Signs and symptoms of chronic HIV disease

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Introduction

Since the mid-1990s, the clinical manifestations of chronic human immunodeficiency virus (HIV) infection have changed dramatically amongst people with access to combination antiretroviral therapy.[1,2] This chapter covers the 'classical' signs and symptoms of unmodified HIV disease that can provide a basis for an initial clinical diagnosis. It also discusses the clinical issues seen in the large proportion of people with HIV infection who are now taking combination antiretroviral therapy.

Acquired Immunodeficiency Syndrome (AIDS) was characterised in the early 1980s before HIV had been identified. The Centers for Disease Control (CDC) in the USA listed a group of secondary conditions that suggested immunodeficiency which had been identified in clusters. The original case definition of AIDS has been modified somewhat over the years but it remains a list of conditions, now rare in the Australian setting, that are seen predominantly in people who present late with untreated HIV infection and severe immunodeficiency (Table 6.1). AIDS remains notifiable in Australia, but the prognostic significance is less important in treated populations than other markers of HIV, such as CD4 cell count and viral load (Chapter 10).

Many HIV specialist clinicians and people with HIV infection now favour terms such as 'early' and 'late' HIV disease rather than 'AIDS'. Alternatively, clinicians may describe patients in terms of their surrogate markers and clinical status.

When should HIV be considered in the differential diagnosis?

The focus of this chapter is on specific clinical illnesses, laboratory abnormalities and aberrant responses to therapeutic interventions which may indicate HIV infection as a differential diagnosis to the astute clinician (see Table 6.2). Whenever HIV antibody testing is recommended, there should be an awareness of the psychosocial impact of testing and full pre-test discussion should be undertaken (Chapter 9).

Key points

- Clinical diagnosis of HIV infection requires consideration of HIV aetiology in relation to a range of sub-acute, chronic and acute clinical presentations.
- Chronic symptoms of immune activation (e.g. lymphadenopathy, night sweats, fever) may indicate HIV infection.
- Mild, HIV-related immune deficiency may be indicated by persistent oral or skin conditions.
- Laboratory markers such as thrombocytopenia, neutropenia and lymphopenia may suggest HIV infection.
- The incidence of 'classical' AIDS-defining illnesses has fallen dramatically in Australia since the introduction of combination antiretroviral therapy. These conditions are now most common among patients with advanced HIV disease whose HIV status has been undiagnosed.
- Combination antiretroviral therapy has dramatically altered the course of clinical HIV disease. Immune reconstitution illness and treatment-related side-effects are now common causes of clinical symptoms.

A differential diagnosis of HIV may be considered in individuals who report exposure risks for HIV infection during general health assessments. Testing for HIV is commonly part of the management of pregnant women and as part of screening for sexually transmissible infections (STIs). HIV antibody screening is performed as part of blood, tissue and organ donation, prior to military service and may be requested for some visas and work permits. Consideration should be given to HIV infection amongst other risks for immunosuppression prior to live viral vaccinations, at consideration of transplantation and when prescribing immunosuppressant medications. The assessment of HIV risk and subsequent counselling and management of the patient are detailed in Chapters 2, 3 and 9.

Immune activation symptoms – primary infection

The acute retroviral syndrome characteristic of primary HIV infection includes prominent features of immune activation, such as fever, night sweats, myalgia, arthralgia and lymphadenopathy (Chapter 4).

For a proportion of people with HIV, these symptoms may become chronic, indicating persistent activation of the immune system.

Clinical latency

The long phase of clinical latency that follows primary HIV infection conceals substantial virological and immunological activity.[3] Some HIV-infected people are able to control HIV replication and to maintain CD4 cell levels for an extended period; they are known as 'slow progressors' or 'long-term non-progressors'. A small but significant proportion of people with HIV have been infected for close to 20 years but still have low viral loads and near normal immune function. For most untreated people with HIV infection, however, there is a gradual decrease in CD4 cell numbers over a period of 5–10 years, when clinical HIV disease becomes apparent.

Mild immunodeficiency

A variety of infectious agents can become more troublesome relatively early in the course of untreated HIV infection when the CD4 cell count falls below 500 cells/μl (Tables 6.1–6.3). Most of these are other chronic viral infections and the appearance of clinical disease in people with HIV infection is usually due to re-activation of latent virus rather than new infection.

Shingles

An episode of classical herpes zoster can often occur quite early in the course of chronic HIV infection, particularly after another illness such as a respiratory infection. It can be managed effectively using aciclovir, valaciclovir or famciclovir. Admission to hospital for intravenous aciclovir may be warranted for those with severe pain or multi-dermatomal or disseminated herpes zoster.

Herpes simplex

Orofacial and anogenital herpes simplex outbreaks occur more frequently in people with HIV infection. These may be extensive and persistent. In people with more advanced disease, the ulcers often coalesce, especially around the anus, to form large, extremely painful ulcers. Herpes lesions continuously present for more than a month were part of the original case definition for AIDS. However, the advent of effective treatment for the herpes simplex virus (HSV) means that symptomatic chronic herpes is now rare. Recurrent or persistent herpes may be a sign of HIV infection in undiagnosed patients and may be a trigger for risk assessment and further physical examination.

Kaposi's sarcoma

This malignancy, which in the days before the HIV epidemic was seen only in elderly men, is now known to be caused by human herpesvirus type 8 (HHV-8). HHV-8 appears to be sexually transmitted. Additionally, high levels of virus have been demonstrated in saliva. In Africa, horizontal transmission among children may be important. In Australia, Kaposi's sarcoma is a sign of HIV infection, especially in healthy men.

Kaposi's sarcoma is most commonly manifested as purple, nodular lesions on the skin or oral mucosa (Figure 6.1) but can occur in visceral organs such as the lungs and the gastrointestinal system. Unpleasant or unsightly local tumours are amenable to local therapy, intralesional chemotherapy or palliative

TABLE 6.1 **AIDS indicator diseases**
• Candidiasis (oesophagus)
• Cryptococcosis (invasive)
• Cervical carcinoma (invasive)*
• Cryptosporidiosis with diarrhoea > 1 month
• Cytomegalovirus of retina, brain, spinal cord, gastrointestinal tract
• Herpes simplex mucocutaneous ulcer > 1 month
• HIV-associated dementia, disabling cognitive ± motor dysfunction
• HIV-associated wasting loss >10% body weight plus diarrhoea, weakness and fever > 30 days*
• Isosporiasis with diarrhoea > 1 month*
• Kaposi's sarcoma
• Lymphoma, brain or non-Hodgkin's (B-cell or immunoblastic)
• Mycobacterium avium complex or kansasii (disseminated)
• Mycobacterium tuberculosis disseminated or pulmonary*
• *Pneumocystis jiroveci* pneumonia
• Pneumonia (recurrent bacterial)*
• Progressive multifocal leukoencephalopathy
• Salmonella septicaemia (non-typhoidal, recurrent)*
• Toxoplasmosis (brain)
* Requires HIV diagnosis.

FIGURE 6.1 Kaposi's sarcoma

radiotherapy. For progressive disseminated disease, systemic chemotherapy is often beneficial but the mainstay of management involves restoration of immune function by controlling HIV replication through antiretroviral therapy.

Anogenital warts and squamous dysplasia

Anogenital warts are common in people with HIV infection and usually represent re-activation of a previous viral infection of the skin with the human papillomavirus (HPV). In patients without an HIV diagnosis, anogenital warts, especially recurrent warts, indicate the need for HIV risk assessment and further examination.

Anal or genital warts in the presence of HIV infection may be conservatively managed, particularly if the person is considering the institution of antiretroviral therapy for HIV. Warts often regress spontaneously.

Standard methods of treatment may be employed. In the case of surgically removed anal warts, biopsy tissue should be sent for histopathology. Squamous dysplasia is often seen and indicates that close follow-up is required. There is some evidence to suggest that squamous carcinoma of the anal canal is more common in people with HIV and is probably related to HPV infection.

Cervical carcinoma is significantly more prevalent in women with HIV and is also probably related to HPV infection. It is generally recommended that Papanicolaou smear cytology be performed every 6–12 months in this group, with management of abnormalities undertaken according to the usual approach.

Molluscum contagiosum

These nodular lesions with a central punctum commonly occur on the face, neck or anogenital area. Although it does occur in people without HIV infection, persistent appearance of molluscum contagiosum in adults should lead to consideration of HIV infection. Molluscum contagiosum is caused by a poxvirus and, in people with HIV infection, its incidence and severity relate to the degree of immunosuppression. The condition is diagnosed clinically. Differential diagnosis in the patient with HIV infection would include cutaneous cryptococcosis infection and, in people from South East Asia, infection with Penicillium marneffei. Lesions commonly regress with immune recovery due to antiretroviral therapy or may be controlled with local therapy.

Dermatoses

Rashes are common in people with HIV infection at any level of immune function. Persistent, new or unusual skin conditions may be the first symptom of HIV infection. The clinician should be alert to the possibility of HIV infection and undertake a full risk assessment and physical examination if extensive, atypical or persistent rash is encountered.

TABLE 6.2 **Alarm bells suggestive of HIV infection**
Clinical conditions where HIV should be considered
• Oral candidiasis (especially in the absence of antibiotic use)
• Atypical mononucleosis syndrome (not EBV- or CMV-related)
• Aseptic meningitis with severe systemic symptoms
• Difficult to manage psoriasis, dermatoses
• Tuberculosis
• Non-Hodgkin's lymphoma
• Cerebral space-occupying lesions
• Persistent lymphadenopathy and symptoms of immune activation
• Chronic vaginal thrush
Laboratory abnormalities where HIV should be considered
• Thrombocytopenia, neutropenia, lymphopenia without cause
• Anergy unexplained
• Hypergammaglobulinemia new or unexplained
Therapeutic responses where HIV should be considered
• Pneumonia unresponsive to standard therapy
• Recurrent antibiotic-associated rash

TABLE 6.3 **Febrile syndromes in people with HIV infection**	
Differential diagnosis of undifferentiated fever in the patient with HIV infection	
Current or nadir CD4 cell count < 200 cells/μL	**Current or nadir CD4 cell count ≥ 200 cells/μL**
• Disseminated Mycobacterium avium complex	• Bacterial infections, e.g. pneumonia, septicaemia
• Pneumocystis jiroveci pneumonia	• Drug fever
• Cryptococcal infection	• Tuberculosis
• CMV infection	• Disseminated Salmonella, Campylobacter infection
• Toxoplasmosis	• Fever associated with malignancy, e.g. lymphoma
• Less common infections, e.g. Histoplasma, Bartonella	

The most common form of rash associated with HIV infection is seborrhoeic dermatitis (Figure 6.2) which is seen in most people at some stage in the disease. It occurs at the classical sites of scalp, ears, eyebrows, chest, axillae, groin and feet. Standard treatment with steroid creams or topical ketoconazole is often effective in controlling the problem but recurrence is usual. This condition generally improves dramatically when effective antiretroviral treatment is instituted. Dermatophyte infections are also very common and can sometimes be difficult to differentiate from seborrhoea. These infections can be very extensive, particularly on the feet, and secondary bacterial infection is common. Misdiagnosis of a dermatophyte infection leads to ineffective treatment with steroid creams that may in turn modify the clinical appearance of the condition.

Other puzzling rashes are often seen in people with HIV infection. Early skin biopsy may be a useful guide when response to therapy is inadequate. Eosinophilic pustular folliculitis is one such pruritic papular condition that commonly occurs on the upper arm and chest for which phototherapy has induced response in many patients. Antiretroviral therapy often leads to resolution of dermatoses.

Psoriasis occurs in people with HIV infection with the typical erythematous scaly lesions occurring over elbows, hands and feet. The guttate form is also common. Pre-existing psoriasis can be exacerbated by HIV infection and newly diagnosed psoriasis has also been described. Immune recovery has been shown to improve these psoriatic lesions in people with HIV infection.

Oral conditions

A condition called oral hairy leukoplakia is commonly seen prior to serious HIV-related opportunistic infections. It is manifest as distinctive white areas on the lateral margins of the tongue that cannot be rubbed off with gauze (unlike candidiasis). Its aetiology remains unclear, although one theory is that oral hairy leukoplakia is a manifestation of mucosal Epstein-Barr virus (EBV) infection. The condition is almost pathognomonic of HIV infection and will sometimes prompt the consideration of HIV testing when noticed by an astute dentist or medical clinician at routine examination.

Oropharyngeal candidiasis becomes more common in HIV disease when immunosuppression occurs. Often it has the classical appearance of cheesy plaques that can be rubbed off; occasionally, it is subtler with an area of slightly furry reddening, particularly on the palate. Candidiasis is much less common in HIV-infected individuals who are taking effective antiretroviral therapy. Mycological examination of a wet swab will confirm the diagnosis. Treatment is only required when the condition is symptomatic, and topical amphotericin lozenges will often be effective for mild disease. If the disease is more severe and persistent, a course of oral fluconazole will usually control it for a period.

Aphthous mouth ulcers appear to be more common and more persistent in people with HIV than among the HIV-negative population. These ulcers may be quite large and are painful. When simple measures are ineffective, topical steroids appear to be beneficial in a proportion of patients and, in very severe cases, thalidomide may be useful with appropriate precautions.

A particularly aggressive form of gum disease, known as acute necrotizing ulcerative gingivitis is commonly seen in the months before clinical progression of HIV. Skilled care from a dentist who is sensitive to

FIGURE 6.2 Seborrhoea

the needs of people with HIV infection is required to prevent the loss of otherwise healthy teeth. Once again, the condition is likely to abate significantly with the commencement of effective antiretroviral therapy for HIV infection. Severe gingivitis may be suggestive of possible HIV infection and may prompt further enquiry in the undiagnosed patient.

Hepatitis co-infection

As other HIV-related opportunistic infections are prevented or controlled, liver disease secondary to co-infection with HBV or HCV and liver toxicity from antiretroviral agents have become more prominent. Co-infection may cause difficulty tolerating HIV antiretroviral therapy, especially in the initial immune reconstitution phase when hepatic transaminase levels may rise. Close monitoring of liver function is required at this time.[4]

The presence of HIV leads to more aggressive HCV disease and higher HCV viral load, and the use of interferon and ribavirin in people with co-infection requires consideration of treatment for the hepatitis prior to initiation of antiretroviral therapy if possible, or modification of the antiretroviral regimen to enable concomitant treatment with pegylated interferon and ribavirin. Careful monitoring of liver function tests and markers of HCV infection (polymerase chain reaction and genotype), and avoidance of other hepatotoxins, such as alcohol, is recommended (Chapters 10 and 11).

In the person with HIV infection, infection with HBV may be associated with flares of hepatitis during immune deficiency, especially if lamivudine (which is active against both HIV and HBV) is withdrawn. Optimal management of HIV-HBV co-infection has not yet been defined.

Immune reconstitution disease

In untreated people with advanced HIV infection (CD4 cell count below 100 cells/μL), marked immunodeficiency inhibits the inflammatory response that would normally occur to a variety of infectious agents such as cytomegalovirus (CMV), HCV and Mycobacterium avium complex. When treatment reduces HIV viral load, there is rapid restoration of the ability to mount inflammatory reactions. Consequently, infectious agents that have 'peacefully co-existed' with the host during extreme immunodeficiency are met with a marked inflammatory response, and clinical disease becomes apparent where few signs or symptoms were evident previously (Figure 6.3). This phenomenon has been named 'immune reconstitution disease' and was first described in Australia.[5] An immune reconstitution illness is usually transient because the inflammatory effect is ultimately successful at combating the infectious agent. However, immune reconstitution illnesses can be clinically significant while present. In the case of CMV retinitis, vision can be permanently impaired by an episode of intense inflammation during immune reconstitution.

FIGURE 6.3 Immune reconstitution and *Mycobacterium avium* complex (MAC)

When a patient presents with new symptoms soon after starting antiretroviral therapy, immune reconstitution should be considered as a possible cause and appropriate referral and investigation is advised.

Severe immunodeficiency

More serious, life-threatening opportunistic infections generally appear when the CD4 count falls below 200–250 cells/μL (Tables 6.1–3).

Pneumocystis jiroveci pneumonia

In the untreated person with HIV, Pneumocystis jiroveci pneumonia (previously known as Pneumocystis carinii pneumonia, PCP) is often the first serious opportunistic infection. In the early days of HIV management, PCP was often fatal. Risk of PCP increases when the CD4 cell count falls below about 200 cells/μL.

It is often insidious in onset and typically presents as a persistent, dry cough and exertional dyspnoea, sometimes accompanied by mild-to-moderate constitutional upset with fevers, sweats, lethargy and fatigue. If left untreated, respiratory function can decline dramatically, leading to the need for ventilation and intensive care management. The diagnosis can often be made from a chest X-ray and is confirmed by microbiological examination of sputum induced by inhalation of nebulised hypertonic saline. The condition is now uncommon in people with an HIV diagnosis because simple and effective prophylaxis is available. Double-strength co-trimoxazole taken once daily by people with CD4 cell counts below 250 cells/μL has dramatically reduced the incidence of this condition.

In Australia and other countries where antiretroviral therapy and PCP prophylaxis are widely available, PCP is now most often seen in people with longstanding, but undiagnosed, HIV infection.

Mycobacterium avium complex (MAC)

Systemic infection with atypical mycobacteria is commonly seen in people with CD4 cell counts below 50–100 cells/µL. It produces a syndrome of non-specific malaise, often accompanied by night sweats, weight loss, anaemia and sometimes respiratory or abdominal symptoms. Its symptoms merge with those of advanced HIV itself and a high index of suspicion is required. MAC is an important differential diagnosis of non-specific fever in people with HIV infection (Table 6.3). The diagnosis of MAC is confirmed by culture of blood collected in special media. However, the organism is slow to grow, so treatment with a combination of anti-mycobacterial drugs is often commenced presumptively. In those with epidemiological risk factors, tuberculosis should be considered as a differential diagnosis and isoniazid added to presumptive therapy until tuberculosis is excluded.

Upon treatment, significant clinical improvement is usually seen and maintenance therapy is continued indefinitely, unless marked and sustained immune recovery is achieved with antiretroviral treatment. Effective prophylactic regimens for MAC are now available. Azithromycin given as a single dose of 1200 mg weekly is most widely used and is usually commenced when the CD4 cell count is consistently below 100 cells/µL.

Diarrhoeal diseases

Diarrhoea is an extremely common condition in people with HIV infection.

Among patients with known HIV infection, diarrhoea is often related to the adverse effects of antiretroviral medication, particularly some protease inhibitors. When advanced immunodeficiency is present (CD4 cell count below 100 cells/µL), opportunistic infections due to Cryptosporidium and Microsporidium should be considered. Stool examination is recommended if no obvious cause for persistent diarrhoea is found in a person with HIV infection. It is also important to ask the laboratory to look specifically for parasites, such as Microsporidium species, as this requires special processing of the specimen. Colonoscopy and mucosal biopsy may reveal CMV colitis in people with very severe immunosuppression.

Advanced HIV disease is associated with diarrhoea and, if no specific cause is found after a full diagnostic assessment, anti-diarrhoeal agents such as loperamide may be effective. The prolonged use of quite high doses is not uncommon. Bulking agents such as psyllium husk may also be useful.

Non-Hodgkin's lymphoma

People with HIV infection have a 250- to 650-fold increased risk of AIDS-related lymphoma over the background population, with lymphoma occurring most frequently in people with CD4 cell counts below 100 cells/µL. Eighty-five percent of all AIDS-related lymphomas are systemic non-Hodgkin's lymphoma (SNHL), 15% are primary central nervous system lymphoma (PCNSL), while primary effusion lymphomas occur uncommonly. Almost all AIDS-related lymphomas are high-grade diffuse large B-cell (immunoblastic variant) or Burkitt's-like lymphomas. EBV has a clear pathogenetic role in PCNSL, a probable role in SNHL, and also may be involved in primary effusion lymphoma where HHV-8 is implicated in disease pathogenesis. Isolated enlarged lymph nodes, systemic febrile illnesses and focal neurological abnormalities are among the common presentations. Referral to specialists in oncology and HIV-related malignancies is recommended. Chemotherapy, radiotherapy and combination antiretroviral treatment provide the usual basis of therapy.

Neurological conditions

The direct effects of HIV on the brain can be evident at any level of immune function but may become more prominent as the disease progresses. Minor cognitive deficits are quite common and, in the absence of treatment, a significant minority of people with HIV infection will develop a clinical brain disorder. In the early phase, this may manifest as a syndrome that is almost indistinguishable from mania, but a progressive, subcortical dementia commonly evolves. The condition is characterised particularly by extreme slowness of movement and mentation which are severely disabling. HIV-associated dementia often responds dramatically to antiretroviral treatment; however, the regimen must be carefully chosen as only some of the available agents penetrate the blood-brain barrier.

Space-occupying lesions of the brain also are relatively common in people with advanced HIV infection. The most likely diagnoses are primary lymphoma of the brain and abscess resulting from reactivation of toxoplasmosis. Toxoplasma abscesses respond to appropriate antibiotic therapy, so early diagnosis is important.

Other neurological conditions that were common in the days before combination antiretroviral therapy are cryptococcal meningitis and progressive multifocal leukoencephalopathy.

Referral to an infectious diseases physician is recommended when a neurological condition is suspected in a patient with HIV infection.

Body composition changes

Weight loss and preferential loss of lean body tissue is characteristic of progressive HIV infection and was common in people with AIDS in the 1980s and early 1990s. Although this condition is still seen in people who are unable to tolerate antiretroviral medication, or where viral resistance limits its effectiveness, most bodily changes in people with HIV infection now appear to be related to treatment.

Loss of facial and peripheral fat can be striking in people taking antiretroviral therapy, creating a distinctive and easily identifiable appearance (Figure 6.4). Patients may sometimes complain first of 'varicose veins' when their healthy leg veins become more obvious as the surrounding subcutaneous tissue is lost. The latest research suggests that this syndrome may be related in part to prolonged exposure to nucleoside analogue reverse transcriptase inhibitor (NRTI) drugs.[6]

A proportion of people with HIV infection on therapy also develop accumulation of fat in the abdomen and sometimes the 'buffalo hump' over the lower neck posteriorly. Protease inhibitors are associated with marked dyslipidaemia in a high proportion of patients and also may be involved in this fat accumulation.

Psychosocial issues

In cases where clinical signs and symptoms lead to a HIV diagnosis, consideration should be given to the management of psychosocial concerns as well as the clinical manifestations of the infection. Post-test discussion and psychosocial follow-up are fundamental following a positive HIV result and issues for assessment and discussion may include relationships, family, sex, work and disclosure (Chapter 9).

People with HIV infection now face a variety of serious challenges, including new manifestations of HIV-related illnesses and medication-related toxicities. While improved prognosis has led some patients with HIV infection to reassess issues such as education, work and relationships, difficulty with adherence to therapies and chronic toxicities have in some cases led to a re-evaluation of lifestyle, self-image or sense of wellbeing. In addition, the challenges of living with a chronic or life-threatening condition, HIV infection itself and some medications' side effects may induce symptoms of depression or anxiety which require acknowledgment and management (Chapter 10).

FIGURE 6.4 Body composition changes

Conclusion

Although the rate of HIV infection in Australia is relatively low, the primary care clinician may give consideration to HIV infection in relation to a range of conditions, particularly when present in young and otherwise healthy individuals. In the age of combination antiretroviral therapy, clinical diagnosis of HIV infection is likely to lead to improved health and extended lifespan in the patient.

While prescribing antiretroviral therapy requires special training, many people with HIV infection also visit general practitioners, who are ideally placed to detect adverse developments at an early stage and to facilitate optimal therapy. Chapter 10 addresses management of the patient with HIV infection, particularly in regard to antiretroviral therapy, psychosocial management, and support and referral.

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