AIDS: Clinical Manifestations

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In the course of time human immunodeficiency virus (HIV) notably affects the host's immune system. As a result, HIV-infected people can experience a wide range of clinical manifestations, especially if the infection is not being treated duly with combination antiretroviral therapy (cART). At such an advanced stage of the disease, patients eventually face severe illnesses. Of these, more than 20 conditions, including opportunistic infections and malignancies, have been classified as AIDS (acquired immune deficiency syndrome)-defining illnesses to date. Recently, clinical research has also focused on serious non-AIDS-related events (SNAEs). This term refers to an increasing rate of illnesses such as cardiovascular, liver and renal diseases as well as neoplasms occurring in long-term-treated patients on the basis of longer life expectancy. However, there are still significant differences in access to and availability of antiretroviral therapy throughout the world which leads to contrasting patterns in the spectrum of AIDS-defining illnesses in resource-limited settings and developed countries.

Introduction

The first cases of a new disease, which became known subsequently as acquired immune deficiency syndrome (AIDS) were identified in 1980 and were presented as case reports in the medical literature in 1981 (Gottlieb *et al*., 1981; Hymes *et al*., 1981). Following these initial descriptions of Kaposi sarcoma (KS) and *Pneumocystis carinii* pneumonia (PCP), several other opportunistic infections were identified as occurring among predominantly homosexual men and injecting drug users. By 1982, the initial surveillance case definition of AIDS was released by the Centers for Disease Control and Prevention (CDC) (Centers for Disease Control, 1982). **See also**: Acquired Immune Deficiency Syndrome (AIDS); Human Immunodeficiency Viruses (HIV)

This article covers the changes in the AIDS case definition as increasing knowledge accumulated of the clinical manifestations arising from human immunodeficiency virus (HIV)-induced immunodeficiency. The changing spectrum of AIDS clinical manifestations since the introduction of opportunistic infection prophylaxis and antiretroviral therapy is detailed, along with determinants for the clinical spectrum of AIDS-defining illness. The contrast between the clinical spectrum of AIDS-defining illnesses in industrialized and developing (where more than 90% of people with HIV infection are living) countries is also described.

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AIDS Surveillance Definitions

In 1982, a case definition was published by the CDC in Atlanta, Georgia. This surveillance definition required the 'reliable diagnosis of a disease that was moderately predictive of a defect in cell-mediated immunity in the absence of known causes of immune deficiency'. The

Table 1 Surveillance definitions of acquired immune deficiency syndrome

Infection or cancer	Site
1982	
Cryptosporidiosis	Stools (diarrhoea for >1 month)
Pneumocystis carinii (now: *P. jiroveci*)	Lungs
Strongyloidosis	Other than gastrointestinal tract
Toxoplasmosis	Other than liver, spleen, lymph nodes
Candidiasis	Oesophagus
Cryptococcosis	CNS or disseminated
Mycobacterium avium	Other than lungs, lymph nodes
Mycobacterium kansasii	Other than lungs, lymph nodes
Cytomegalovirus	Other than liver, spleen, lymph nodes
Herpes simplex virus	Mucocutaneous (chronic), lungs, gastrointestinal tract
Progressive multifocal leucoencephalopathy	Brain
Kaposi sarcoma	All (in persons <60 years)
Lymphoma	Brain
1985	
The above diseases plus the following with laboratory evidence of HIV infection	
Histoplasmosis	Disseminated
Candidiasis	Bronchi, lungs
Isosporiasis	Gastrointestinal tract
Non-Hodgkin lymphoma	All
Kaposi sarcoma	All (in persons >60years)
Lymphoid interstitial pneumonitis	Lungs (in children <13 years)
1987	
All the above diseases plus the following with laboratory evidence of HIV infection	
Multiple pyogenic bacteria	All (in children <13 years)
Coccidioidomycosis	All
HIV encephalopathy	Brain
Mycobacterium tuberculosis	Extrapulmonary
HIV wasting syndrome	Not applicable
Salmonella bacteraemia	Blood
Presumptive diagnoses of	
Candidiasis	Oesophagus
Cytomegalovirus	Eyes
Kaposi sarcoma	All
Mycobacteriosis	Disseminated
P. carinii (now: *P. jiroveci*)	Lungs
Toxoplasmosis	Brain
Lymphoid interstitial pneumonitis	Lungs
1993	
All the above diseases plus the following with laboratory evidence of HIV infection	
M. tuberculosis	Lungs
Recurrent bacterial pneumonia	Lungs
Invasive cervical cancer	Cervix

Notes: CNS, central nervous system and HIV, human immunodeficiency virus.
Source: Centers for Disease Control (1982, 1985, 1987, 1993).

diseases that were indicative of AIDS were specified and included 10 opportunistic infections and 2 cancers (**Table 1**).

Since the isolation in 1983 of the virus that caused AIDS (Barré-Sinoussi *et al*., 1983), subsequently named human immunodeficiency virus type 1 (HIV-1), there have been three further revisions of the surveillance definition of AIDS, in 1985, 1987 and 1992 (Centers for Disease Control, 1985, 1987, 1993) with the addition of several further diseases (**Table 1**). **See also**: Human Immunodeficiency Viruses (HIV)

Table 2 1993 Revised classification system for HIV infection and expanded AIDS surveillance case definition for adolescents and adults

	Clinical categories		
CD4+ T-cell categories	(A) Asymptomatic, acute (primary) HIV or PGL	(B)[a] Symptomatic, not (A) or (C) conditions	(C)[b] AIDS indicator conditions
(1) $>500\,\mu L^{-1}$	A1	B1	C1
(2) $200–499\,\mu L^{-1}$	A2	B2	C2
(3) $<200\,\mu L^{-1}$ AIDS indicator T-cell count	A3	B3	C3

Notes: Shaded cells illustrate the expanded AIDS surveillance case definition. Persons with AIDS indicator conditions (category C), as well as those with CD4+ T-lymphocyte counts $<200\,\mu L^{-1}$ (categories A3 or B3), were reportable as AIDS cases in the United States and territories from 1 January 1993.

[a]Category B conditions include: bacillary angiomatosis; candidiasis, oropharyngeal (thrush); candidiasis, vulvovaginal – persistent, frequent or poorly responsive to therapy; cervical dysplasia (moderate or severe), cervical carcinoma *in situ*; constitutional symptoms, such as fever (38.5°C) or diarrhoea lasting >1 month; hairy leucoplakia, oral; herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome; idiopathic thrombocytopenic purpura; listeriosis; pelvic inflammatory disease and peripheral neuropathy.

[b]AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus and PGL, persistent generalized lymphadenopathy.

Source: Centers for Disease Control (1993).

The 1993 CDC revision (**Table 2**) emphasized the clinical importance of the CD4+ T lymphocyte count in the categorization of HIV-related clinical conditions. Thus, the AIDS surveillance case definition was expanded to include all HIV-infected persons with fewer than 200 CD4+ T lymphocytes per microlitre (μL) or a CD4+ T lymphocyte percentage of total lymphocytes of less than 14%. This expansion also included the addition of three clinical conditions – pulmonary tuberculosis, recurrent pneumonia and invasive cervical cancer – and retained the 23 clinical conditions in the AIDS surveillance case definition published in 1987 (Centers for Disease Control, 1987). **See also**: T Lymphocytes: Helpers

To take into account that recent advances in HIV treatment had slowed the progression of HIV disease the CDC issued 'Guidelines for National Human Immunodeficiency Virus Case Surveillance' in 1999 which incorporated the revised 1993 AIDS surveillance definitions (Centers for Disease Control, 1999a, b).

As the majority of AIDS-defining illnesses under the CDC surveillance definition require diagnostic services beyond the capacity of most developing countries, in 1990 (interim) and 1994 (expanded) the World Health Organization (WHO) formulated separate clinical case definitions for AIDS which formed the basis of AIDS surveillance in subSaharan Africa and other resource-poor settings (World Health Organization, 1994). In the following years, confusion between clinical staging definitions and surveillance definitions for HIV/AIDS increased so that in 2005 (interim) and 2007 (final) the WHO issued a revision combining both (**Table 3** and **Table 4**) (World Health Organization, 2005, 2007).

Clinical Manifestations of AIDS

The importance of defining locally the clinical spectrum of AIDS is highlighted by the considerable variation in the reported clinical spectrum of AIDS-defining illnesses in countries of North America, Europe, subSaharan Africa and the Asia-Pacific region (**Table 5**) (Ansari *et al*., 2002; Mocroft *et al*., 2000; Dore *et al*., 2002; Zhou *et al*., 2005; Centers for Disease Control, 1999a, b). These clinical spectra are derived predominantly from hospital-based clinic sites in each country, although some are based on routine AIDS surveillance data.

The most obvious distinguishing feature within this spectrum is the division between industrialized and developing countries, with PJP (formerly PCP) the major AIDS-defining illness in the United States, Europe and Australia, in contrast to tuberculosis as the major AIDS-defining illness in Thailand and Botswana (**Table 5**), and in clinical series from several other developing countries in Asia and subSaharan Africa (Grant *et al*., 1997; Zhou *et al*., 2005). Fungal infections, in particular oral–oesophageal candidiasis and cryptococcal disease, are relatively common in both industrialized and developing settings. **See also**: AIDS as a World Health Problem

Tuberculosis

With more than 90% of global HIV infection occurring in the developing world, and a prevalence of tuberculosis of 30–50% in the AIDS clinical series of many developing countries (see **Table 5**), tuberculosis represents the most common AIDS-defining illness on a global scale. The impact of the HIV epidemic on the incidence of tuberculosis has been clearly demonstrated in both subSaharan Africa and Asia, where several countries have experienced an increased incidence of cases.

In the United States and Europe, although tuberculosis occurs at a lower rate than in developing country settings among people with HIV infection, some groups are at particular risk. These include injecting drug users, the homeless and people born in countries with high

Table 3 WHO clinical staging of HIV/AIDS for adults and adolescents with confirmed HIV infection

Clinical stage 1
Asymptomatic
Persistent generalized lymphadenopathy
Clinical stage 2
Moderate unexplained weight loss (< 10% of presumed or measured body weight)
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulceration
Papular pruritic eruptions
Seborrhoeic dermatitis
Fungal nail infections
Clinical stage 3
Unexplained severe weight loss (> 10% of presumed or measured body weight)
Unexplained chronic diarrhoea for longer than 1 month
Unexplained persistent fever (approximately 37.6°C intermittent or constant, for longer than 1 month)
Persistent oral candidiasis
Oral hairy leucoplakia
Pulmonary tuberculosis (current)
Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained anaemia, neutropaenia or chronic thrombocytopaenia
Clinical stage 4
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal for longer than 1 month or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis
Disseminated nontuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis (with diarrhoea)
Chronic isosporiasis
Disseminated mycosis (coccidiomycosis or histoplasmosis)
Recurrent nontyphoidal *Salmonella* bacteraemia
Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

Source: Adapted from World Health Organization (2007).

background rates of tuberculosis, such as eastern European states.

The clinical features of AIDS-related tuberculosis differ somewhat from those of tuberculosis occurring among non-HIV-infected persons. These include a younger age distribution, a higher proportion of extrapulmonary tuberculosis, less cavitatory pulmonary disease, a higher proportion of smear-negative pulmonary disease and a substantially greater 12-month mortality rate. A large proportion of HIV wasting (previously commonly known

as 'slim' disease) in subSaharan African countries can be attributed to disseminated tuberculosis. **See also**: Tuberculosis

Pneumocystis jiroveci (formerly *Pneumocystis carinii*) pneumonia

Although previously described in non-HIV-infected immunocompromised patients, *Pneumocystis jiroveci* pneumonia (PJP) (formerly PCP) became a major opportunistic infection with the emergence of AIDS in the 1980s. Since the initial descriptions of cases of PJP among homosexual men in San Francisco and New York, this almost exclusively pulmonary infection has remained the most common AIDS-defining illness in industrialized countries (see **Table 5**). The increasing use of co-trimoxazole and other agents as prophylaxis against PJP has led to a significant decline in the risk of PJP among people with HIV infection in the 1990s (Dore *et al*., 2002), but in those presenting with advanced or undiagnosed HIV infection, in particular, PJP still persists as a major cause of AIDS-related morbidity and mortality.

The lower rate of reported PJP in clinical series from subSaharan Africa and Asia (**Table 5**) may reflect a lack of diagnostic capability. However, even in autopsy series from subSaharan Africa, with specific staining for detection of *P. jiroveci*, the prevalence of PJP was considerably lower than in AIDS clinical series from industrialized countries (Ansari *et al*., 2002). **See also**: Pneumocystis

Table 4 Criteria for diagnosis of advanced HIV (including AIDS) for reporting

Clinical criteria for diagnosis of advanced HIV in adults with confirmed HIV infection: presumptive or definitive diagnosis of any stage 3 or stage 4 condition (**Table 3**)
and/*or*;
Immunological criteria for diagnosing advanced HIV in adults with confirmed HIV infection:
CD4 count less than 350 per mm^3 of blood in an HIV-infected adult

Source: Adapted from World Health Organization (2007).

Bacterial infections

Recurrent bacterial pneumonia was included in the CDC 1993 revised AIDS case surveillance definition (Centers for Disease Control, 1993). Although bacterial organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus*, which commonly cause pneumonia in immunocompetent patients, are also causative organisms for pneumonia in people with HIV, Gram-negative organisms such as *Pseudomonas* spp. are often isolated from patients with HIV-related pneumonia. In addition to mixed bacterial flora, pneumonia in people with HIV often includes mixed pathology with fungal and *P. jiroveci*

Table 5 Spectrum of AIDS-defining illnesses among adults in selected countries and regions

AIDS illness	Australia[a] ($n = 2043$) Initial	Europe[b] ($n = 1667$)	Botswana[c] ($n = 104$) Autopsy	Asia-Pacific[d] ($n = 1166$)	United States[e] ($n = 12\,982$) Initial	United States[e] ($n = 12\,982$) Total
Pneumocystis carinii/*jiroveci* pneumonia	26.1	9	11	31.4	36	53
Tuberculosis	2.3	–	40	54.5	7	11
Oesophageal candidiasis	15.5	16	–	7.5	12	24
Cryptococcosis	3.6	–	7	6.8	4	8
Toxoplasmosis	3.2	–	1	6.1	3	7
Cytomegalovirus disease	3.6	8	15	1	7	33
Mycobacterium avium complex	6.6	6	2	4.4	6	30
AIDS dementia	5.8	7	–	0.4	4	14
Kaposi sarcoma	9.7	7	11	0.6	12	23
Non-Hodgkin lymphoma	5.4	6	3	0.8	3	6
Cryptosporidiosis	2	–	–	1.4	3	6
HIV wasting disease	10.5	7	–	3	8	21
Bacterial pneumonia	1.6	–	23	1	3	7

Notes: Values are percentages. Initial, initial AIDS-defining illnesses and total, all AIDS-defining illnesses.
[a]AIDS cases over the period 1996–2000 (Dore *et al*., 2002).
[b]AIDS cases from 51 centres in Europe over the period 1994–1998 (Mocroft *et al*., 2000).
[c]Pathological findings among HIV-positive cases in Botswana in 1997–1998 (Ansari *et al*., 2002).
[d]AIDS-defining illnesses from 11 sites in the Asia-Pacific region by May 2004 (Zhou *et al*., 2005).
[e]AIDS cases from sentinel surveillance 1992–1997 (Centers for Disease Control, 1999a, b).

infections. **See also**: Respiratory System: Bacterial Infections

Salmonella septicaemia appears to be a common HIV-related condition in developing countries, particularly among children with HIV infection. In contrast to the majority of HIV-related opportunistic infections, bacterial sepsis is common at all levels of immunodeficiency. Risk factors for HIV-related bacterial infection include neutropenia, hospitalization and injecting drug use. **See also**: Neutropenia

Fungal infections

Oropharyngeal candidiasis, a relatively early clinical manifestation of HIV infection, develops in the majority of people with HIV infection, and when present predicts more rapid progression to AIDS. Oesophageal candidiasis, an AIDS-defining illness, is associated with more severe immunodeficiency and, like cryptococcosis, appears to be relatively common within industrialized and developing countries. Although a diagnosis can be made on presumptive grounds in a person with oral candidiasis and odonyphagia, a definitive diagnosis requires endoscopy. This may explain the relatively low rate of reported oesophageal candidiasis in some clinical series from developing countries.

Cryptococcosis appears to be an important AIDS-related illness in both industrialized and developing countries. In the United States, Europe and Australia, cryptococcosis, the vast majority of which presents as cryptococcal meningitis, represents 3–5% of initial AIDS-defining illness (**Table 5**), with a further 4% developing the disease subsequent to an AIDS diagnosis. Cryptococcosis appears to be rather common in subSaharan Africa and the Asia-Pacific region, representing approximately 7% of initial AIDS-defining illnesses. In people with HIV infection, cryptococcosis is almost exclusively due to infection with *Cryptococcus neoformans* var. *neoformans*, which has been isolated from soil and pigeon excrement in various parts of the world. The other major strain, *C. neoformans* var. *gattii*, is seen only rarely among people with HIV infection, even in areas where it is commonly isolated from immunocompetent patients.

Disseminated infection with the fungus *Penicillium marneffei* (penicilliosis) has been reported from southern China, Thailand and other areas of Southeast Asia. Although occasionally reported among people without HIV infection, penicilliosis has both a more rapid onset and more severe clinical picture when associated with HIV infection. The substantial geographical variation of this fungal infection is evidenced by the contrasting incidence, even within Thailand. In the northern region of Thailand it is one of the major AIDS-defining illnesses; however, in Bangkok and other areas of Thailand it is relatively uncommon (Lee, 2008).

Other AIDS-related fungal infections include aspergillosis, histoplasmosis and coccidioidomycosis. Disseminated histoplasmosis is common among people with HIV infection in South America and areas of the United States. Thus, fungal infections constitute a considerable proportion of HIV-related morbidity in both industrialized and developing countries. **See also**: Fungal Pathogens of Humans

Gastrointestinal disease

AIDS-defining gastrointestinal disease includes Cytomegalovirus (CMV) disease (oesophagitis, gastritis and colitis) and chronic cryptosporidiosis; however, several other organisms are responsible for gastrointestinal symptoms in people with HIV. These include protozoal agents such as microsporidia, *Isospora belli* and *Entamoeba histolytica*. **See also**: Cryptosporidiosis

HIV-related cholangiopathy generally presents with right upper quadrant abdominal pain and is diagnosed by the presence of features including papillary stenosis, common bile duct dilatation and intrahepatic cholangitis on imaging of the biliary system. *Cryptosporidium* spp. is commonly isolated in association with HIV-related cholangiopathy, although microsporidia and CMV may also be aetiological agents.

Neurological disease

In industrialized countries, AIDS dementia complex (ADC) is the initial AIDS illness in approximately 5% of AIDS cases, with a lifetime-estimated risk of 10–20% (**Table 5**). ADC presents as a progressive cognitive and motor deficit, and, although supported by the presence of cerebral atrophy on cerebral imaging and/or an increase in cerebrospinal fluid markers (β2-microglobulin and neopterin), the diagnosis is made on clinical grounds. The apparent absence of ADC in many clinical series from developing countries may reflect either the lack of awareness of the diagnosis or again may be related to the relative lack of survival to very advanced immune deficiency; as with CMV and *Mycobacterium avium* complex (MAC), ADC generally presents when the CD4 cell count is less than $50\,\mu L^{-1}$. Since the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s the incidence of ADC has fallen markedly. However, the prevalence of ADC among patients with AIDS increased from 5.2% in the pre-HAART era to 6.8% post-HAART which is directly attributable to an increased survival in patients (Dore *et al.*, 2003).

Toxoplasmosis occurs in 5–10% of people with AIDS in developed countries (**Table 5**), depending on the background prevalence of the causative protozoal agent *Toxoplasma gondii*, higher in European countries than in North America. Cerebral toxoplasmosis constitutes the vast majority of cases of AIDS-related toxoplasmosis, although retinal, pulmonary and cardiac cases are also seen. Based on autopsy series from subSaharan Africa, toxoplasmosis also appears to be a fairly common AIDS illness in developing countries, with the absence of cerebral

imaging techniques being an explanation for underdiagnosis in some clinical series. **See also**: Toxoplasmosis

Other AIDS-defining CNS neurological conditions include cryptococcal meningitis, primary CNS lymphoma, and progressive multifocal leucoencephalopathy. Although not AIDS-defining, peripheral neurological disorders such as myelopathy, polyradiculopathy and peripheral neuropathy are common disorders in advanced HIV disease. **See also**: AIDS and the Nervous System

AIDS-defining malignancies

Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL) are considerably more common among people with HIV infection than in the general population. Fortunately incidence rates have been decreasing since the introduction of combination antiretroviral therapy (cART) in 1996 (Grulich, 2000). **See also**: Non-Hodgkin Lymphomas

In industrialized countries AIDS-associated KS has been seen predominantly among homosexual men, with a prevalence of 20–30% in some AIDS clinical series. The prevalence among other HIV exposure groups is considerably lower. The only region where KS is relatively common among people with heterosexually acquired HIV infection is subSaharan Africa, where KS was present before the HIV epidemic (African endemic KS). In contrast, most developing countries of the Asia-Pacific region do not have pre-existing endemic KS (**Table 5**) which almost certainly explains the low prevalence of KS in clinical series. *Human herpes virus 8* (HHV-8) is the probable causative agent for KS, with demonstration of HHV-8 in the vast majority of KS tissue specimens examined and serological evidence of infection strongly predicting subsequent development of KS. **See also**: Herpesviruses (Human); Oncogenic Viruses

Approximately 6% of people with AIDS in industrialized countries develop NHL (**Table 5**), with Burkitt lymphoma, large-cell immunoblastic NHL and primary central nervous system (CNS) lymphomas described. The latter form of NHL is associated with more advanced immune deficiency, and carries the poorest prognosis. In contrast, NHL has been relatively uncommon in clinical and autopsy series from developing countries in subSaharan Africa and Asia. **See also**: Leukaemias and Lymphomas; Non-Hodgkin Lymphomas

Cervical cancer was included in the AIDS case definition in 1993 and, although its HIV-related risk is possibly only 2–3-fold higher, the relative frequency of this malignancy in the general population makes it a significant public health issue for women with HIV infection.

Serious non-AIDS-related illnesses

Owing to a longer life expectancy by the use of cART as well as ongoing chronic immune activation resulting in depressed immune defence, non-AIDS-related illnesses have become more important in the post-HAART era, including conditions such as cardiovascular, liver and renal disease as well as malignancies (Cooper, 2008).

Over the past years, the main focus of clinicians and scientists has been on cardiovascular disease (CVD). With an increase in life expectancy, patients are now more prone to age-related diseases. Additionally, the development of CVD can be linked to antiretroviral therapy itself. Over the long term some ART classes have been shown to cause metabolic side effects comprising elevated blood lipids, insulin resistance and diabetes mellitus – all of which are known risk factors for atherosclerotic heart disease. Furthermore, several cohort studies have also demonstrated that there is a strong gradient for the development of these non-AIDS illnesses (Cooper, 2008).

Two main factors are contributing to non-AIDS-related liver disease: Co-infection with hepatitis B and/or C virus and (antiretroviral) drug-related toxicities. These have lead to an increase of end-stage liver disease in the post-HAART era.

ART-related toxicity is also regarded as the main cause for kidney disease in HIV patients. Both liver and kidney diseases are now accounting for a significant number of deaths due to non-AIDS causes (Hooshyar *et al*., 2007).

However, it should be pointed out that results from the large, international SMART (*S*trategies for *M*anagement of *A*ntiretroviral *T*herapy) study have shown that the risk of developing one of the preceding conditions is even higher if cART is interrupted episodically (Strategies for Management of Antiretroviral Therapy (SMART) Study Group *et al*., 2006).

Although reductions in the incidence of KS and NHL have been observed over the last years, the emergence of non-AIDS-defining malignancies – such as Hodgkin lymphoma (HL), invasive anal carcinoma, lung cancer – hepatocarcinoma and skin cancers has become a new challenge for HIV-treating clinicians (Spano *et al*., 2008). For cervical and anal cancer an association with oncogenic subtypes of human papillomavirus (HPV) has been shown (Spano *et al*., 2008). Future research will elucidate the long-term effectiveness of preventive vaccines against these viral agents to reduce the incidence of both cancers.

Diseases of very advanced immune deficiency

CMV disease and MAC infection occur when immune deficiency is very advanced, with the majority of cases presenting subsequent to AIDS diagnosis and associated with a CD4 cell count of less than $50\,\mu L^{-1}$. The most common presentation of CMV disease in people with HIV infection is retinitis, with other sites including gastrointestinal (oesophagitis, gastritis and colitis) and neurological (encephalitis and polyradiculopathy) involvement.

MAC generally presents as a disseminated infection with diarrhoea, fevers and weight loss, although localized disease including pulmonary infection is seen. The relative absence of both these conditions in clinical series from developing countries may indicate either a lack of diagnostic services or a contrasting natural history of

HIV disease. If people with HIV infection in developing countries are dying from other opportunistic infections, such as tuberculosis, before the development of very advanced immune deficiency, then conditions such as CMV disease and MAC infection will be relatively uncommon. However, autopsy and specific diagnostic studies in developing countries demonstrate a much higher prevalence of both CMV disease and MAC infection than observed in clinical series (**Table 5**), and would suggest that limited diagnostic capability may be the major factor for this apparent disparity. **See also**: Cytomegalovirus Infections in Humans

Determinants of the AIDS Clinical Spectrum

The development of opportunistic infections in people with HIV is clearly correlated with the severity of immune deficiency. Although non-AIDS-defining conditions such as herpes zoster, oral candidiasis, seborrhoeic dermatitis and oral hairy leucoplakia commonly occur when immune deficiency is moderate (CD4 cell count 200–500 μL^{-1}), the vast majority of AIDS-related opportunistic infections occur when immune deficiency is advanced. Among a large cohort of people with AIDS in Australia, the median CD4 cell count for each major AIDS-defining opportunistic illness was approximately 50 μL^{-1} (Dore *et al*., 2002). In contrast, the initial AIDS-defining illness in developing countries often occurs when immune deficiency is less advanced. This is partly due to the high prevalence of tuberculosis, which can present at all stages of HIV disease, with up to one-third of cases associated with a CD4 cell count approximately 500 μL^{-1}.

Although the level of immune deficiency defines the risk of development of HIV-related opportunistic infection, the major determinant of the clinical spectrum in a particular setting is the environmental and human microbial habitat. Some organisms are virtually ubiquitous, others vary widely in prevalence and others have relatively confined geographical habitats. **See also**: Immunity: Humoral and Cellular

A high background prevalence of *Mycobacterium tuberculosis* infection in developing countries enables both reactivation of latent infection as immune deficiency develops among people with previous exposure, and primary infection, which is often progressive, in those previously unexposed. In most industrialized countries the low background prevalence of *M. tuberculosis* has meant that those with HIV infection who are at greatest risk of AIDS-related tuberculosis are people who have migrated from countries of high prevalence (e.g. eastern Europe) and who may be latently infected. An exception to this has been seen in parts of the United States and southern Europe, where injecting drug users and other socio-economically disadvantaged groups with HIV infection have also been at considerable risk of tuberculosis, with *M. tuberculosis* transmission responsible for a large proportion of cases in these groups. The emergence of HIV-related tuberculosis in the United States in the 1980s was accompanied by increasing levels of multidrug-resistant (MDR) cases, although improvements in tuberculosis control programmes in the 1990s have generally led to reductions in rates of drug resistance. Nowadays MDR and extensively drug-resistant (XDR) tuberculosis is a rapidly emerging problem in eastern European countries as it is associated with a much higher mortality rate because of a reduced number of effective treatment options along with the capability of causing epidemics in populations which are already stricken by HIV and therefore more susceptible to TB infection. **See also**: Tuberculosis; Bacterial Antibiotic Resistance

P. marneffei appears to have a unique environmental habitat, with infection endemic in southeast Asia and China, where the fungus has been isolated from bamboo rats.

Other organisms, such as CMV, MAC and *T. gondii*, would appear to be more ubiquitous, with the incidence of infection in different settings dependant more on the level of diagnostic capability and length of survival at very advanced immunodeficiency, particularly in the case of CMV disease and MAC infection.

Mode of HIV transmission is another determinant of AIDS clinical spectrum. The most striking example of this is KS, which has a considerably higher prevalence among homosexual men with AIDS than other HIV-risk groups, presumably due to a higher level of sexual transmission of HHV-8. Other HIV-related conditions that appear to be more common among homosexual men are CMV disease, cryptosporidiosis, chronic herpes simplex infection and HPV-related anal cancer. Injecting drug users with HIV infection are at an increased risk of recurrent bacterial pneumonia, bacterial sepsis, oesophageal candidiasis and tuberculosis. Although mode of HIV transmission is a predictor of clinical spectrum, there appears to be little difference based on sex. An exception is higher rates of oesophageal candidiasis among women in some clinical series, possibly associated with the presence of vaginal candidiasis. **See also**: AIDS: Understanding HIV Transmission; HIV Life Cycle and Inherited Coreceptors

The other major determinant of both clinical spectrum and HIV disease progression is the availability of antiretroviral therapy and prophylaxis against common opportunistic infections. The introduction of prophylaxis against PJP in the mid–late 1980s led to a substantial reduction in incidence in industrialized countries. During the early 1990s prophylaxis against other common opportunistic infections, such as MAC infection, CMV disease and fungal infections, was introduced. However, the major impact on the incidence of AIDS-related opportunistic infections has been the introduction of highly active antiretroviral therapy (HAART) since the mid-1990s. Several industrialized countries have reported considerable delays in HIV disease progression, with overall reductions in incidence of opportunistic infections of 50–80%, and equivalent reductions in mortality rates.

Unfortunately, these improvements in survival for people with HIV infection have been confined to industrialized countries with ready access to these improved therapies. In the recent past, this development has forced researchers and politicians to look for additional ways of HIV prevention especially in developing countries besides promoting condom use, such as use of microbicidal gels and male circumcision. To date, establishing male circumcision as a means of HIV prevention in high prevalence African countries has been limited by financial constraints, cultural hurdles and a shortage of skilled medical health personnel (Pincock, 2007). **See also**: Acquired Immune Deficiency Syndrome (AIDS); Antiviral Drugs; Retroviral Replication

Before the availability of effective antiretroviral therapy, progression from HIV infection to AIDS was more rapid, and survival following AIDS was shorter for people living with HIV infection even in developing countries. Progression of HIV disease may be more rapid in a developing country setting due to reactivation of more virulent opportunistic infections at higher CD4 cell counts, or a more rapid decline in immune function, or both. Tuberculosis, the most common AIDS-related illness in developing countries, can occur at a relatively early stage of HIV disease. Underlying malnutrition and a higher prevalence of non-AIDS-related infections may be additional factors that also enhance HIV disease progression in developing country settings. **See also**: AIDS as a World Health Problem

Conclusion

Although there is considerable variation in the clinical spectrum of AIDS-related illness, the major difference lies in the contrast between industrialized and developing countries. In developing countries, tuberculosis is the major contributor to HIV-related morbidity and mortality, whereas PJP is the most common AIDS-related illness in developed countries, despite the availability of effective prophylaxis. Other conditions that present at very advanced immunodeficiency, such as CMV disease and MAC infection, also appear to be more common in industrialized countries. Improvements in immune function through the use of cART have led to a considerable reduction in the risk of AIDS-related opportunistic infections and malignancies for people with HIV infection, at least in industrialized countries.

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