

Clinical manifestations and the natural history of HIV

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The natural history of HIV infection has been gleaned from a number of observational cohort studies. These studies initially involved mainly people with haemophilia and gay men, the majority of whom were Caucasian. The first of these studies, the US Multicenter AIDS Cohort Study (MACS), is an ongoing prospective study of HIV-1 infection in almost 7000 homosexual and bisexual men from four US cities. Participants in this study had interviews, physical examinations, laboratory testing and storage of biological samples performed bi-annually since the initial enrolment period from April 1984 to March 1995;¹ further enrolments have since taken place. Although this study provides a number of very important insights into the natural history of HIV infection, the generalisability of these findings to other populations has been questioned.

Recently, cohorts in Europe, Canada and Australia have been included in a large database of 13 030 patients from different ethnic and transmission groups with known dates of seroconversion. This network, called the Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) Collaboration, has reported 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 (MSM).²⁻⁴

The Therapeutics Research, Education and AIDS Training in Asia (TREAT Asia) HIV Observational Database has recently established an observational cohort study to assess the natural history of HIV in treated and untreated patients in the Asia-Pacific region. Preliminary results confirm that baseline CD4 cell count is the strongest predictor of short-term disease progression; overall response to antiretroviral therapy in the Asian population is similar to that seen in Western countries.^{5,6}

12.1 Acute primary illness

12.1.1 Clinical features

The group of symptoms characterising acute HIV infection has been called primary HIV illness, acute primary illness, acute 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 12.1).

ARVS usually begins between ten days and six weeks after HIV exposure, at a median of 21 days post-exposure.⁸⁻¹¹ 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), parvovirus, influenza, cytomegalovirus and toxoplasmosis.

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}

12.1.2 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 cells) leading to an inverted CD4:CD8 ratio.¹⁶ This CD8 lymphocytosis will decrease over time, but absolute numbers of CD8 cells usually remain higher than the number of CD4 cells, maintaining an inverted 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 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 12.1.

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

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Table 12.1 Clinical manifestations of acute retroviral syndrome

System	Common	Uncommon
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

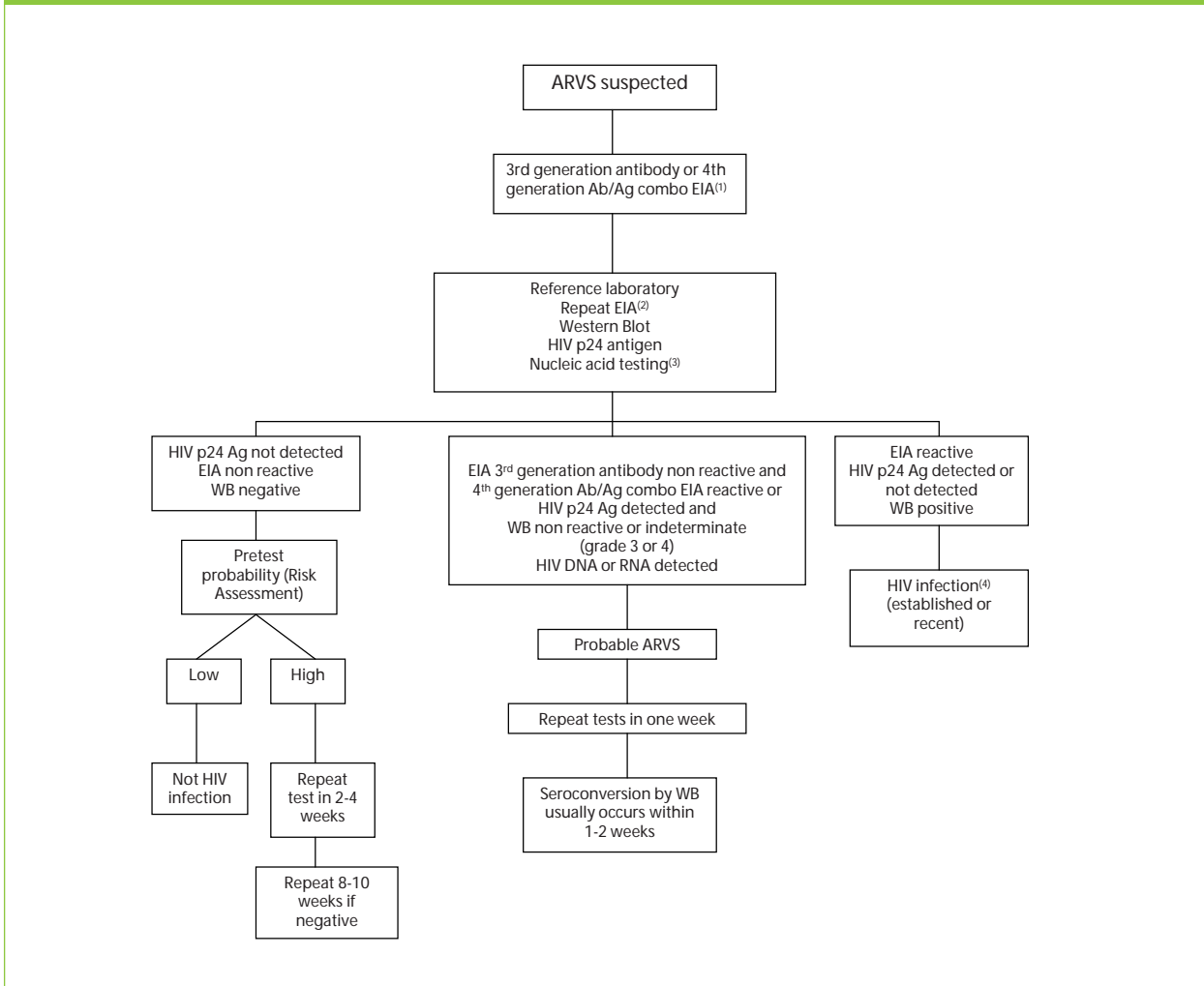
will show very high levels (10^5 to 10^6 copies/mL) of circulating HIV RNA, consistent with uncontrolled viral replication. False-positive results occur in less than 10% of cases; these results usually involve low RNA levels (less than 10^4 copies/mL) and are not reproducible.

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 four 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.

Figure 12.1. 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. 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, VIC.^c (Used with permission)

12.2 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.

12.3 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 leukoplakia²¹ and linear gingival erythema.²² Acute necrotising ulcerative gingivitis (also known

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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

12.4 AIDS

Patients with a CD4 cell count of less than 200 cells/ μ L 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 12.2. These individual conditions primarily include opportunistic infections, malignancy and neurological disorders.

12.5 Late presentation

Late presentation has been defined as either an AIDS diagnosis at the time of HIV diagnosis²⁶ or diagnosis of an AIDS-defining condition within eight weeks of HIV diagnosis.²⁷ Most 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.^{26,28} Late presenters still constitute about a quarter (24%) of new

Table 12.2. Case definitions for AIDS-defining illnesses which are nationally 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 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, oesophagitis	Histology or cytology in tissue Culture/detection of antigen in fluid/tissue	No presumptive
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's sarcoma	Histology or cytology	Characteristic gross appearance on skin or mucous membrane
Non-Hodgkin's lymphoma, primary of brain	Histology or cytology in tissue or at autopsy	No presumptive
Non-Hodgkin's lymphoma, Burkitt's lymphoma	Histology or cytology in tissue or at autopsy	No presumptive
Non-Hodgkin's lymphoma, large B cell/immunoblastic	Histology or cytology in tissue or at autopsy	No presumptive

AIDS diagnoses in the era of cART. However, late presenters are now more likely to be older, bisexual or heterosexual and born in Asia, southern Europe or South America.²⁷ In Australia, 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 remained relatively unchanged over time and included older age, having been born in Asia and an HIV exposure history of heterosexual contact or an 'other/undetermined' exposure.²⁹ For the first time in 2006, the number of AIDS cases for which the HIV diagnosis was made greater than three months prior, was

less than the number of AIDS cases for which the HIV diagnosis had occurred in the preceding three months.³⁰ Although the absolute numbers are small, the proportion of cases of late presentation among people born in the Middle East or North Africa in 2006 was notably high.³⁰

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.³¹ 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 classic opportunistic infections.³²

Table 12.2 Case definitions for AIDS-defining illnesses which are nationally notifiable within Australia (continued)

Condition	Definitive criteria for diagnosis	Presumptive criteria for diagnosis
<i>Mycobacterium tuberculosis</i> , any site, pulmonary or extrapulmonary	Isolation of <i>M. tuberculosis</i> from a clinical specimen	Acid-fast bacilli in clinical specimen in 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 <i>Mycobacterium avium</i> 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
<i>Pneumocystis jirovecii</i> pneumonia	Histology or cytology	History of dyspnoea or non-productive cough <3 months + consistent chest X-ray + arterial PO ₂ <70 mmHg + no evidence of bacterial pneumonia
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 on CT or MRI + antibody to toxoplasma or response to anti-toxoplasmosis therapy
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 <i>Haemophilus</i> spp., <i>Streptococcus pneumoniae</i> or other pyogenic bacteria	No presumptive
Lymphoid interstitial pneumonia, and/or pulmonary lymphoid hyperplasia in child aged <13 years	Histology or cytology	Lymphoid interstitial pneumonia on 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 National Council on AIDS (ANCA) Bulletin 18: Definition of HIV infection and AIDS-defining illnesses. Canberra: ANCA. April 1994. Available at http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndsd-casedefs-cd_aids.htm (cited April 2008).

12.6 The influence of cART on the natural history of HIV

The natural history of HIV disease is altered dramatically by the use of antiretroviral therapy. With control of viral replication, immune restoration occurs with CD4 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.^{33,34} 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 (three months) and later (18 months) treatment time points.³⁵ Increased age at seroconversion is also associated with shorter survival, even with the use of combination antiretroviral therapy (cART)³⁶ and HCV co-infection has been shown to blunt CD4 cell recovery with cART.³⁷

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 cART has made opportunistic processes such as HIV-associated retinopathies,³⁸ microsporidiosis³⁹ and cryptosporidiosis⁴⁰ occur less commonly.⁴¹

cART has also led to a decreased incidence of some HIV-associated malignancies such as Kaposi's sarcoma and AIDS-related non-Hodgkin's lymphoma.⁴²⁻⁴⁵ However the impact of cART on other malignancies, such as Hodgkin's disease, human papilloma virus-associated tumours including invasive cervical carcinoma and anal carcinoma, is less clear with no significant change in incidence.⁴² All HIV-associated malignancies remain increased in the population with HIV compared with the population without HIV,⁴⁶ although these data are largely from the pre-cART era.

Survival rates of patients diagnosed with AIDS have increased dramatically since the introduction of potent antiretroviral therapy.⁴⁷ 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 antiretroviral therapy combinations.⁴⁸ In developed countries with access to cART, 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.⁴⁹

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