Lepr Rev (2002) **73,** 197–205

FURTHER EDUCATION SERIES—HIV

Clinical features of HIV disease in developing countries

A. GRANT
Senior Lecturer, London School of Hygiene and Tropical Medicine, and Honorary Consultant Physician, Hospital for Tropical Diseases, London, UK

Accepted for publication 24 April 2002

Summary HIV disease progresses from an asymptomatic period of variable duration, through mild symptoms, to severe disease characteristic of cellular immunodeficiency. The rate of progression from infection to severe disease is probably similar world-wide. However, individuals in developing countries have more symptomatic disease, in keeping with the high incidence of morbidity in the general population, and poor survival with advanced disease. The clinical manifestations of severe HIV-related immunosuppression vary with geographical region. Tuberculosis (TB) is the most important severe opportunistic disease in developing countries: the clinical presentation may differ from TB in the immunocompetent. Bacterial infections, particularly due to *Streptococcus pneumoniae* and non-typhoid *Salmonella* spp., are also important causes of morbidity and mortality. Fungal diseases such as *Pneumocystis carinii* pneumonia (PCP), cryptococcosis, histoplasmosis and penicilliosis vary in prevalence in different geographical regions. A high index of suspicion of HIV infection and knowledge of the local spectrum of HIV disease are important for early diagnosis and appropriate management of HIV-related disease.

Introduction

In industrialized countries, the clinical features of human immunodeficiency virus (HIV) disease have been described comprehensively. There is less detailed information from developing countries, where the burden of disease falls most heavily, largely because of limited access to the expensive diagnostic facilities required to make definitive diagnoses of many HIV-related diseases.

Natural history of HIV disease

As described in an earlier article in this series,[1] in the absence of antiretroviral therapy, HIV infection results in progressive loss of immune function. Typically the clinical course

Correspondence to: Alison Grant, Clinical Research Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK (e-mail: alison.grant@lshtm.ac.uk)

0305-7518/02/064053+07 $1.00

comprises an asymptomatic period of variable length, followed by the onset of diseases characteristic of cellular immunodeficiency. The term 'AIDS' (acquired immunodeficiency syndrome) is often used to describe advanced HIV disease with severe immunosuppression. However, AIDS includes a wide range of conditions, some of which can occur relatively early in the course of HIV infection, and others are only seen in very advanced disease. Case definitions for AIDS were introduced in the early 1980s, before HIV was identified, to allow epidemiological investigations into the cause of this syndrome. Subsequently AIDS case definitions have been modified;[2–4] they are primarily intended for epidemiological purposes, to allow individuals with advanced immunosuppression to be identified for surveillance purposes. AIDS case definitions are not reliable as prognostic markers in individual patients; laboratory markers or clinical staging systems are required for this purpose. With the advent of antiretroviral therapy (ART), AIDS case definitions are becoming much less useful because many individuals with advanced disease start ART before they fulfill AIDS case definitions.

SEROCONVERSION

Some individuals experience a clinical illness shortly after acquiring HIV infection. This illness, referred to as seroconversion illness or acute (primary) HIV infection, usually occurs about 2 weeks after infection, and ranges in severity from minor symptoms to a severe illness requiring hospitalization. The best-recognized seroconversion syndrome is an illness with fever, lymphadenopathy and pharyngitis and resembles glandular fever, but the range of clinical features described is very wide, including diarrhoea, rash and lymphocytic meningitis. The majority of patients have a mild, self-limiting illness with few if any symptoms and do not seek medical attention. Symptomatic seroconversion and longer duration of seroconversion illness predict more rapid progression to advanced HIV disease. At the time of seroconversion, the concentration of HIV in the blood is very high, and individuals are highly infectious at this time. Patients with known or suspected seroconversion illness should be advised to modify their behaviour to minimize the risk of HIV transmission.

ASYMPTOMATIC PHASE

Following seroconversion, HIV-infected individuals remain asymptomatic for a variable period of time. This asymptomatic period was originally considered to be a 'latent period' in which the virus was inactive. It is now appreciated that viral replication continues rapidly during the asymptomatic phase but is initially contained by the activity of the immune system. The speed of progression to symptomatic disease varies widely between individuals. The main host factor determining the rate of disease progression is age at the time of infection, progression being faster among older individuals. In addition, the role of genetic determinants of the immune response is increasingly recognized.[1] There has been considerable debate concerning the effect of acute infectious diseases on the rate of progression. HIV viral load has been noted to be higher among individuals with acute infectious diseases, and it is proposed that this may accelerate HIV disease progression, especially in the case of tuberculosis. However, data from a small but well-conducted study of HIV-infected individuals in rural Uganda with well-defined dates of seroconversion suggests that the rate of progression from seroconversion to the onset of severe disease differs little from that observed in industrialized countries in the pre-antiretroviral era.[5] This observation suggests

that a high incidence of infectious disease, such as is experienced in rural Uganda, does not result in more rapid HIV disease progression. Survival with advanced disease is shorter in low-income countries because of lack of access to care.

Viral factors may also affect the rate of disease progression. HIV-2 is much less pathogenic than HIV-1; compared with HIV-negative individuals, mortality among HIV-2-infected adults is doubled,[6] whereas HIV-1-infection increases mortality 10-fold.[7] It follows logically that there could be differing rates of progression for different subtypes of HIV-1, but there is little evidence to support this idea.[8]

PROGNOSTIC MARKERS

The best markers of disease progression are the CD4+ lymphocyte count and the concentration of HIV RNA in peripheral blood (HIV 'viral load'). The CD4 count gives an indication of the degree of damage to the immune system and hence the risk of HIV-related disease, which increases as the CD4 count falls. (The normal range for CD4 counts varies by laboratory: for example, at University College London Hospitals, the quoted normal range is $270–1350 \times 10^6$/l. The normal range may also vary by ethnic group.) The viral load is an indicator of the speed of disease progression. Where these laboratory markers are not available, clinical staging systems developed by WHO/UNAIDS can be used:[9] these also have prognostic value.[10,11]

EARLY SYMPTOMATIC DISEASE

Early disease often manifests itself in the skin and mucous membranes. Skin manifestations include herpes zoster, molluscum contagiosum, seborrhoeic dermatitis and other fungal infections, and pruriginous dermatitis. In regions with high HIV prevalence, manifestations such as herpes zoster are highly predictive of HIV infection.[12] Oral manifestations include candidiasis, and hairy leukoplakia, a white lesion with a feathery appearance, usually on the lateral aspect of the tongue. Among women, amenorrhoea is a common early symptom. Constitutional symptoms such as fever, weight loss and diarrhoea, may occur. Bacterial infections, particularly pneumococcal disease, and tuberculosis (TB) can occur at any stage and although both become more frequent as HIV disease becomes more advanced, they are also important as causes of early morbidity.

ADVANCED DISEASE

As immunosuppression progresses, HIV-infected individuals become increasingly susceptible to supervening infections and tumours. In industrialized countries, severe disease is unusual until the CD4 count falls below 200×10^6/l, when individuals become at risk of disease due to opportunistic pathogens (organisms which have low pathogenic potential in immunocompetent individuals). In many developing countries, the predominant causes of HIV-related disease are ubiquitous pathogens such as *Mycobacterium tuberculosis* and bacteria of high pathogenicity (e.g. *S. pneumoniae* and non-typhoid *Salmonella* spp.) rather than opportunistic organisms. The spectrum of HIV-related disease varies by geographic region, as discussed in an earlier article in this series.[13] Table 1 shows common causes of HIV-related disease in Africa, Latin America and Asia. Comparisons between the studies summarized in the table must be made with caution because different study methods

Table 1. Spectrum of clinical disease among HIV-infected adults in Africa, Latin America and Asia

Region	Sub-Saharan Africa		Latin America	Asia	
Country	Côte d'Ivoire[14]	Kenya[15–17]	Brazil[18]	India[19]	Thailand[20]
Population	Hospitalized HIV+ patients[a]	HIV+ medical ward admissions	Patients with AIDS, specialist clinic	AIDS cases, national surveillance	Hospitalized patients with AIDS
No HIV+ patients	349	95	111	3551	1553
Tuberculosis	28%	18%	32%	62%	37%
Bacteraemia	18%	26%	–	–	<1%[b]
HIV wasting	11%	–	–	–	8%
Isosporiasis	7%	–	6%	–	0
Bacterial pneumonia	6%	16%[c]	16%	–	<1%[2]
Cerebral toxoplasmosis	6%	–	14%	3%	2%
Bacterial enteritis	5%	–	6%	–	–
Non-specific diarrhoea	5%	15%	–	–	–
Oesophageal candidiasis	3%	–	24%	57%[d]	3%
Cryptoccosis	2%	1%	5%	4%	38%
Kaposi's sarcoma	1%	2%	5%	<1%	<1%
Cytomegalovirus	0	–	5%[e]	1%	4%
PCP	0	–	22%	3%	5%
Cryptosporidiosis	0	–	8%	4%	2%
Penicilliosis	0	–	–	–	3%
Histoplasmosis	0	–	–	–	2%

–Indicates data not available. Patients could have more than one diagnosis.
[a]Patients admitted to infectious diseases and respiratory wards.
[b]Recurrent.
[c]'Acute cough and fever': 46% had pneumococci isolated from blood culture.
[d]Oral and oesophageal.
[e]CMV chorioretinitis.

were used, but the data illustrate the importance of TB and bacterial infections and highlight regional differences, particularly in fungal diseases.

Clinical manifestations of HIV disease in developing countries

RESPIRATORY MANIFESTATIONS

TB is the most important cause of serious respiratory disease in HIV-infected individuals in developing countries; a high index of suspicion is required, because the presentation may be atypical, as will be described later. Bacterial pneumonia is also important; *S. pneumoniae* is the most common cause, followed by other causes of community-acquired pneumonia common locally. *Pneumocystis carinii* pneumonia (PCP) is an important cause of morbidity in individuals with advanced disease in industrialized countries; it is also common in Asia and Latin America. By contrast, and for reasons that are not clear, PCP is unusual in adults in sub-Saharan Africa, despite being common in HIV-infected infants in this region. Other, less frequent, causes of respiratory disease include pulmonary Kaposi's sarcoma, nocardiosis and fungi including *Cryptococcus neoformans* and *Histoplasma capsulatum*.

GASTROINTESTINAL MANIFESTATIONS

Diarrhoea is a very common symptom. In studies to investigate the aetiology of diarrhoea among HIV-infected people, the most common causes include protozoa such as *Cryptosporidium parvum*, microsporidia and in some regions *Isospora belli*. Bacterial pathogens, particularly non-typhoid salmonellae, are also common, particularly in areas where sanitation is poor. Less often, *Entamoeba histolytica* and *Giardia lamblia* are found. In about 50% of cases, no cause is identified. In some cases, diarrhoea may be attributable to HIV itself. Cytomegalovirus can cause colitis in patients with advanced immunosuppression, but this is difficult to diagnose in low income settings. Kaposi's sarcoma and non-Hodgkin's lymphoma may involve the gastrointestinal tract. Oral and oesophageal candidiasis (causing pain on swallowing) are common world-wide.

NEUROLOGICAL MANIFESTATIONS

Meningitis is a frequent syndrome: in addition to the bacterial causes found in immunocompetent individuals, important pathogens include *Cryptococcus neoformans* and *Mycobacterium tuberculosis*. Space-occupying lesions are another frequent presenting syndrome. Likely aetiologies include cerebral toxoplasmosis, tuberculomata and lymphoma; the frequency of toxoplasmosis varies depending upon the prevalence of previous toxoplasma infection in the population. HIV itself can cause encephalopathy, which usually presents as a progressive dementia. Other cerebral lesions include cytomegalovirus encephalitis, and progressive multifocal leukoencephalopathy, a selective demyelination of cerebral white matter due to JC virus, causing a progressive focal neurological deficit such as hemiparesis or dysphasia. Cytomegalovirus can cause retinitis, with loss of vision if it affects the central retina; but this is rare until the CD4 count falls below 100×10^6/l and is relatively unusual in African countries, probably because of short survival with advanced disease. A range of peripheral nerve lesions is also common, in particular a symmetrical painful peripheral

neuropathy. This may be a result of pyridoxine deficiency, exacerbated by isoniazid in the context of treatment for tuberculosis, but may also be due to HIV itself.

FEVER WITHOUT CLEAR LOCALIZING SIGNS

In HIV-infected individuals who present with fever without clear signs to localize the source, TB should always be considered. In studies of HIV-infected patients admitted to hospital with fever in African countries, up to 42% have bacteraemia, particularly due to non-typhoid *Salmonella* spp. and *S. pneumoniae*.[21] Since facilities for blood cultures are often not available, bacteraemia is underdiagnosed.

Fungal diseases should also be considered. PCP can cause prominent fever, usually associated with breathlessness and dry cough. Cryptococcal disease most often manifests as meningitis, but can also present with fever, diffuse pneumonia or umbilicated skin lesions. Histoplasmosis may complicate advanced HIV infection, particularly in endemic areas (southern USA, Central and South America); the manifestations include fever and weight loss, hepatosplenomegaly, lymphadenopathy, respiratory symptoms and skin lesions. Penicilliosis (due to *Penicillium marneffei*) is a relatively frequent complication of advanced HIV disease in south-east Asia, presenting with fever, weight loss and generalised skin lesions, usually papules with central necrosis.

In the context of very advanced immunosuppression, disseminated infection with *Mycobacterium avium-intracellulare* and cytomegalovirus may cause fever; many organ systems may be involved. Definitive diagnosis of these infections requires access to laboratory facilities, which are often not available in low-income settings. In studies from Africa, even when appropriate diagnostic techniques are used, these infections are unusual, probably because survival at this stage of advanced immunosuppression is short. They are, however, more common in Asia and Latin America. In malarial areas, malaria must always be considered as a cause of fever; the interaction between HIV and malaria will be discussed later.

DERMATOLOGICAL MANIFESTATIONS

The skin is frequently affected at all stages of HIV disease, with manifestations ranging from bacterial, viral and fungal infections to tumours such as Kaposi's sarcoma. Drug eruptions are also more frequent in HIV infection. These will be considered in more detail in an article later in this series.

GYNAECOLOGICAL DISEASE

Amenorrhoea is very common in HIV-infected women and may be one of the earliest symptoms. Vaginal candidiasis is also common and may be recurrent. Pelvic inflammatory disease is more severe in the context of HIV infection. Cervical intraepithelial neoplasia is more common in HIV-infected women. In industrialized countries, HIV infection is associated with invasive cervical carcinoma. This association may be less strong in areas where there is limited access to ART and survival with advanced disease is short.

NEOPLASTIC DISEASE

The most common HIV-related neoplasms are Kaposi's sarcoma, caused by human herpesvirus 8, and non-Hodgkin's lymphoma. Kaposi's sarcoma usually presents as small,

flat or raised red, purple or black skin lesions, which are often multiple, initially painless and affect the limbs, trunk, face and hard palate. Kaposi's sarcoma may involve lymph nodes, resulting in peripheral lymphoedema. Visceral Kaposi's sarcoma may involve the respiratory tract, seen on chest radiography as coarse reticulonodular shadows in the lower zones, sometimes with pleural or pericardial effusions, which may be blood stained. It can also involve the gastrointestinal tract, and (very rarely) the central nervous system.

Non-Hodgkin's lymphoma can occur at a number of sites (lymph nodes, GI tract, central nervous system) and can occur in early as well as late disease. Squamous cell carcinoma of the conjunctiva is a rare cancer that is strongly associated with HIV infection; its incidence has increased dramatically in some countries in Eastern Africa in parallel with the HIV epidemic.

Interaction between HIV and endemic infectious disease in developing countries

TUBERCULOSIS

TB is undoubtedly the most important severe HIV-related disease worldwide. HIV infection is a powerful risk factor for TB: HIV-infected people are at increased risk both of reactivation of latent TB infection and of rapid progression from new TB infection to symptomatic disease. The clinical features of TB may be altered as HIV-related immunosuppression becomes more profound. In advanced HIV disease, pulmonary TB is less likely to cavitate and there is less upper lobe predominance, whereas diffuse infiltrates and lymphadenopathy are more common. The chest radiograph can also be normal. Extrapulmonary (particularly pleural and pericardial) and disseminated disease is more likely. A high index of suspicion of TB is needed in HIV-infected individuals. In an autopsy study from Africa, tuberculosis was the most common cause of death,[22] and should always be considered as a possible underlying cause of HIV wasting syndrome (defined as 10% or more loss of body weight plus fever and/or diarrhoea for at least 1 month).

LEISHMANIASIS

Visceral leishmaniasis is a relatively common complication of advanced HIV disease in Mediterranean countries, particularly among intravenous drug users, and is also seen in the north and east of Africa and in South America. Zymodemes of *Leishmania infantum*, which normally cause cutaneous disease, may cause visceral disease in the context of HIV-related immunosuppression.[23] As the prevalence of HIV infection increases in India, HIV-associated visceral leishmaniasis may become a major problem in areas where leishmaniasis is endemic.

MALARIA

HIV-infected pregnant women are at greater risk of malaria and of placental malaria than their uninfected counterparts. Children with malarial anaemia are at increased risk of acquiring HIV infection from transfused blood if this is not adequately screened. Recent studies from Uganda have shown that the prevalence of malarial parasitaemia and of clinical malaria increase with decreasing CD4 count.[24,25] However, malaria is not a common cause of mortality in HIV-infected individuals, and the significance of these observations is not yet clear.

CHAGAS' DISEASE

In Latin America, asymptomatic infection with *Trypanosoma cruzi* may reactivate in the context of HIV-related immunosuppression. This may manifest as meningoencephalitis, or one or more cerebral mass lesions. Myocarditis is a common histological finding at autopsy, but is rarely apparent clinically.[26]

ENDEMIC DISEASES APPARENTLY NOT INTERACTING WITH HIV INFECTION

A number of diseases endemic in tropical countries might be expected to interact with HIV infection, but appear not to do so: these include leprosy, African trypanosomiasis, strongyloidiasis and amoebiasis.

Conclusions

Among HIV-infected individuals in developing countries, much disease is caused by infections that are also common in the HIV-negative population, particularly TB and bacterial infections. In populations with a lower incidence of endemic infectious diseases and better access to care, disease due to opportunistic pathogens becomes more important. The spectrum of disease varies with geographic region, and knowledge of conditions common locally is crucial to guide appropriate strategies of management, especially if access to diagnostic facilities is limited.

Further reading

Adler MW (ed) *ABC of AIDS*. BMJ Publishing, London, 2001.

Cahn P, Belloso WH, Murillo J, Prada-Trujillo G. AIDS in Latin America. *Infect Dis Clin North Am*, 2000; **14**: 185–209.

Clezy K, Sirisanthana T, Sirisanthana V, Brew B, Cooper DA. Late manifestations of HIV in Asia and the Pacific. *AIDS*, 1994; **8**: S35–S43.

Grant AD, Djomand G, De Cock KM. Natural history and spectrum of disease in adults with HIV/AIDS in Africa. *AIDS*, 1997; **11**: S43–S54.

Grant AD, Katabira ET, Marum LH, De Cock KM. HIV/AIDS. In: Parry E, Godfrey R, Mabey D, Gill G (eds) *Principle of medicine in Africa*, 3rd edition. Cambridge University Press, Cambridge, 2002 (in press).

Kaplan JE, Hu DJ, Holmes KK *et al.* Preventing opportunistic infections in human immunodeficiency virus-infected persons: implications for the developing world. *Am J Trop Med Hyg*, 1996; **55**: 1–11.

References

1 Cowley S. The biology of HIV infection. *Lepr Rev*, 2001; **72:** 212–220.

2 World Health Organization. Acquired immunodeficiency syndrome (AIDS): WHO/CDC case definition for AIDS. *Weekly Epidemiol Rec*, 1986; **61:** 69–73.

3 Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR*, 1992; **41:** 1–19.

4 World Health Organization. WHO case definitions for AIDS surveillance in adults and adolescents. *Weekly Epidemiol Rec*, 1994; **69:** 273–280.

5 Morgan D, Mahe C, Mayanja B, Whitworth JAG. Progression to symptomatic disease in people infected with HIV-1 in rural Uganda: prospective cohort study. *BMJ*, 2002; **324:** 193–197.

6 Poulsen A-G, Aaby P, Larsen O *et al*. 9-year HIV-2-associated mortality in an urban community in Bissau, west Africa. *Lancet*, 1997; **349:** 911–914.

[7] Nunn AJ, Mulder DW, Kamali A *et al.* Mortality associated with HIV-1 infection over five years in a rural Ugandan population: cohort study. *BMJ*, 1997; **315:** 767–771.

[8] Hu DJ, Buvé A, Baggs J *et al.* What role does HIV-1 subtype play in transmission and pathogenesis? An epidemiological perspective. *AIDS*, 1999; **13:** 873–881.

[9] World Health Organization. Acquired immunodeficiency syndrome (AIDS): interim proposal for a WHO staging system for HIV infection and disease. *Wkly Epidemiol Rec*, 1990; **65:** 221–224.

[10] Malamba SS, Morgan D, Clayton T *et al.* The prognostic value of the World Health Organization staging system for HIV infection and disease in rural Uganda. *AIDS*, 1999; **13:** 2555–2562.

[11] French N, Mujugira A, Nakiyingi J *et al.* Immunologic and clinical stages in HIV-1-infected Ugandan adults are comparable and provide no evidence of rapid progression but poor survival with advanced disease. *J Acquir Immune Defic Syndr*, 1999; **22:** 509–516.

[12] Mayanja B, Morgan D, Ross A, Whitworth J. The burden of mucocutaneous conditions and the association with HIV-1 infection in a rural community in Uganda. *Trop Med Int Health*, 1999; **4:** 349–354.

[13] Lucas SB. The pathology of HIV infection. *Lepr Rev*, 2002; **73:** 64–71.

[14] Grant AD, De Cock KM. The growing challenge of HIV/AIDS in developing countries. *Br Med Bull*, 1998; **54:** 369–381.

[15] Gilks CF, Brindle RJ, Otieno LS *et al*. Extrapulmonary and disseminated tuberculosis in HIV-1-seropositive patients presenting to the acute medical services in Nairobi. *AIDS*, 1990; **4:** 981–985.

[16] Gilks CF, Brindle RJ, Otieno LS *et al*. Life-threatening bacteraemia in HIV-1 seropositive adults admitted to hospital in Nairobi, Kenya. *Lancet*, 1990; **336:** 545–549.

[17] Gilks CF, Otieno LS, Brindle RJ *et al*. The presentation and outcome of HIV-related disease in Nairobi. *Q J Med*, 1992; **82:** 25–32.

[18] Moreira ED, Silva N, Brites C *et al*. Characteristics of the acquired immunodeficiency syndrome in Brazil. *Am J Trop Med Hyg*, 1993; **48:** 687–692.

[19] Misra SN, Sengupta D, Satpathy SK. AIDS in India: recent trends in opportunistic infections. *Southeast Asian J Trop Med Public Health*, 1998; **29:** 373–376.

[20] Tansuphaswadikul S, Amornkul PN, Tanchanpong C *et al*. Clinical presentation of hospitalized adult patients with HIV infection and AIDS in Bangkok, Thailand. *J Acquir Immune Defic Syndr*, 1999; **21:** 326–332.

[21] Grant AD, Katabira ET, Marum LH, De Cock KM. HIV/AIDS. In: Parry E, Godfrey R, Mabey D, Gill G (eds) *Principles of medicine in Africa* (3rd edition). Cambridge University Press, Cambridge, 2002 (in press).

[22] Lucas SB, Hounnou A, Peacock C *et al*. The mortality and pathology of HIV infection in a West African city. *AIDS*, 1993; **7:** 1569–1579.

[23] Herwaldt BL. Leishmaniasis. *Lancet*, 1999; **354:** 1191–1199.

[24] Whitworth J, Morgan D, Quigley M *et al*. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. *Lancet*, 2000; **356:** 1051–1056.

[25] French N, Nakiyingi J, Lugada E *et al.* Increasing rates of malarial fever with deteriorating immune status in HIV-1-infected Ugandan adults. *AIDS*, 2001; **15:** 899–906.

[26] Cahn P, Belloso WH, Murillo J, Prada-Trujillo G. AIDS in Latin America. *Infect Dis Clin N Am*, 2000; **14:** 185–209.