical course). Monitoring the number of peripheral blood CD4 T lymphocytes provides a reasonable picture of the current risk of opportunistic infection and may guide specific prophylactic

**TABLE 3****CLINICAL FEATURES OF PRIMARY HIV INFECTION****General**

Fever  
 Pharyngitis  
 Lymphadenopathy  
 Arthralgia and myalgia  
 Fatigue  
 Anorexia and weight loss

**Dermatological**

Erythematous maculopapular rash  
 Urticaria  
 Desquamation  
 Alopecia

**Neurological**

Headache  
 Meningoencephalitis  
 Peripheral neuropathy  
 Radiculopathy  
 Guillain-Barré syndrome  
 Cognitive or mood change

**Gastrointestinal**

Mucocutaneous ulceration  
 Oropharyngeal candida  
 Nausea and vomiting  
 Diarrhoea

and antiretroviral therapy. However, this expensive technology is restricted to developed countries, and is not available in Papua New Guinea. Therefore clues regarding the extent of immune deficiency should be sought from clinical features. For example, the first advent of oral candidiasis or recurrent herpes genitalis implies early immunodeficiency, whereas CMV retinitis typically occurs when there is profound loss of T cell numbers. In addition, a differential white cell count may be used to enumerate the number of peripheral blood lymphocytes. Even allowing for the uncertain number of the subpopulations ( $CD4^+$  T cells,  $CD8^+$  T cells and B cells), the presence of a total lymphocyte count of  $500 \text{ cells/mm}^3(\mu\text{l})$  or less in an HIV-positive patient is highly likely to indicate significant immunodeficiency.

Early signs of HIV infection are usually related to the virus itself (Table 4) and frequently occur before any significant immune deficiency has developed; for example, the  $CD4$  count may still be in the normal range of  $700\text{-}1500 \text{ cells/mm}^3(\mu\text{l})$ .

For the asymptomatic patient, who has no clinical or laboratory clues to immunodeficiency or complicating illness, outpatient visits should be routinely arranged approximately every three months, and should include a physical examination and blood count with a differential.

**Symptomatic HIV infection**

HIV-related complications are rarely

**TABLE 4**

## CLINICAL FEATURES OF PATIENTS WITH EARLY HIV INFECTION

<b>Constitutional</b>	Fevers, malaise, fatigue, night sweats, lymphadenopathy, diarrhoea, unexplained weight loss
<b>Dermatological</b>	Recurrent herpes simplex, facial seborrhoeic dermatitis, molluscum contagiosum, folliculitis, impetigo, shingles

encountered in patients with CD4 T-cell counts greater than 500 cells/mm<sup>3</sup>( $\mu$ l). Recurrent mucocutaneous herpes simplex (HSV), herpes zoster (VZV), oral candidiasis and oral hairy leukoplakia may occur when the lymphocyte number starts to fall. Oral acyclovir is effective in the treatment and prophylaxis of herpes simplex infections, and the treatment of herpes zoster. Oral candidiasis will usually respond to topical antifungal therapies including nystatin, amphotericin or miconazole. Immune thrombocytopenia (ITP) occurs in association with HIV and often presents early in the clinical course. Effective therapies include antiretroviral treatment with zidovudine, corticosteroids and splenectomy.

The risk of developing opportunistic infections and malignancies typical of AIDS increases progressively as CD4 counts fall below 200 cells/mm<sup>3</sup>. At this stage the use of prophylactic antimicrobials to prevent or delay the onset of infections has been shown to be effective (Table 5).

The clinical manifestations of infections or

malignancies associated with AIDS tend to fall into well-recognized patterns of presentation (Table 6). The investigation and management of these complications will typically require referral to a specialist service. As tuberculosis and cryptococcosis are relatively common infections in Papua New Guinea and are known to be associated with HIV infection, these two infections are likely to dominate the clinical picture of AIDS in PNG. In addition, as recurrent *Salmonella* bacteraemia is common in patients with HIV/AIDS, those areas of PNG where typhoid is prevalent are likely to find this infection commonly in patients with HIV. Equally important is the potential for the growing numbers of HIV-infected patients to provide a reservoir for transmission of tuberculosis and typhoid to non-HIV-infected individuals.

Treatment of AIDS-related infections is frequently divided into a phase of therapy designed to control the infection (with apparent eradication of the organism), followed by a maintenance regimen intended to prevent relapse, which is common if ongoing therapy is

**TABLE 5**

## PROPHYLAXIS AGAINST AIDS-RELATED OPPORTUNISTIC INFECTIONS

<i>Pneumocystis carinii</i> pneumonia (PCP)	Cotrimoxazole Dapsone and trimethoprim Nebulized or intravenous pentamidine
Oral or oesophageal candida	Ketoconazole Fluconazole
Recurrent mucocutaneous herpes simplex virus (HSV) infection	Acyclovir
Disseminated <i>Mycobacterium avium</i> complex (MAC)	Rifabutin

**TABLE 6**

PATTERNS OF CLINICAL PRESENTATION IN AIDS

<b>Presentation</b>	<b>Common causes</b>	<b>Investigations</b>
Pneumonia	<i>Pneumocystis carinii</i> Pneumococcus <i>Haemophilus influenzae</i> Tuberculosis	Chest X-ray Sputum examination Sputum culture
Dysphagia, odynophagia	Candidiasis CMV HSV Kaposi's sarcoma	Endoscopy and biopsy
Diarrhoea	Cryptosporidia Microsporidia MAC CMV HIV enteropathy	Stool microscopy and culture Sigmoidoscopy and biopsy
Neurological symptoms	Cryptococcosis Toxoplasmosis Lymphoma HIV encephalitis PML	Lumbar puncture
Fever, wasting, anaemia	Tuberculosis Salmonellosis MAC CMV Lymphoma	Sputum, stool or blood culture Bone marrow biopsy and culture Lymph node biopsy
Visual loss	CMV	Ophthalmological review
CMV	Cytomegalovirus	
HSV	Herpes simplex virus	
MAC	<i>Mycobacterium avium</i> complex	
HIV	Human immunodeficiency virus	
PML	Progressive multifocal leucoencephalopathy	

not undertaken. Standard combination antituberculous therapy has been shown to be effective for patients with HIV and TB, although the relapse rate is significantly higher than in non-HIV-infected patients. Similarly, standard antifungal therapy for cryptococcal meningitis is effective for patients with HIV and cryptococcosis. In Papua New Guinea, emphasis in patient care should be placed on diagnosis and management of the major treatable conditions associated with HIV: tuberculosis, cryptococcosis and salmonella

infections; as well as the more common minor infections – oro-oesophageal candidiasis and recurrent herpes simplex.

Malignant disease in patients with HIV infection also occurs in a characteristic pattern. Only two tumours are prevalent – Kaposi's sarcoma and non-Hodgkin's lymphoma. Squamous cell carcinoma of the anogenital area and cervix, and basal cell carcinoma of the skin are also found with increased frequency. Kaposi's sarcoma appears to be a tumour of

vascular endothelial cells, is often multicentric, is nonmetastasizing and rarely involves the central nervous system. The lesions are typically mucocutaneous, appear as purple or bluish-brown papules, and may accumulate to several hundred in number. High grade non-Hodgkin's lymphomas of B-cell origin are relatively common in patients with AIDS. These lymphomas are strongly associated with Epstein-Barr virus infection in the tumour, may occur with a primary focus in the central nervous system, and generally have a poor prognosis.

In addition to opportunistic infections and tumours, patients with HIV infection are susceptible to neurological disorders directly attributable to the neurotropic character of HIV. Early in the clinical course, aseptic meningitis and peripheral neuropathy may occur. As the HIV infection advances, a subacute dementia referred to as the AIDS dementia complex (ADC) may develop. Although this syndrome may occur at a time when significant immune deficiency has not yet developed, typically ADC happens late in the AIDS illness. ADC is characterized by a progressive cognitive deterioration in association with ataxia, wasting and weakness, as well as urinary incontinence. The only therapy shown to slow the progression of ADC is the antiretroviral agent, zidovudine.

### Antiretroviral therapy

Antiretroviral agents are commonly prescribed for patients with HIV/AIDS. The substantial cost of each of these drugs has prohibited their widespread use in developing countries. Zidovudine (ZDV, formerly known as AZT), didanosine (dideoxyinosine; ddI) and zalcitabine (dideoxycytidine; ddC) are the three agents currently licensed for use in many countries. Each of these agents has been shown

to inhibit HIV replication by inhibition of reverse transcription. They improve CD4 cell counts and reduce the likelihood of opportunistic infections developing in patients with HIV infection. ZDV, the first drug evaluated, has been shown to prolong survival in patients with AIDS and also to delay the progression to AIDS in patients with HIV infection.

A growing body of evidence suggests that combination therapy with these agents and with newer drugs with different modes of inhibition of HIV activity is likely to be the future standard therapy. It remains unclear as to the ideal timing for the initiation of antiretroviral treatment. Current practice ranges from treatment commenced when the CD4 cell count falls below 500 cells/mm<sup>3</sup> to deferring therapy until CD4 counts are as low as 300 cells/mm<sup>3</sup> and HIV-related symptoms have developed. ZDV alone, or combinations of ZDV with ddI or ddC, may be prescribed.

Multiple newer drugs which target other stages of the replicative cycle of HIV have been developed, many with potent antiviral effects. These drugs include the inhibitors of HIV protease. It is hoped that in combination with existing and novel antiretroviral agents these drugs will provide a treatment strategy to allow long-term control of HIV disease.

### REFERENCES

- 1 **Stewart G, ed.** *Could It Be HIV? The Clinical Recognition of HIV Infection*, 2nd edition. Sydney: Australasian Medical Publishing Company, 1994.
- 2 **Gold J, Penny R, Ross M, Morey S, Stewart G, Donovan B, Berenger S, eds.** *The AIDS Manual. A Comprehensive Reference on the Human Immunodeficiency Virus (HIV)*, 3rd edition. Sydney: MacLennan and Petty, 1994.