Human immunodeficiency virus (HIV)

Laboratory case definition

The Public Health Laboratory Network (PHLN) has developed standard case definitions for the diagnosis of key diseases in Australia. This document contains the laboratory case definition for *human immunodeficiency virus*.

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1. PHLN Summary Laboratory Definition

Reporting

Laboratories and clinicians should notify confirmed and probable cases to the local jurisdictional public health unit consistent with jurisdictional guidelines.

1.1 Condition:

Human Immunodeficiency Virus (HIV) infection

1.1.1 Definitive Criteria for confirmed case - Children aged >18 months and adults

Repeatedly reactive HIV antibody or HIV antigen/antibody combination assay

AND

- Positive western blot immunoassay

OR

- Detection of HIV-1 p24 antigen, confirmed by neutralisation

OR

- *Detection of HIV nucleic acid (RNA or DNA) by an HIV nucleic acid test

1.1.2 Definitive Criteria for a confirmed case - Children aged <18 months

- ^Detection of HIV-1 p24 antigen, confirmed by neutralisation, on two separate specimens on different days

  OR
- #*Detection of HIV nucleic acid (RNA or DNA) by an HIV nucleic acid test, on two separate specimens on different days

1.1.3 Suggestive criteria for a probable case - Children aged >18 months and adults

- Detection of HIV-1 p24 antigen, confirmed by neutralisation

  OR
- *Detection of HIV nucleic acid (RNA or DNA) by an HIV nucleic acid test

1.1.4 Suggestive criteria for a probable case - Children aged <18 months

- ^Detection of HIV-1 p24 antigen, confirmed by neutralisation

  OR
- #*Detection of HIV nucleic acid (RNA or DNA) by an HIV nucleic acid test

*HIV nucleic acid testing should be performed on a dedicated specimen not previously used for other testing

^sample must be from a child >1 month of age

sample cannot be cord blood

Special considerations and guide for use:

- Consistent with international guidelines, diagnostic confirmation of an AIDS-defining condition without definitive laboratory evidence of HIV infection is insufficient to classify an individual as HIV-infected.
- Some rapid HIV tests have been registered on the ARTG for use at point-of-care (POC). The definitive and suggestive criteria for a confirmed or probable case apply to laboratory tests only, not POC tests.

2. Introduction

Human Immunodeficiency Virus has two known subtypes - HIV-1 and HIV-2, of which HIV-1 causes the overwhelming majority of infections in Australia, where the only known reservoir is humans. The viruses are enveloped plus-stranded RNA viruses within the family *retroviridae*. HIV-1 was isolated from a patient in 1983, and HIV-2 was reported in 1986. HIV-1 is subdivided into four genetic groups M (subtypes A-K), O, N and P while HIV-2 has eight subtypes (A-H).

HIV-1 has been reported globally, while HIV-2 has remained limited primarily to West Africa and to migrants from West Africa. Both HIV-1 and HIV-2 are most commonly transmitted sexually, but vertical transmission is a common method of transmission in developing countries. Infection may occur through parenteral means including inoculation of infected blood through sharing of contaminated needles or equipment, transfusion of infected blood products, and transplantation of infected tissues.

The natural history of infection is divided into three phases. Acute retroviral syndrome occurs two to six weeks post exposure, presenting with fever, maculopapular rash, oral ulcers, lymphadenopathy, malaise, weight loss, arthralgia, night sweats, or pharyngitis, with an associated high HIV viral load. The second clinical phase of infection is clinical latency, which is usually several years or more without symptoms. The third phase is Acquired Immune Deficiency Syndrome (AIDS) where the patient presents with either opportunistic infections or certain cancers, characterized virologically by high viral loads and low CD4 T-cell counts, typically < 200 cells/mm3. There are over 20 clinical syndromes identifying AIDS in HIV-infected individual globally with the most common being *Pneumocystis jirovecii* pneumonia, HIV wasting syndrome and oesophageal candidiasis. However in Australia, earlier identification and treatment have changed this spectrum considerably.

HIV infection is commonly diagnosed via detection of HIV antibody using a test that includes antigen and antibody targets, with confirmation using a supplemental test. The assays detecting antigen and/or antibody (Ag/Ab “combo” tests), are currently the predominant assays used in patient screening/testing. HIV antibody becomes detectable approximately 3 weeks after infection whereas p24 antigen becomes transiently detectable from one to two weeks after infection until anti-p24 antibody is produced a week or two later. Qualitative NAT assays, which diagnose and characterise HIV viraemia, are the first tests to become detectable in acute HIV infection, usually around one week after infection. They are used as part of tissue and blood donation screening as well as part of patient laboratory screening algorithms.[1] Quantitative viral load assays measure the quantity of HIV-1 or HIV-2 RNA in plasma or in whole blood as surrogate prognostic markers, to monitor therapy, and to determine infectiousness.

Australian laboratories operate using instrument-based assays, under quality management systems monitored with quality assurance programs from the Royal College of Pathologists of Australia Quality Assurance Program (RCPAQAP) or the National Serology Reference Laboratory (NRL) to regularly check performance. All first-time positive HIV diagnoses should be confirmed with a second independent sample to exclude any pre-analytical (patient labelling) or laboratory error.

HIV is a notifiable disease in all Australian states and territories with similar, although not identical, mechanisms of notification.

3. Tests

Test regulation

HIV diagnostic tests are referred to as *in vitro* diagnostic medical devices (IVDs) by the Therapeutic Goods Administration (TGA). The system for regulation of IVDs in Australia is risk based. HIV is considered to be a disease that poses high risk to individuals and to the public and therefore, HIV diagnostic tests are assigned to class 4, the highest risk class of the TGA IVD Framework.[2] This means that tests to diagnose HIV infection are assessed to the highest stringency of performance. Tests that are used for monitoring or characterising HIV infection once it has been diagnosed are assigned as Class 3 IVD’s from a regulatory perspective. Once a test is assessed as appropriate for its intended use in Australia, it is registered on the Australian Register of Therapeutic Goods (ARTG).[3]

Serological tests

The serological tests for establishing HIV infection in an individual are referred to as either screening or supplemental (confirmatory) tests. The format of screening serological assays is commonly enzyme-linked immunoassay (EIA) or chemiluminescent immunoassay (CIA) where both HIV antigen and antibody is detected, but not reported separately. Common applications for serological testing for HIV are for primary diagnosis, screening of blood products, organ and tissue donor screening, management of women when pregnant, in labour and delivery, evaluation of occupational exposure to blood or body fluid, and epidemiological purposes. There are many commercial serology assays available in Australia, please refer to the ARTG3 for individual test details. Supplemental testing in Australia involves Western blot (WB) testing, virus core protein (p24 antigen) testing or HIV nucleic acid testing (NAT).

HIV-1 and HIV-2 antigen and antibody screening tests

Following infection with HIV, p24 antigen appears in the blood within two to three weeks, around the time of seroconversion illness which occurs in 40–48% of affected individuals. Antigenemia and viraemia precedes the appearance of antibody by up to two weeks. In some individuals, serological assays may show delayed seroconversion, especially with the use of pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP) or prompt antiretroviral therapy.[4]

Early screening tests were designed to detect antibody to HIV. The HIV combo tests, are fourth generation immunoassays, so named because they detect both HIV antigen and antibody simultaneously in serum and plasma. These combo assays are now used for screening in most centres and have been shown to detect infection earlier than tests that detect antibody alone. The assays are easily performed, robust, automated and have high throughput with short turnaround times. The recombinant antigens and/or synthetic antigens used in the assays allow antibody to both HIV-1 and HIV-2 to be detected, together with HIV-1 p24 antigen.

In almost all cases a negative combo assay six weeks after an exposure excludes HIV infection, but a test at 12 weeks post exposure is recommended. The occurrence of a second diagnostic window (between loss of detectable antigen before the appearance of detectable antibody) with certain 4th generation HIV assays has to be considered.[5] False positive results can occur infrequently with screening tests, and hence screening test results should be reported as reactive rather than positive. Most manufacturers of HIV screening assays recommend samples that are initially reactive be retested in duplicate in the same assay to confirm the result, as part of NPAAC guidelines.[6] Specimens reactive on retesting are referred to as repeat reactors. Repeat reactors on combo assays are then tested on supplemental assays, commonly using a WB assay and a p24 antigen-specific assay to determine if the reactivity is due to the presence of antigen alone, suggestive of recent infection, or antibody. HIV NAT may be used and can be positive before the appearance of p24 antigen or HIV antibody. It is recommended that all newly diagnosed patients have a repeat test on a second blood sample collection.[7]

HIV supplemental serological assay – Western Blot

During the immune response to HIV, antibodies to the various antigens of HIV appear in serum after different times. These different antibodies can be identified using the WB assay. The WB assay should

only be performed on sera that are reactive on a screening assay as they have not been validated as screening assays. The common commercial HIV-1 WBs detect antibodies to individual HIV-1 antigens and include an antigen strip for HIV-2 detection. Specific HIV-2 WBs are available in some reference laboratories.

Western blot HIV-1 assays detect antibodies in patient sera to a number of different viral proteins. These viral proteins represent the gag (structural proteins, e.g. p24), pol (enzymes, e.g. reverse transcriptase), and env (envelope proteins, e.g. gp41) which are separated into bands of distinct molecular weight using protein gel electrophoresis then transferred (blotted) to a solid material (such as nitrocellulose strips). The pre-prepared strips are bathed in patient serum for binding of reactive antibodies to the antigens on the strip. The antibodies in the serum can be identified after the addition of enzyme labelled conjugate and reaction with substrate.

The development of a positive WB takes approximately six weeks from infection, although the evolution of the blot pattern is affected by PrEP[8] and early primary treatment with antiretroviral drugs. Due to this delay, and the frequency of negative p24 antigen assays in acute HIV infection, confirmation of acute HIV infection can be achieved by HIV NAT. WB patterns of reactivity detected during the immune response that do not meet the criteria for an interpretation of “positive” (often with missing bands) are referred to as indeterminate. Some of these patterns can also be seen in uninfected individuals. In 1992 the Australian National HIV Reference Laboratory in collaboration with state reference laboratories published a classification of the positive, negative and indeterminate WB patterns based on patterns of reaction using the NRL WB.[9] This classification had been used since that time throughout Australia and New Zealand, until the introduction of the IVD TGA legislation governing Class 4 IVDs. Previous to the IVD framework, the NRL WB interpretation results were regarded as negative if there were no reaction of the patient`s serum with any protein bands. A positive result was defined by detection of antibodies to all of the three main groups of HIV proteins – one env (gp 160, or gp120, or gp 41), plus 3 other viral specific bands from the gag (p24) and pol (p66 or p51) series. HIV-1 WB-indeterminate patterns were assigned to four groups (1 to 4) which stratified the likelihood of true acute HIV infection. Indeterminate groups 3 and especially 4 WB patterns were seen early in the immune response to HIV, although they could also be seen in uninfected individuals. Conversely, with late-stage disease progression (advanced AIDS), gag antibodies may become undetectable and the WB pattern may revert from positive to indeterminate group 4, with reappearance of p24 antigen.

Since introduction of the TGA IVD legislation, interpretation of the WB used must follow that recommended by the manufacturer of the ARTG licensed WB assay. If further interpretation is applied to the WB then data must be available to validate the accuracy of the result to TGA IVD class 4 standards. In patients with repeatedly reactive screening and indeterminate WB results, follow up samples should be tested for HIV nucleic acid and for WB seroconversion. Any positive WB should be confirmed by testing a second sample.

P24 antigen assays

Specificity is insufficiently high for p24 antigen tests to be useful as a screening test with too many false positives generated.[10] Samples reactive on p24 antigen assays must be retested after neutralisation before the results are reported. In vertical infection p24 antigen tests are usually

negative until one to three months of age and false negatives are more likely if neonatal antiviral therapy is given. Caution should be exercised with very low p24 antigen results as the use of optical density values below the cut-off for calculation of neutralisation can produce false positive neutralisation results. In pre-seroconversion acute HIV in adults and older children a positive p24 antigen result should be confirmed with repeat testing for seroconversion and detection of HIV nucleic acid.

Suitable specimens

Serum samples are used routinely for standard HIV antibody and antigen determinations, although plasma samples are also acceptable. Dried blood spots can be used for diagnosis in children who are less than 18 months old. Urine, oral fluid as well as dried blood spot are approved for use in some rapid HIV antibody kits.

As per manufacturer's instructions serum should be promptly separated from the clot/cellular elements and refrigerated at +2 °C to +8 °C. If the test is not performed within seven days, the serum specimens should be frozen at −20 °C or lower. Serum can be transported either at room temperature if it is expected to be processed in four to six hours of collection, or refrigerated if transportation takes place within seven days of collection.

Test performance characteristics

Test specificity depends upon several factors, including pre-test probability, population prevalence and population incidence. The proportion of reactive results that are false are higher in low prevalence populations. Consequently, although they have a have a high specificity (>99.8%), false positive results can occur infrequently.[11] Laboratory confirmation of infection in Australia is therefore required. Factors associated with false positive results include frequent blood transfusion, pregnancy, autoimmune diseases, vaccination, and laboratory errors of procedure or specimen handling.

Factors associated with false negative combo assay results include testing during the window period, immunosuppressed patients and patients receiving post-exposure prophylaxis, patients on PrEP, patients who have advanced HIV infection, as well as laboratory errors.[12]

Western blot indeterminate results in infected individuals are related to several factors such as early seroconversion, incomplete HIV-1 antibody evolution, cross-reactivity with HIV-2 proteins, and cross reactivity with HIV-1 subtype O proteins. Western blots can produce indeterminate results in uninfected individuals associated with multiple transfusions, hypergammaglobulinemia, recent vaccination, advanced AIDS and autoimmune diseases.

Suitable internal controls

Commercial kit and a third party low positive control and negative control should be used in every run as recommended by NPAAC, although they are not mandatory. These are in addition to the mandatory use of kit controls.

Suitable external quality assurance program (QAP) program

QAP programs are provided by the Royal College of Pathologists of Australasia (RCPA) serology quality assurance program (SQAP) and the National Serology Reference Laboratory (NRL).

HIV nucleic acid testing

Molecular based methods for detection of viraemia are available with qualitative NAT and quantitative molecular methods (such as end point and real time PCR, transcription-mediated amplification) for monitoring of viral load and response to antiviral drugs. Some of these commercial NAT assays have a TGA IVD class 4 claim for diagnostic purposes.[3]

Increasingly, molecular tests (qualitative and quantitative) are requested by clinicians for early detection of HIV infection prior to full seroconversion, to facilitate early antiretroviral therapy[1] or to diagnose HIV in infants.[13] NAT assays able to be performed on small volumes (0.1 mL) of whole blood and dried blood spots are used for diagnosis of HIV in infants, enabling the detection of HIV RNA and proviral DNA.

Quantitative viral load assays determine the amount of HIV-1 RNA circulating in the blood of an infected individual. Differences exist in the absolute copy number generated by different viral load assays. International units (IU/mL) are used to report results where 1IU equates to approximately 0.6 copies to allow comparison between different assays, although ideally, the same assays should be used to follow up an individual's viral load.

In Australia, the HIV NAT assays available and their TGA IVD class can be found on the ARTG.

Suitable specimens

The viral load tests are most commonly performed on plasma, which is the validated specimen type for nucleic acid detection. For transport and storage of specimens for HIV NAT, adherence to the manufacturer's instructions is especially important to ensure that RNA degradation does not occur.[12]

These assays have also been used on serum, CSF, cervical secretion, semen and dried blood spot where clinical need has been indicated, although the manufacturer's instructions should be reviewed to ensure the assay is validated for use in these specimens. Sample types outside of the scope of the manufacturer's indications must to be validated by the laboratory to class 4 IVD standards.

Test sensitivity

HIV NAT can detect very low amounts of HIV RNA. The quantitative assays have a large dynamic quantifiable range, depending on the assay, from 20 to 150 copies/mL up to 107 to 108 copies/mL and can detect HIV-1 Group M subtypes A-H and Group O genotypes. Commercial HIV-2 quantitative assays are not available but in-house HIV-2 viral load assays are available in some reference laboratories.

Test specificity

Test specificity varies between assays with indicative specificities approaching 100%. To avoid laboratory contamination, dedicated specimens should be used. Specimens previously used in the serology laboratory should not be then used for HIV NAT.

Suitable internal controls

High positive, low positive, and negative test kit controls must be used in every run. Internal QC samples should be used regularly to monitor assay performance.

Suitable external QAP

These are provided by the RCPA SQAP and the NRL.

HIV proviral DNA PCR

Although HIV-1 DNA PCR has been used as an investigational tool for more than decade, there is no HIV proviral DNA NAT assay registered on the ARTG. Such an assay is of diagnostic use for the detection of HIV infection in infants born to mothers infected with HIV-1. HIV NAT that use whole blood or dried blood spots detect total (RNA and proviral DNA) HIV nucleic acid and may be a suitable alternative.

Antiretroviral drug resistance testing

The replication rate of HIV is very high and there is no viral proof reading during replication, as a result mutations appear readily. Mutations that alter the reverse transcriptase (RT), protease and integrase enzymes may result in antiviral resistance. The resistance profiles are assessed and detected using genotypic methods. Phenotypic testing is restricted to research laboratories. Genotypic drug resistance testing should be performed in treatment naïve patients before initiation of treatment and in cases of virological failure (i.e. failure to decrease the viral load by 1 log after 4 to 6 weeks of treatment) or incomplete viral suppression (undetectable viral load in 4 to 6 months of treatment not achieved).[14]

Genotypic HIV drug resistance testing

A genotypic assay provides an indirect measure of drug resistance because it is based on detection of the mutations known to be associated with resistance.[7] Sanger-based sequencing methods are commonly used, but more recently, some laboratories have introduced next generation sequencing (NGS) targeting specific regions of the HIV genome or whole genome sequencing to determine drug resistance. Typically, Sanger-based sequencing is only able to identify drug resistant mutants at a threshold of 20% of the virus population. It is important to realise that this detects the dominant viruses circulating in the plasma at the time of testing. Low level viruses with different resistance profiles may be present in the blood or in proviral DNA which can re-appear once the antiretroviral therapy changes.[15] By contrast, NGS is able to detect drug resistant mutants at a threshold of <5%. The improved sensitivity of NGS to detect low frequency mutations may be of relevance in the era of two-drug antiretroviral therapy regimens. In general, both methods require the HIV viral load to be >1000 copies/mL to be successful.

Phenotypic HIV drug resistance testing

Phenotypic assays are no longer used in routine diagnostic laboratories due to the intense labour involved, long turnaround times, and the requirement of a PC3 facility. Phenotypic assays assess the ability of the virus to grow in various concentrations of a given antiretroviral drug. These assays are currently only available in Australia in clinical trials. They involve the insertion of RT or protease gene sequences into a plasmid vector, then culturing a hybrid virus containing that vector in the presence of antiviral drugs, with comparison to a drug-susceptible wild- type HIV.

Suitable specimens for genotypic testing

Plasma collected from EDTA or plasma separator tube can be used. The plasma must be separated from the cellular elements within 6 hrs of collection and frozen immediately.

Utility

Treatment may be altered in the knowledge that a patient is carrying a virus resistant to one or more antiretroviral medications. This leads to improved virological suppression in patients whose therapeutic choices have been guided by the use of resistance testing.

Suitable external QAP program

Several programs (QCMD and Instand) are offered.

HIV viral isolation

Although a positive culture provides direct evidence of HIV infection, HIV culture is no longer used for routine diagnosis, as it has long turnaround time, low sensitivity and it is labour-intensive. It was useful before the development of NAT in detecting infection in infants born to mothers with HIV infection. Its use is now confined primarily to research laboratories.

In the assay, patient specimens are first cultured by mixing patient peripheral blood monocyte cells (PBMCs) or serum with PBMCs from healthy donors stimulated with phytohemagglutinin and IL-2. Freshly stimulated donor cells must be added weekly, because HIV-1 causes cell death. Viral growth is detected by the presence of RT or p24 antigen released in the culture supernatant.

Point of care testing

Rapid POC assays that detect HIV specific antibodies have been available in Australia since 2012, and their use has increased in the past decade. These assays require less technical expertise to perform and are commonly used to increase HIV testing, particularly in high-risk groups (such as men who have sex with men) that are unwilling (e.g. due to concerns about stigma and discrimination) or unable to access health care facilities. The reduced turnaround times of results compared to standard laboratory-based diagnostic tests also make POC tests attractive in this group. POC testing is generally not appropriate in populations with low prevalence or pre-test probability of HIV infection due to the potential for false reactive results. POC tests should be used as screening tests only, and reactive results need to be confirmed by conventional testing. POC tests are not appropriate for testing persons with a seroconversion illness or during the window period of HIV infection as the test may be falsely negative [ASHM]. Depending on the POC assay used, suitable samples include

capillary blood and saliva. Only POC tests registered on the ARTG can be used, and testing must be conducted under an appropriate framework that ensures the required quality and safety.[16]

Diagnosis of HIV in neonates and children < 18 months of age

HIV infection in neonates or children < 18 months born to HIV-infected mothers cannot be diagnosed by serological tests due to the passively acquired maternal antibodies, which may persist for up to 18 months.[17,18] Diagnosis in this period can be established using molecular testing such as proviral HIV DNA testing on whole blood or dried blood spots, or HIV RNA NAT on plasma. These virological assays are considered to be the reference standard for diagnosis of HIV infection in children younger than 18 months. Testing of cord blood is not recommended as there is a chance of contamination of the cord blood by maternal blood which can lead to false positive results.

In the diagnosis of HIV in neonates, proviral HIV DNA or RNA must be tested at different time points as NAT sensitivity increases with age in infants.[19] Regimens include testing at three time points - within the first 7 days of life, at 6 weeks and 3 months.[20] A definitive diagnosis of HIV-1 infection can be made on the basis of positive HIV proviral DNA or RNA assay results from two or more separate samples.[18] HIV infection can be presumptively excluded based on two negative virological test results, one obtained at 6 weeks and one obtained at 3 months of age. HIV antibody testing is performed at 18 months of age to document the clearance of maternal HIV antibodies (seroreversion) and to confirm the infant's HIV negative status.

HIV-exposed infants are usually formula-fed in Australia, although breastfeeding for up to six months may be considered in mothers with undetectable viral loads. However, if the infant is still breastfeeding from an infected mother, negative results need to be repeated at 4-6 weeks after cessation of breastfeeding to confirm that the infant is not infected.

HIV screening in solid organ and blood donors

Traditionally HIV seropositive donors have not been utilized in transplantation, due to the known risk of transmission to the recipient. HIV-1 and HIV-2 serology results are required for all potential donors. HIV transmission from an antibody-negative organ donor can occur if the donor is in the serological window period after infection but prior to development of anti-HIV antibody. Therefore HIV-1 NAT testing is also performed on organ donors and cadaveric tissue donors, as it has been on blood donors for many years. Any positive screening test for either HIV-1 or HIV-2 should be confirmed, as for standard confirmation of HIV infection. Although previously considered a contraindication to transplantation, HIV infection in the recipient is no longer an absolute exclusion as many patients with HIV on effective antiretroviral therapy are living longer and are far less immunocompromised, and end-stage organ failure rather than HIV is their survival-limiting condition.

Snomed- Clinical Terms (Ct) terminology

SNOMED Code System Concept Code	86406008
Read Code	X70M6
Code System Concept Name	Human immunodeficiency virus infection (disorder)
Code System Preferred Concept Name	Human immunodeficiency virus infection
Concept Status	Published
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ICD10 codes	B210 B211 B201 B200 B219 B202 B209 B208 B205 B204 B24X B206 B230 B218 B232 B220 B227 B221 B231 B212 B203 B222 B207 B213 B217 B238

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