Print

Clinical manifestations of HIV infection

Michelle Giles: Infectious Diseases Unit, The Alfred Hospital, Melbourne, VIC
Cassy Workman: Enmore Medical Practice, Sydney, NSW
Craig Rodgers : East Sydney Doctors, Sydney, NSW

Since the original description in 1981 of an unusual cluster of cases of *Pneumocystis carinii* pneumonia and Kaposi sarcoma in previously healthy men who have sex with men, substantial advances in our understanding of the acquired immune deficiency syndrome (AIDS) have been achieved. The identification of a cytopathic retrovirus in 1983 and the development of a diagnostic serological test for human immunodeficiency virus (HIV) in 1985 have served as the basis for developing improvements in diagnosis.

In addition, therapy was dramatically altered with the introduction of antiretroviral drugs in 1987 and revolutionised by combination treatment, referred to as highly active antiretroviral therapy (HAART), in 1996.

The natural history of HIV infection has been investigated in a number of observational cohort studies. These studies initially involved mainly people with haemophilia and gay men, the majority of whom were predominantly of European origin. The Multicenter AIDS Cohort Study is the first and largest study specifically created to examine the natural history of AIDS. This ongoing prospective study, which is now in its third decade, involves nearly 7000 gay men at four US universities: University of California at Los Angeles (UCLA), Northwestern University in Chicago, the University of Pittsburgh, and Johns Hopkins University in Baltimore. After more than 25 years, the cumulative drop-out rate is less than 15%, reflecting a high level of commitment and interest on the part of the participants. Although this study provides a number of very important insights into the natural history of HIV infection, the application of these findings to other populations has been questioned.[1]

In 1997, a network of epidemiologists, statisticians, virologists and clinicians from major HIV institutions in 15 European countries as well as in Australia, Canada, and Africa created the Concerted Action on Seroconversion to AIDs and Death in Europe Collaboration (CASCADE). CASCADE constitutes more than 21,000 people with HIV infection drawn from over 300 clinics.

CASCADE's main aim is to monitor people with new HIV infection and those already enrolled in studies, covering the entire duration of HIV infection. By pooling data from many different cohorts, CASCADE has been able to address issues which cannot be reliably addressed from single studies alone, particularly the differences in the natural history of HIV infection in men and women and in different risk groups other than men who have sex with men.[2][3][4]

The Therapeutics Research, Education and AIDS Training in Asia (TREAT Asia) HIV Observational Database has also established an observational cohort study to assess the natural history of HIV infection in treated and untreated patients in the Asia-Pacific region. Results have confirmed that baseline CD4 T-lymphocyte (CD4) cell count is the strongest predictor of short-term disease progression in the Asian population with overall response to antiretroviral therapy similar to that seen in Western countries.[5][6]

Acute primary illness

Clinical features

The group of clinical manifestations characterising acute HIV infection has been called primary HIV syndrome, HIV seroconversion illness and acute retroviral syndrome (ARVS). The first description of this syndrome was by a group of Australian researchers early in the epidemic in the 1980s.[7] They described an acute mononucleosis-like illness accompanied by fevers, sweats, malaise, lethargy, anorexia, nausea, myalgia, arthralgia, headache, sore throat, diarrhoea, lymphadenopathy and rash. This description has been expanded as other symptoms have been reported (Table 1).

Table 1 Clinical manifestations of acute retroviral syndrome

System	Common manifestations	Uncommon manifestations
Systemic	Fever Extreme fatigue Weakness Malaise Anorexia Weight loss Dehydration Night sweats Lymphadenopathy	Rigors
Neurological	Headache Aseptic meningitis	Encephalopathy Peripheral neuropathy Cranial neuropathy Spinal myoclonus Neuralgia Guillain-Barré syndrome Delirium
Oral	Pharyngitis Superficial aphthous ulcers Candidiasis Herpes ulcers	Gingivitis Stomatitis
Gastrointestinal	Nausea Diarrhoea Hepatomegaly Splenomegaly Odynophagia Oesophageal ulceration	Vomiting Hepatitis Jaundice Abdominal pain
Respiratory	Cough	Pneumonitis Bronchitis Shortness of breath
Musculoskeletal	Arthralgia Myalgia	Back pain Rhabdomyolysis
Ophthalmological	Retro-orbital pain Photophobia	Conjunctivitis
Dermatological	Macular erythematous rash	Herpes zoster Eczema Dermatitis Urticaria
Genitourinary	Genital ulceration Anal ulceration Vaginal candidiasis	Haematuria Dysuria
Psychological	Mood changes Irritability	Anxiety Depression Confusion

ARVS usually begins between 10 days and 6 weeks after HIV exposure, at a median time of 21 days post-exposure.[8][9][10][11] The symptoms and signs of ARVS are non-specific and the differential diagnosis includes infectious mononucleosis, secondary syphilis, acute infection with hepatitis A virus (HAV) or hepatitis B virus (HBV), toxoplasmosis and infection with parvovirus, influenza virus and cytomegalovirus.

Attempts have been made to evaluate which, if any, of these symptoms may be more specific to ARVS than to any other flu-like viral illness. The Options Project in San Francisco has reported fever, rash, oral ulcers, arthralgias, pharyngitis, anorexia, weight loss of more than 2.5 kg, malaise and myalgias to be associated with the diagnosis of ARVS. Fever and malaise were found to be the most sensitive of these symptoms, while weight loss and oral ulcers were the most specific. Other common symptoms of ARVS such as night sweats, headache and diarrhoea were found to be just as common in other illnesses.[12] Additional features which vary in ARVS are the duration and severity of illness and the frequency of medical intervention. A study comparing patients with ARVS and those with non-HIV-related flu-like symptoms found that the majority of patients with ARVS consulted a medical practitioner (87% versus 20%) and hospitalisation occurred more frequently with ARVS than with other flu-like illnesses (12% versus 0%).[13]

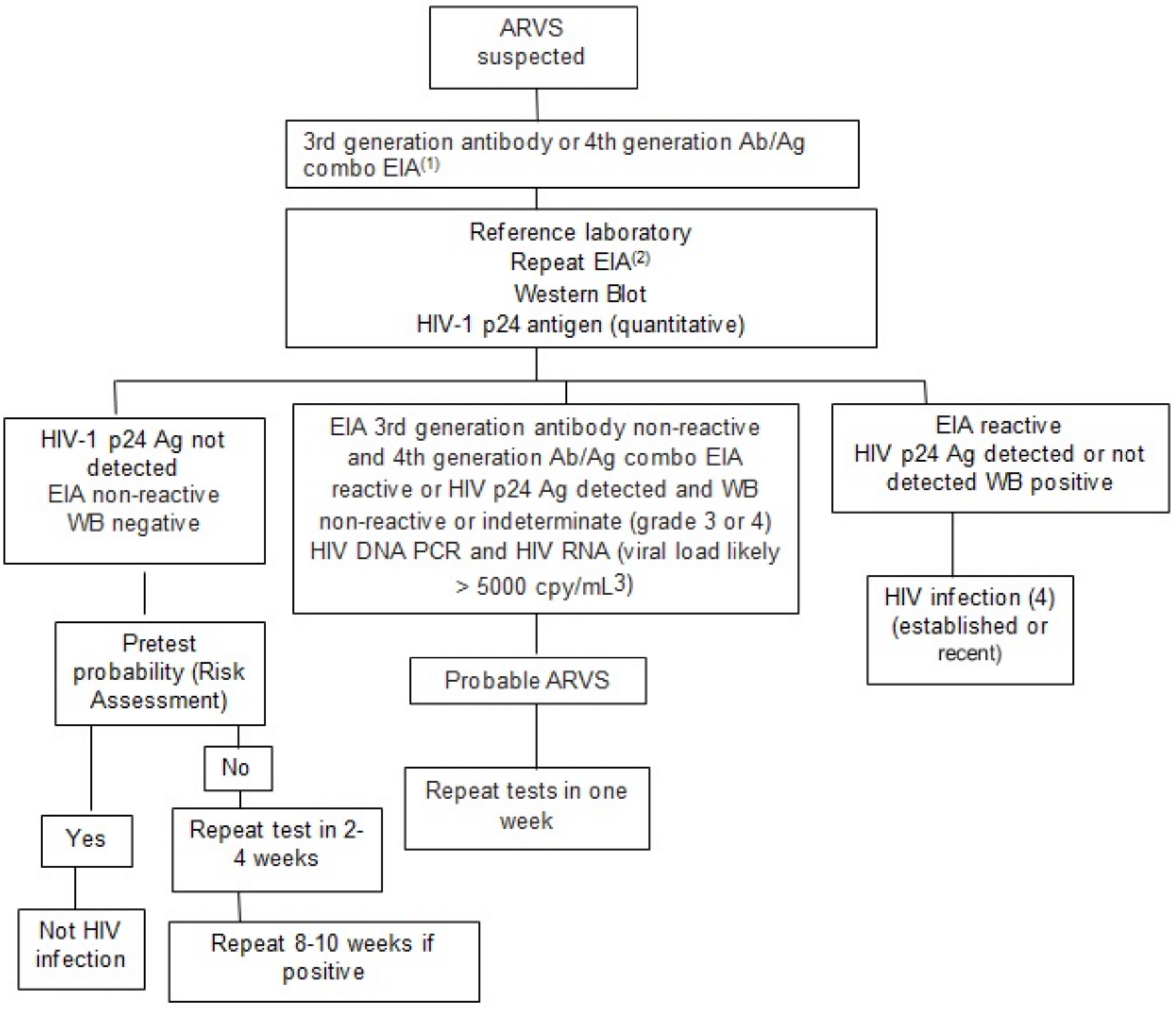
The non-specific nature of the symptoms and signs of ARVS makes it difficult to accurately determine the proportion of patients with acute HIV infection who experience ARVS. However, it is generally accepted that between 50% and 90% of patients with acute infection manifest ARVS.[14][15]

Diagnosis

Results from haematology and biochemistry tests are non-specific and can include moderate neutropenia, moderate thrombocytopenia, mild anaemia and moderately raised serum alanine aminotransferase and aspartate aminotransferase levels. Atypical lymphocytes may be noted on the blood film of the patient. Early on there may be a lymphopenia followed by a lymphocytosis (predominately CD8+ T cells) leading to an inverted T cell CD4:CD8 ratio.[16] This CD8 lymphocytosis will decrease over time, but absolute numbers of CD8+ T cells usually remain higher than the number of CD4 cells, maintaining an inverted T cell CD4:CD8 ratio.[17]

Serological testing is essential in diagnosing acute infection with HIV. Following acute infection, the HIV enzyme-linked immunosorbent assay (ELISA) may initially be negative while there is active viral replication demonstrated by either the presence of HIV p24 antigen or HIV nucleic acids (RNA or DNA). In addition, the Western blot assay, the gold standard for confirmation of HIV infection, may be negative or indeterminate if conducted very early in ARVS. An algorithm for diagnosis when ARVS is suspected is provided in Figure 1.

Figure 1. Algorithm for serological testing for the diagnosis of HIV infection when acute retroviral syndrome (ARVS) is suspected



1. Assay used depends on local availability
2. Often different EIA are used for repeat testing. Improves positive predictive value

3. Qualitative HIV proviral DNA or viral load assay to quantify HIV RNA may be used as a supplementary test where it is thought appropriate although low level false positives do occur. HIV proviral DNA is currently not widely available in Australia. HIV RNA is not registered for use as a diagnostic test in this setting
4. Incidence ELISA is used for epidemiological purposes to monitor population incidence rates. Not widely available and is not available for clinical management purposes

ARVS = acute retroviral syndrome; EIA =enzyme immunoassay; WB = Western Blot; Ag = antigen; Ab = antibody; p24= a core HIV protein, the primary protein detected by the HIV antigen test

Source: Giles M,a Cunningham P,b Birch C,c Lewin S.a The Alfred Hospital, Melbourne VIC,a St Vincent's Hospital, Sydney NSW,b The Victorian Infectious Diseases Reference Laboratory VICc. (Used with permission)

HIV type 1 (HIV-1) RNA testing by reverse transcriptase polymerase chain reaction (RT-PCR) is not recommended as a first-line test in the diagnosis of acute HIV infection in Australia but it can be a useful tool if the pre-test probability of acute infection is high. In acute infection, most true-positive results will show very high levels (105 to 106 copies/mL) of circulating HIV RNA, consistent with uncontrolled viral replication. False- positive results occur in less than 10% of cases; these results usually involve low RNA levels (less than104 copies/mL) and are not reproducible.

Fourth-generation assays that simultaneously detect HIV antigen and antibody have been compared with third-generation ELISA which detect antibody alone, the p24 antigen test and HIV RNA in a multicentre evaluation. Results showed that the fourth-generation tests reduced the diagnostic window by an average of 4 days compared with third-generation tests.[18] Detuned ELISAs can also be used to detect recent HIV infection. This method uses both a sensitive and less sensitive ELISA testing strategy. The sensitive test should detect both early and chronic HIV infection while the less sensitive test will only detect chronic HIV infection.

Diagnosis of acute HIV infection is not one of exclusion and it is important to always consider that patients may present with co-infections such as syphilis, HAV, HBV, hepatitis C virus (HCV), herpes simplex virus, Epstein-Barr virus and cytomegalovirus. The clinician should test appropriately for other infections as suggested by the patient's clinical history, laboratory findings and risk factors.

Clinical latent period with or without persistent generalised lymphadenopathy

Most patients in this stage of disease have few symptoms, but persistent generalised lymphadenopathy may continue from the time of ARVS. To be defined as persistent and generalised, lymphadenopathy must involve at least two non-contiguous sites with the axillary, cervical and inguinal chains being most frequently involved. Dermatological complications are common, including seborrhoeic dermatitis, especially involving the hairline or the nasolabial fold,[19] and new onset or worsening psoriasis.[20] Autoimmune conditions, including idiopathic thrombocytopenia purpura, polymyositis, Guillain-Barré syndrome and Bell's palsy, may also be seen at this stage.

Early symptomatic infection

Dermatological, oral and constitutional complications are more common in this phase of disease. These complications may occur in association with many other disorders but tend to be more frequent, severe and resistant to treatment when associated with HIV infection.

Skin conditions include herpes zoster, bacterial folliculitis, eosinophilic folliculitis, molluscum

contagiosum, seborrhoeic dermatitis, dermatophyte infections, psoriasis and rashes of unknown origin. Warts occurring on both the skin and anogenital area are also common and may be resistant to therapy. Oral complications include aphthous ulceration, oral candidiasis, oral hairy leukoplakia[21] and linear gingival erythema.[22] Acute necrotising ulcerative gingivitis (also known as necrotising ulcerative periodontitis) is a particularly difficult oral complication to treat.[23]

Constitutional symptoms that may develop include episodes of fever, weight loss, fatigue, myalgia, arthralgia and headache. Recurrent diarrhoea may be problematic. Sinusitis becomes more common during this phase of disease and is usually caused by bacteria rather than fungi or other unusual organisms.[24] HIV-associated nephropathy may also occur in patients at this stage of infection.[25]

AIDS

Patients with a CD4 cell count of < 200 cells/μL are usually regarded as having late-stage disease. Opportunistic illnesses are a substantial cause of morbidity and mortality in this group, and may include unusual presentations and rare infections as well as the more commonly associated AIDS-defining conditions. AIDS is a notifiable disease in Australia, and the list of AIDS-defining conditions is found in Table 2. These individual conditions primarily include opportunistic infections, malignancy and neurological disorders.

Table 2 Case definitions for AIDS-defining illnesses which are notifiable within Australia

Condition	Definitive criteria for diagnosis	Presumptive criteria for diagnosis
Candidiasis of bronchi, trachea or lungs	Gross inspection at endoscopy or autopsy Histology/cytology of tissue, not culture	No presumptive
Candidiasis, oesophageal	Gross inspection at endoscopy or autopsy Histology/cytology of tissue, not culture	Retrosternal pain + oral candidiasis diagnosed by either gross inspection or microscopy of uncultured oral mucosa scraping
Cervical cancer, invasive	Histology	No presumptive
Coccidiomycosis, disseminated or extrapulmonary	Histology or cytology in tissue Culture/detection of antigen in fluid/tissue	No presumptive
Cryptococcosis, extrapulmonary	Histology/cytology in tissue Culture/detection of antigen in fluid/tissue	No presumptive
Cryptosporidiosis, of more than one month's duration	Histology/cytology in tissue Culture/detection of antigen in fluid/tissue	No presumptive
Cytomegalovirus disease, other than liver, spleen or nodes	Histology or cytology in tissue Culture/detection of antigen in fluid/tissue	No presumptive
Cytomegalovirus retinitis, with loss of vision	Histology or cytology in tissue Culture/detection of antigen in fluid/tissue	Characteristic appearance on serial ophthalmoscopic examination
Encephalopathy, HIV-related	Progressive, disabling cognitive or motor dysfunction interfering with occupation or activities of daily living in the absence of causative concurrent illness – other neurological disease must be excluded by CSF exam + CT/MRI or autopsy	No presumptive
Herpes simplex: chronic ulcer(s) of more than one month's duration, bronchitis, pneumonitis,	Histology or cytology in tissue Culture/detection of antigen in fluid/tissue	No presumptive

oesophagitis		
Histoplasmosis, disseminated or extrapulmonary	Histology or cytology in tissue Culture/detection of antigen in fluid/tissue	No presumptive
Isosporiasis, chronic intestinal, of more than one month's duration	Histology/cytology in tissue Culture/detection of antigen in fluid/tissue	No presumptive
Kaposi sarcoma	Histology or cytology	Characteristic gross appearance on skin or mucous membrane
Non-Hodgkin lymphoma, primary of brain	Histology or cytology in tissue or at autopsy	No presumptive
Non-Hodgkin's lymphoma, Burkitt lymphoma	Histology or cytology in tissue or at autopsy	No presumptive
Non-Hodgkin lymphoma, large B cell/ immunoblastic	Histology or cytology in tissue or at autopsy	No presumptive
Mycobacterium tuberculosis, any site, pulmonary or extrapulmonary	Isolation of *M. tuberculosis* from a clinical specimen	Acid-fast bacilli in clinical specimen from a patient with illness compatible with tuberculosis or evidence of resolution of disease with two or more antituberculous medications.
Mycobacterial disease, (other or unidentified species including *Mycobacterium avium* complex), disseminated or extra pulmonary	Culture from normally sterile body fluid	Acid-fast bacilli in stool, normally sterile body fluids, tissue not including lungs, skin, cervical or hilar lymph node
Pneumocystis jirovecii pneumonia	Histology or cytology	History of dyspnoea or non-productive cough
Pneumonia, recurrent bacterial	≥2 acute bacterial pneumonia episodes within 12 months, proven by culture, + new chest X-ray findings consistent with pneumonia	Clinical or radiological evidence of ≥2 episodes of acute pneumonia within 12 months
Progressive multifocal leukoencephalopathy	Histology/cytology in tissue; detection of JC virus DNA in CSF	No presumptive
Salmonella septicaemia, recurrent	Culture of blood	No presumptive
Toxoplasmosis	Histology or cytology	Recent onset focal neurological abnormality or reduced consciousness + mass lesion
Wasting syndrome, due to HIV infection	Involuntary weight loss >10% of body weight + chronic diarrhoea for >30 days + chronic weakness and fever >30 days in absence of other causative illness/condition	No presumptive
Bacterial infection, multiple or recurrent in child aged <13 years	Laboratory evidence of ≥2 of acute septicaemia, pneumonia, meningitis, bone or joint infection, internal abscess caused by *Haemophilus spp., Streptococcus pneumoniae* or other pyogenic bacteria	No presumptive
Lymphoid interstitial pneumonia, and/or		Lymphoid interstitial pneumonia on

pulmonary lymphoid hyperplasia in child aged <13 years	Histology or cytology	chest X-ray for ≥2 months with no pathogen identified and no response to antibiotic therapy

CSF = cerebrospinal fluid; CT = computed tomography; MRI = magnetic resonance imaging; JC = John Cunningham.
Reference: Adapted from the Australian Government. Acquired immunodeficiency syndrome (AIDS) case definition [internet] Page last updated: 12 March 2004. Available at http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_aids.htm (last accessed 21 August 2015).

Late presentation

Late presentation has been defined as either an AIDS diagnosis at the time of HIV diagnosis[26] or diagnosis of an AIDS-defining condition within 8 weeks of HIV diagnosis.[27] Many studies examining late presentation were conducted early in the epidemic before the availability of potent antiretroviral therapy. Studies comparing early and late presentation showed that at this stage of the epidemic, late presenters were about a third (22-39%) of all patients with a new AIDS diagnosis.[28][29] Late presenters still constitute about a quarter (24%) of new AIDS diagnoses in the era of antiretroviral therapy (ART).

However, late presenters are now more likely to be older, bisexual or heterosexual and born in Asia, southern Europe or South America.[30]

In Australia, a late diagnosis is defined by a CD4 cell count of < 350 cells/μL at HIV diagnosis. Despite government and community-based testing campaigns, widespread access to HIV testing and anonymous testing sites in many capital cities, some patients continue to present late in the disease. The percentage of AIDS cases in Australia with late HIV presentation increased significantly from 18% in 1992-96 to 33% in 1997 and to 50% in 2001. Predictors of late presentation included older age, having been born in Asia and an HIV exposure history of heterosexual contact or another or undetermined exposure.[31] For the first time in 2006, the number of AIDS cases for which the HIV diagnosis was made greater than 3 months before, was less than the number of AIDS cases for which the HIV diagnosis had occurred in the preceding 3 months.[32]

In the past 10 years the proportion of cases diagnosed with advanced HIV infection (measured by a CD4 cell count of < 200 cells/μL) has remained relatively stable at about 20% with the proportion of late diagnoses also remaining stable at 39%. Advanced and late HIV diagnoses were actually least common among men who have sex with men. In 2009 – 2013, around 15% and 3% of HIV diagnoses among men who have sex with men were advanced and late HIV diagnoses, respectively, whereas advanced and late diagnoses accounted for 29% and 40% of diagnoses among people who injected drugs and for 34% and 56% of diagnoses among people with a history of heterosexual contact. People born in high HIV prevalence countries in sub-Saharan Africa and South East Asia also had a relatively high rate of diagnosis with advanced HIV infection.[33]

Isolated cases of late presentation following vertical transmission have been reported. In one case, the child was 13 years of age before developing symptoms and seeking medical care.[34] HIV infection should be considered in children with recurrent bacterial infections, failure to thrive and unexplained organomegaly, as well as in those presenting with the classical opportunistic infections.[35]

The influence of antiretroviral therapy on the natural history of

HIV

T2 weighted image + T cell recovery. The rate of CD4 cell recovery is affected by the baseline CD4 cell count, the baseline viral load and by both initial and continued viral suppression.[36][37] In addition, age is important for CD4 cell recovery; people over 55 years have a smaller rise in CD4 cell counts from nadir at early (3 months) and later (18 months) treatment time points.[38] Increased age at seroconversion is also associated with shorter survival, even with the use of ART,[39] and HCV co-infection has been shown to blunt CD4 cell recovery with ART.[40]

Many of the symptoms of disease described in the intermediate and late stage of infection which were extremely problematic to treat, such as molluscum contagiosum, necrotising ulcerative periodontitis and seborrhoeic dermatitis are uncommon in treated populations. The CD4 cell recovery associated with the use of ART has made opportunistic processes such as HIV-associated retinopathies,[41] microsporidiosis[42] and cryptosporidiosis[43] occur less commonly.[44]

Antiretroviral therapy has also led to a decreased incidence of some HIV-associated malignancies such as Kaposi sarcoma and AIDS-related non-Hodgkin lymphoma.[45][46][47][48] However the effect of ART on other malignancies, such as Hodgkin disease, human papilloma virus-associated tumours including invasive cervical carcinoma and anal carcinoma, is less clear with no significant change in incidence.[49] All HIV-associated malignancies remain increased in the population with HIV compared with the population without HIV,[50] although these data are largely from the pre-ART era.

Survival rates of patients diagnosed with AIDS have increased dramatically since the introduction of potent ART.[51] AIDS-related deaths and disease rates have declined. However despite this, mortality rates remain higher in people with HIV infection compared with the general population. The Australian HIV Observational Database reported a crude mortality rate of 1.58 per 100 person-years, ten-fold greater than the general population, 40% of which were HIV related. Independent risk factors for a HIV-related death included a low CD4 cell count and the receipt of a large number of ART combinations.[52] In developed countries with access to ART, overall death rates are low but the proportion of deaths attributable to non-AIDS diseases such as hepatic, cardiovascular and pulmonary diseases along with non-AIDS malignancies is increasing.[53]

The question of when to start ART has been discussed for many years. Until recently observational cohort studies had reported conflicting results on whether there were clinical advantages of starting treatment earlier (that is, with a CD4 cell count > 500 cells/μL), and randomised studies had been deferring treatment until even lower CD4 cell cut-offs (< 350 cells/μL). Recently published data from the Strategic Timing of AntiRetoviral treatment (START) study have finally provided robust evidence to justify commencing ART at higher CD4 cell counts.

The primary research question of the START study was whether the benefits and risks of starting ART at high CD4 cell counts (> 500 cells/μL) outweighed the benefits and risks of waiting until the CD4 cell count decreased to 350 cells/μL. The study enrolled 4685 HIV-positive people at 211 sites in 35 countries from April 2009 to December 2013.

The two groups in START were compared based on the different rates of serious clinical events. These events included important AIDS-related and non-AIDS-related illnesses together with deaths from all causes. Numerous sub-studies were included to examine the effect of both HIV and ART on other key areas of health in early infection, including bone heath, neurological function, cardiovascular risks, lung function and quality of life. The study was stopped early based on an interim analysis that showed the risk

of serious AIDS events, and deaths due to non-AIDS events including major cardiovascular events, renal and liver disease and cancer was reduced by more than 50% among those in the early treatment group compared to those in the deferred group. Reductions due to early treatment were also seen in both serious AIDS and serious non-AIDS events with the effect of early treatment on AIDS being greater than on non-AIDS events. The most common AIDS-related events were pulmonary tuberculosis, Kaposi sarcoma and non-Hodgkin lymphoma. The most common non-AIDS events were cancer, cardiovascular events and other causes (including traffic accidents, assault, suicide and overdose).

The START study has therefore shown that treatment at all stages of infection extends survival and prevents serious disease complications in people living with HIV infection.[54]

---

1. Kaslow RA, Ostrow DG, Detels R, et al. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. Am J Epidemiol 1987;126:310-8
2. The Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) Collaboration. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. Collaborative Group on AIDS Incubation and HIV Survival including the CASCADE EU Concerted Action. Lancet 2000;355:1131-7
3. The Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) Collaboration. Differences in CD4 cell counts at seroconversion and decline among 5739 HIV-1-infected individuals with well-estimated dates of seroconversion. J Acquir Immune Defic Syndr 2003;34:76-83
4. Touloumi G, Pantazis N, Babiker AG, et al. for the CASCADE Collaboration. Differences in HIV RNA levels before the initiation of antiretroviral therapy among 1864 individuals with known HIV-1 seroconversion dates. AIDS 2004;18:1697-705
5. Zhou J, Kumarasamy N; TREAT Asia HIV Observational Database. Predicting short-term disease progression among HIV-infected patients in Asia and the Pacific region: preliminary results from the TREAT Asia HIV Observational Database (TAHOD). HIV Med 2005;6:216-23
6. Zhou J, Kumarasamy N, Ditangco R, et al for the TREAT Asia HIV Observational Database. The TREAT Asia HIV Observational Database: baseline and retrospective data. J Acquir Immune Defic Syndr 2005;38:174-9
7. Cooper DA, Gold J, Maclean P, et al. Acute AIDS retrovirus infection. Definition of a clinical illness associated with seroconversion. Lancet 1985;1:537-40
8. Clark SJ, Saag MS, Decker WD. High titers of cytopathic virus in plasma of patients with symptomatic primary HIV-1 infection. N Engl J Med 1991;324:954-60
9. Goldman R, Lang W, Lyman D. Acute AIDS viral infection. Am J Med 1986;81:1122-3
10. Oksenhendler E, Harzic M, Le Roux JM, et al. HIV infection with seroconversion after a superficial needlestick injury to the finger. N Engl J Med 1986;315:582
11. Isaksson B, Albert J, Chiodi F, et al. AIDS two months after primary human immunodeficiency virus infection. J Infect Dis 1988;158:866-8
12. Hecht FM, Busch M, Rawal B, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. AIDS 2002;16:1119-29
13. Tindall B, Barker S, Donovan B, et al. Characterization of the acute clinical illness associated with human immunodeficiency virus infection. Arch Intern Med 1988;148:945-9
14. Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. N Engl J Med 1998;339:33-9
15. Quinn TC. Acute primary HIV infection. J Am Med Assoc 1997;278:58-62
16. Pedersen C, Dickmeiss E, Gaub J. T-cell subset alterations and lymphocyte responsiveness to mitogens and antigen during severe primary infection with HIV: a case series of seven consecutive HIV seroconverters. AIDS 1990;4:523-6
17. Cooper DA, Tindall B, Wilson EJ, et al. Characterization of T lymphocyte responses during primary infection with human immunodeficiency virus. J Infect Dis 1988;157:889-96
18. Weber B, Gürtler L, Thorstensson R, et al. Multicenter evaluation of a new automated fourth-generation human immunodeficiency virus screening assay with a sensitive antigen detection module and high specificity. J Clin Microbiol 2002;40:1938-46
19. Soeprono FF, Schinella RA, Cockerell CJ, et al. Seborrheic- like dermatitis of acquired immunodeficiency syndrome. A clinicopathologic study. J Am Acad Dermatol 1986;14:242-8
20. Mallon E, Bunker CB. HIV-associated psoriasis, AIDS Patient Care STDS 2000;14:239-46

21. Tappuni AR, Fleming GJ. The effect of antiretroviral therapy on the prevalence of oral manifestations in HIV-infected patients: a UK study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:623-8
22. Lamster IB, Grbic JT, Bucklan RS, et al. Epidemiology and diagnosis of HIV-associated periodontal diseases. Oral Dis 1997;3:141-8
23. Yeung SC. HIV infection and periodontal disease. Ann R Australas Coll Dent Surg 2000;15:331-4
24. Decker CF. Sinusitis in the Immunocompromised Host. Curr Infect Dis Rep 1999;1:27-32
25. Rao TK, Friedman EA, Nicastri AD. The types of renal disease in the acquired immunodeficiency syndrome. N Engl J Med 1987;316:1062-8
26. Poznansky MC, Coker R, Skinner C, et al. HIV positive patients first presenting with an AIDS defining illness: characteristics and survival. Br Med J 1995;311:156-8
27. Hocking JS, Rodger AJ, Rhodes DG, et al. Late presentation of HIV infection associated with prolonged survival following AIDS diagnosis – characteristics of individuals. Int J STD AIDS 2000;11:503-8
28. Poznansky MC, Coker R, Skinner C, et al. HIV positive patients first presenting with an AIDS defining illness: characteristics and survival. Br Med J 1995;311:156-8
29. Gillieatt SJ, Mallal SA, French MA,et al. Epidemiology of late presentation of HIV infection in Western Australia. Med J Aust 1992;157:117-8
30. Hocking JS, Rodger AJ, Rhodes DG, et al. Late presentation of HIV infection associated with prolonged survival following AIDS diagnosis – characteristics of individuals. Int J STD AIDS 2000;11:503-8
31. McDonald AM, Li Y, Dore GJ, et al. Late HIV presentation among AIDS cases in Australia, 1992-2001. Aust N Z J Public Health. 2003;27:608-13
32. National Centre in HIV Epidemiology and Clinical Research. HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia. Sydney: NCHECR Annual Surveillance Report, 2007
33. The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia. Annual Surveillance Report 2014. Sydney:The Kirby Institute, UNSW; 2014
34. Espanol T, Figueras MC, Soriano V, et al. Very late presentation of vertically transmitted HIV- 1 infection. Acta Paediatr 1996;85:755-7
35. Fein JA, Freidland LR, Rutstein R, et al. Children with unrecognized human immunodeficiency virus infection. An emergency department perspective. Am J Dis Child 1993;147:1104-8
36. Li TS, Tubiana R, Katlama C, et al. Long-lasting recovery in CD4 T-cell function and viral-load reduction after highly active antiretroviral therapy in advanced HIV-1 disease. Lancet 1998;351:1682-6
37. Ledergerber B, Egger M, Opravil M, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. Lancet 1999; 353:863-8
38. Goetz MB, Boscardin WJ, Wiley D, Alkasspooles S. Decreased recovery of CD4 lymphocytes in older HIV-infected patients beginning highly active antiretroviral therapy. AIDS 2001;15:1576-8
39. The CASCADE Collaboration. Survival after introduction of HAART in people with known duration of HIV-1 infection. The CASCADE Collaboration. Concerted Action on SeroConversion to AIDS and Death in Europe. Lancet 2000;355:1158-9
40. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus co-infection: the Swiss HIV Cohort Study. Lancet 2000;356:1800-5
41. Goldberg DE, Smithen LM, Angelilli A, et al. HIV-associated retinopathy in the HAART era. Retina 2005;25:633-49
42. van Hal SJ, Muthiah K, Matthews G, et al. Declining incidence of intestinal microsporidiosis and reduction in AIDS-related mortality following introduction of HAART in Sydney, Australia. Trans R Soc Trop Med Hyg 2007;101:1096-100
43. Carr A, Marriott D, Field A, et al. Treatment of HIV-1-associated microsporidiosis and cryptosporidiosis with combination antiretroviral therapy. Lancet 1998;351:256-61
44. Sepkowitz KA Effect of HAART on natural history of AIDS- related opportunistic disorders. Lancet 1998;351:228-30
45. Gates AE, Kaplan LD. AIDS malignancies in the era of highly active antiretroviral therapy. Oncology (Williston Park). 2002;16: 657-65; discussion 665, 668-70
46. Palmieri C, Treibel T, Large O, et al. AIDS-related non- Hodgkin's lymphoma in the first decade of highly active antiretroviral therapy. Q J Med 2006;99:811-26
47. Cattelan AM, Calabrò ML, De Rossi A, et al. Long-term clinical outcome of AIDS-related Kaposi's sarcoma during highly active antiretroviral therapy. Int J Oncol 2005;27:779-85
48. Polesal J, Clifford GM, Rickenbach M, et al. Non-Hodgkin lymphoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. AIDS 2008;22:301-6
49. Gates AE, Kaplan LD. AIDS malignancies in the era of highly active antiretroviral therapy. Oncology (Williston Park). 2002;16: 657-65; discussion 665, 668-70

50. Grulich AE, van Leeuwen MT, Falster MO, et al. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 2007;370:59-67
51. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 1998;338:853-60
52. Petoumenos K, Law MG; Australian HIV Observational Database. Risk factors and causes of death in the Australian HIV Observational Database. Sex Health 2006;3:103-12
53. Palella FJ Jr, Baker RK, Moorman AC, et al; HIV Outpatient Study Investigators. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 2006;43:27-34
54. Collins S. Early START result recommends ART for all participants: starting HIV meds when the CD4 count is above 500 reduces AIDS-related events. HIV Treatment Bulletin. HIV i-Base. 1 June 2015.. Available at: http://i-base.info/htb/28261 (last accessed 21 August 2015)