

Exposure and acute HIV infection

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Introduction

Early diagnosis, monitoring and treatment of patients with recently acquired human immunodeficiency virus (HIV) infection may alter the long-term course of HIV disease. Knowledge of the clinical signs and symptoms of primary HIV infection, as well as the serological and virological markers, enables early HIV diagnosis by clinicians and provides patients with timely options for intervention choices, as well as opportunities for receiving appropriate referral, support and education on prevention of transmission.

Pathogenesis of acute HIV infection

Knowledge of the pathogenesis of primary HIV infection in adults helps the clinician to understand HIV-related pathology testing. Within 12–24 hours of exposure, cells at the site of a mucosal infection are infected with HIV. Forty-eight hours after exposure, HIV has spread to regional lymph nodes where rapid replication occurs within immune cells, primarily CD4 cells. Cells in the gut become infected as well as those of the central nervous system and the skin.^{1,2} Over the next 5–40 days, the host immune response to massive HIV viraemia results in the production of neutralising antibodies and a cytotoxic T-cell response mounted by CD8 T-cell lymphocytes. The T-helper CD4 cells control the cytotoxic response but also are infected by HIV. Many, but not all, of these infected CD4 cells are killed by the cytotoxic CD8 responses, causing a fall in the CD4 cell numbers. These changes can be observed clinically by monitoring CD4 and CD8 cell counts in the peripheral blood.

The flu-like symptoms of primary HIV infection are caused by the release of cytokines during the process of infection and immune response. As a result of the immune response, the blood concentration of the virus (the viral load) falls and new CD4 cells are produced by the bone marrow via the thymus. For reasons that are unclear, the cytotoxic CD8 cell response is not able to clear or completely control HIV, as occurs with some, but not all viral infections.

Key points

- Early diagnosis of HIV disease has significant potential benefits and the likelihood of ongoing transmission may be reduced through implementation of safe sex and risk reduction strategies.
- Acute HIV infection may be difficult to distinguish from other acute viral illnesses. Clinical features that should alert the clinician to the possibility of acute HIV infection in the presence of a mild-to-severe flu-like illness include a 'glandular fever-like' illness, meningeal involvement, a recent sexually transmissible infection and transient neurological symptoms.
- Post-exposure prophylaxis (PEP) may reduce the risk of HIV infection if offered within 72 hours of HIV exposure.
- When a patient presents reporting a high-risk exposure to HIV, immediate referral to an antiretroviral prescriber, sexual health centre or hospital emergency department is necessary to access non-occupational post-exposure prophylaxis.
- Symptoms of primary HIV infection can usually be managed in the primary care setting by the general practitioner. Decisions about antiretroviral therapy need to be made in conjunction with an HIV-experienced clinician.
- While newly diagnosed patients may require ongoing specialist services from a range of providers, the general practitioner remains an important source of initial and continued information and support.

Detecting primary HIV infection

Primary HIV infection: acute retroviral syndrome

Familiarity with the range of presentations associated with primary HIV infection (also called acute retroviral infection or seroconversion illness) enables the early diagnosis and management of HIV infection. Clinical suspicion of acute HIV infection should be followed by a thorough risk assessment (Chapters 2 and 3). As the symptoms and signs of acute HIV infection are similar to

Table 4.1 Symptoms and signs of primary HIV infection^{9,10}

Symptoms of HIV seroconversion illness		
	Symptom	Frequency
Generalised	Fever	>80%
	Lethargy and general malaise	>70%
	Myalgia and arthralgia	50-70%
	Lymphadenopathy	40-70%
	Night sweats	50%
Gastrointestinal	Pharyngitis	50-70%
	Diarrhoea	30%
	Oral ulcers	10-30%
Neurological	Headache	40-70%
	Aseptic meningitis	
	Transient reversible neurological signs (neuropathies, Guillain-Barré)	Rare
Skin	Rash	40-80%
	Genital ulcers	5-15%
Initial laboratory finding	Thrombocytopenia	45%
	Leukopenia	40%
	Raised liver enzymes	20%
Diseases caused by transient immunosuppression	Oral/oesophageal candidiasis Gut infections Pneumocystis jiroveci pneumonia (PCP)	Rare

those of many common infections, the presence of HIV infection is more likely when a recent high-risk exposure has been reported.

Signs and symptoms

Signs and symptoms of acute HIV infection can present as early as three days or as late as 10 weeks following transmission. Most commonly they occur at 10–14 days. The onset of symptoms often coincides with the appearance of HIV antibodies although the patient may be HIV antibody negative (ELISA) for up to three weeks after onset of symptoms. The duration of the illness is most commonly four to 14 days but may be longer.^{3,4} Approximately 50–90% of patients report signs or symptoms suggestive of primary HIV infection at the time of seroconversion.⁴⁻⁷ Patients who experience symptomatic primary HIV infection appear to have more rapidly progressive HIV disease than those who do not.

The frequency of symptoms varies and severity ranges from very mild to very severe (Table 4.1). No single symptom distinguishes acute HIV infection from other acute viral illnesses. However, there are some factors that should alert the clinician to the possibility of acute HIV infection in the presence of a flu-like illness such as:

- Epstein-Barr seronegative 'glandular fever-like' illness
- 'Flu-like' symptoms outside usual influenza season (e.g. myalgia, arthralgia, headache, malaise)
- Fever for more than three days
- Maculo-papular rash
- Meningeal involvement
- Transient neurological syndromes (e.g. Guillain-Barré syndrome, neuropathies)
- Recent evidence of sexually transmissible infections or genital ulcers
- Recent high-risk exposure

TABLE 4.2 Pathology tests for diagnosis of primary HIV infection

HIV antigen tests	
P24 antigen	P24 antigen may become positive within a few days of symptoms and be absent after two weeks.
Quantitative HIV RNA viral load by reverse transcriptase polymerase chain reaction (RT PCR)	HIV RNA viral load may become positive within a few days. However, the quantitative viral load assay is generally not recommended to diagnose acute HIV infection due to a reported low false-positive rate in the acute setting (usually indicated by low viral levels).
HIV antibody tests	
HIV antibodies (EIA)	EIA may take up to three weeks to become positive after onset of clinical signs and symptoms.
HIV Ag/Ab Combo Test	75% of labs use this test as the standard HIV antibody screening test. This is a combined p24 antigen plus HIV antibody test and so it will become positive before a test using HIV antibody alone in acute infection.
HIV antibodies (Western Blot)	Western Blot may take up to three weeks to become positive after onset of clinical signs and symptoms.
Note: Other tests may be indicated and should be performed in conjunction with specialist centres and laboratories.	

Recent risk exposure

Patients reporting recent risk exposure should be thoroughly assessed and monitored for HIV infection. The possibility of HIV infection can be an emotionally difficult time for the patient. Providing the full pre-test discussion and sharing information are required to prepare the patient for the possibility of a positive diagnosis and to provide him or her with the required information about HIV infection (Chapter 9).

For high-risk HIV exposures that have occurred within the last 72 hours, non-occupational post-exposure prophylaxis (NPEP) should be considered.⁸ Case study 2 and the Box entitled 'Non-occupational post-exposure prophylaxis (NPEP): is prevention of HIV infection possible after exposure?' in this chapter address assessment and referral for NPEP.

Potential exposure to HIV often indicates a risk of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection as well as a risk of other sexually transmitted infections (STIs). Consequently, investigations for STIs prevalent in the community, HBV and HCV should be considered in the context of acute HIV infection.

Investigations

When risk assessment or clinical presentation indicate the possibility of acute HIV infection, laboratory testing ensures correct diagnosis. HIV antibody tests (HIV ELISA and Western Blot) may be negative or equivocal up to three weeks after the start of primary HIV illness (Table 4.2). However, HIV viraemia appears in the blood in the early days of the illness and may allow detection of

virus particles or proteins (antigens) in the absence of antibodies. If available, tests for viral antigens included in later generations of HIV antibody and antigen assays may facilitate early diagnosis of HIV infection during the window period.

It should be noted that the molecular tests currently available in Australia (listed in Table 4.2) do not have approval from the Therapeutic Goods Authority (TGA) needed for their use in the primary diagnosis of HIV infection. Molecular tests should therefore be considered confirmatory (of an indeterminate serology result) when used in this setting.

Interpreting test results with regard to acute HIV infection can be confusing and, if necessary, clinicians are advised to seek guidance from their pathology laboratory or the National Serology Reference Laboratory (Chapter 15).

Management of acute HIV infection and recent exposure

Acute HIV infection

People with primary HIV infection can usually be managed in the community by their own general practitioner (GP), with the support of either an HIV-experienced GP and a hospital-based specialist. Most of the physical symptoms of the infection are treatable with simple analgesics and antiemetics. Occasionally hospital admission may be required for rehydration or management of rare manifestations such as encephalitis or Guillain-Barré syndrome (Table 4.3).

TABLE 4.3 Management of primary HIV infection checklist

- Referral to an HIV-experienced GP and/or a hospital-based clinician
- Support for the primary care clinician from an HIV-experienced GP and/or a hospital-based clinician
- Physical symptom relief such as analgesia for headache, myalgia and arthralgia, and antiemetics for nausea
- Appropriate treatment for opportunistic infections
- Psychosocial support of the patient by the clinician and referral to an experienced mental health professional as appropriate
- Early and frequent follow-up

Very early treatment with antiretroviral therapy – a controversy

Treatment of HIV infection during the early stages of chronic infection remains a controversial and changing area of HIV medicine. Some HIV clinicians treat primary HIV infection with combination antiretroviral medications after one or more of the confirmatory tests have returned positive. The rationale for treatment during this phase of HIV disease is to minimise immune system damage, to lower the viral replication 'set point' (Chapter 1) and to minimise viral dissemination throughout the body.

Others have argued that the early immune response to HIV may require the ongoing presence of HIV antigens and that disturbing this response may be harmful. In addition, short-term and long-term side effects of therapy can be considerable (Chapter 10).

While there are theoretical benefits associated with early treatment, there have been no randomised, controlled trials examining the efficacy of very early treatment in terms of time to progression to AIDS or death. Ongoing randomised studies such as the SPARTAC study (an international trial comparing three different strategies of intervention in patients recently infected with HIV to determine whether early treatment for a limited duration delays damage to the immune system and consequently prolongs time to initiation of long-term antiretroviral therapy) may help provide answers. Clinicians inexperienced in the management of HIV infection need to contact an HIV-experienced GP or a hospital centre to discuss further management.

If the patient proceeds with treatment during primary infection, preferably within a clinical trial, HIV-inexperienced clinicians are encouraged to maintain contact with their patients as part of the treatment team, especially as newly diagnosed and infected people require considerable information and support from a trusted and accessible source.

Contact tracing

Contact tracing of people who may have been exposed to HIV prior to identification of primary infection should be undertaken. Discussion with the patient regarding how to proceed with contact tracing may be appropriate.

The clinician may ask the patient to consider recent blood-to-blood or sexual contacts as well as recent blood donations. Review of appropriate State or Territory guidelines and discussion with public health authorities may be considered.

Public health notification

Public health authorities must be notified when HIV infection has been diagnosed. In most States and Territories notification can be undertaken by clinicians or pathology laboratories, although there are differences in legislative and regulatory requirements (Chapter 14).

Supporting newly diagnosed patients

The ongoing psychological adjustment of patients to HIV infection can be affected by the nature of early consultations with their doctor after diagnosis. In particular, having a long consultation when the HIV diagnosis is given has been positively correlated with better long-term adjustment, as have the quality of information given and the attitude of the person giving the diagnosis.^{11,12}

Newly diagnosed patients have major issues to face and adjustments to make during early consultations. For example, patients may suddenly confront their mortality or have concerns about future income and relationships with partners, family and friends.¹³⁻¹⁵

Patients with children often have concerns about how their children will deal with the diagnosis and whether they will be able to continue to provide for the children materially and emotionally.¹⁶ For women of childbearing age, there may be fears and concerns about how HIV affects their future reproductive life.¹⁷ Simple acceptance, in the face of perceptions of social stigma and discrimination, may be the most valuable support

CASE STUDY 1**Diagnosing and managing HIV seroconversion illness****Severe flu or HIV seroconversion illness?**

John is a 39-year-old engineer who presents to his general practitioner, Dr Lewis, with a flu-like illness in April. He has been unwell for a week with muscle aches and pains, fever, headache and retro-orbital pain, particularly upon lateral gaze. He has spent the last four days on the couch at home and has noticed that his urine is very dark.

Dr Lewis considers a differential diagnosis of HIV seroconversion illness and conducts a risk assessment. 'I need to ask some sensitive questions. Nowadays we need to ask people about risk behaviours for HIV when they present with an unusual flu-like illness. Have you done anything in the past few weeks that might worry you or might put you at risk for HIV? What I mean is, any unprotected sex or sharing needles?'

John relates that he recently started a relationship with Sam and that they have been having sex without condoms for four months. They intended to have HIV tests but 'hadn't got around to it'. While John was HIV-negative when tested last November, he is unsure when Sam was last tested. John has been vaccinated against hepatitis A and B and reports never using needles.

Given his high-risk activity for HIV transmission, Dr Lewis suggests HIV testing to John: 'While lots of other common viruses cause symptoms like this, we should consider testing for HIV infection. The first illness that some people get when they are infected with HIV can look like flu.' Following pre-test

counselling, John consents to testing for HIV and HCV. Three days later, the laboratory rings Dr Lewis about John's test results.

Results

Standard (EIA) test for HIV antibodies – negative
P24 antigen test – positive
Western Blot test result – pending
Liver enzymes – slightly elevated
Hepatitis C antibodies – negative

John's tests confirm a clinical diagnosis of HIV primary infection. He is referred to a GP experienced in the management of HIV infection after indicating that he would prefer to see a community-based HIV clinician. After lengthy discussion about treatment options, the HIV-experienced clinician and John decide to go ahead with antiretroviral treatment.

Dr Lewis continues regular follow-up with John to address his ongoing medical and psychosocial needs following the HIV diagnosis. In addition to assistance in taking medications, John raises relationship and sexuality issues. Dr Lewis refers him to the local AIDS Council for support and offers written resources for HIV-positive people.

CASE STUDY 2**Non-occupational post-exposure prophylaxis (NPEP) presentation and issues of safe sex and disclosure****NPEP, safe sex and disclosure**

David is a middle-aged, married man who presents to his general practitioner, Dr Betheras, for non-occupational HIV post-exposure prophylaxis (NPEP) the morning after a condom break during receptive anal sex in a sex-on-premises venue.

Dr Betheras immediately organises referral to a general practitioner who can prescribe antiretroviral therapy (antiretroviral therapy prescribing practitioners' contact details are listed in the *ASHM Directory* at <http://www.ashm.org.au/ashm-directory/>). Before David leaves for his next appointment, Dr Betheras advises him that he will need to institute condom use when having sex with his wife and any other sexual partners until he has his final, week-24 test results. 'How will I explain this to my wife?' David asks. Dr Betheras explores his concerns about the risk episode and the fear, guilt and shame he is experiencing. She also discusses with him the issues involved in talking about the episode with his wife, if and when he decides to do so.

David returns to see Dr Betheras several days later to discuss the issue of safe sex.

He decides that he must tell his wife but is reluctant to do so immediately. In the meantime, he decides to say that he has a urinary infection and needs to use condoms for a while. Dr Betheras suggests that it might be a good idea to see a counsellor about these issues. David agrees and referral details are provided.

Dr Betheras also discusses the case with her medical insurer and gets advice about the legal issues of duty of care and confidentiality regarding both David and his wife (Chapter 14). She continues to monitor the situation in conjunction with the general practitioner providing NPEP.

a clinician can offer in early consultations. Patients may also need help in deciding whether to disclose their HIV status and, if so, to whom.¹⁸

Emotional support and acceptance can also assist the person to make beneficial alterations to his or her lifestyle, such as changes to diet and exercise, reduced drug and alcohol use and practising safe sex.¹⁴

Support services and the role of the clinician

In addition to the support that clinicians can offer, patients should be referred to other agencies for information, counselling and support as appropriate (Chapter 15). Research has identified the importance of

contact with HIV-positive communities in helping newly diagnosed patients come to terms with their status and continue with their lives.¹⁵

However, while acknowledging that specialist counselling may best meet the psychosocial needs of patients, clinicians must recognise that they may be the first and most important source of this support and information in their patients' lives. This is especially true during the early stages of HIV infection. Maintaining contact with the patient after the initial diagnosis, as either the key HIV-treating clinician or as a partner in care, helps to support the patient through the many difficulties that may lie ahead.

Non-occupational post-exposure prophylaxis (NPEP): Is prevention of HIV infection possible after exposure?

There is some evidence that a four-week course of antiretroviral therapy, commenced as soon as possible within 72 hours of exposure to HIV (whether it be an occupational or non-occupational exposure [NPEP]), can reduce the risk of HIV infection.²⁰ Such therapy is called post-exposure prophylaxis (PEP). Antiretroviral therapy for HIV infection is listed under Section 100 of the Pharmaceutical Benefits Scheme and can only be prescribed by approved clinicians. In addition, none of the individual antiretroviral drugs are licensed for use in post-exposure prophylaxis and must be covered under state-based services. Each state determines how PEP is made available and this is usually through hospital emergency departments and public sexual health clinics. Community s100 prescribers can assess cases and write scripts for PEP, but the drugs are dispensed from hospital pharmacies.

Risk assessment

To respond appropriately to a possible HIV exposure requires an assessment of the likelihood of HIV infection in the source, the risk associated with the exposure and the effectiveness of treatment options. Highest risk is defined as sexual exposure with an HIV-infected person via receptive intercourse (without intact condom) or exposure to HIV-infected blood via injecting equipment where percutaneous exposure has occurred with a used hollow needle (Chapters 2 and 3).

For percutaneous, occupational exposures, the National Needlestick Injury Hotline (1800 804 823) can provide advice to health care workers regarding the level of risk (Chapter 15).

Assessment should address whether the source is known to have HIV infection or viral hepatitis or risk factors for blood-borne viruses, including a history of unprotected sex with homosexual or bisexual men, a history of injecting drug use, or haemophilia (Chapters 2 and 3). If the source is available and willing, testing for HIV and viral hepatitis should be conducted with full pre-test and post-test discussion and information sharing.

NPEP

Following assessment, all individuals with high-risk exposures should be immediately referred to an approved antiretroviral prescriber, a sexual health centre, or the emergency department of a major hospital for provision of NPEP.⁸ The sooner the post-exposure antiretroviral treatment is commenced the greater the theoretical chance of success. Details of how to contact antiretroviral prescribers are given in the ASHM Directory. NPEP involves a one-month course of dual or triple drug therapy. It must be taken strictly as prescribed to reduce the risk of drug resistance. Antiretroviral drugs cause common side-effects such as nausea and diarrhoea as well as rare, severe side-effects, so monitoring by an HIV clinician is required.

The possibility of exposure to HIV causes anxiety and concern. Patients need considerable support at this time, due not only to the possibility of new HIV infection, but also to help manage the adverse effects of the antiretroviral medications. Enabling a patient to examine and modify his or her sexual and injecting drug use risk behaviours is a vital component of the NPEP process. Patients may require referral to an experienced counsellor.

Testing for HIV and other sexually transmitted infections and blood-borne viruses is required at baseline, at three months (HIV and syphilis) and at six months (HCV) after exposure, to exclude the possibility of late seroconversion. During this time, patients should adopt safe sexual practices with all partners and should not donate blood, body tissues or semen, and female patients should not breast-feed infants.

National guidelines on the use of PEP for non-occupational HIV exposures have been produced by ASHM.¹⁹

Other sexually transmitted infections

Assessment for acute HIV and potential recent exposure typically reveals risks for, or symptoms of, other STIs. So, just as the choice of investigations for symptoms must take account of the many possible causes of those symptoms, screening for relevant STIs must be considered standard of care at this time. The detection and treatment of STIs is very important in its own right, but their treatment can also reduce the risk of HIV transmission. Australian non-occupational post-exposure prophylaxis guidelines¹⁹ recommend baseline testing for chlamydia, gonorrhoea (see Chapter 8), hepatitis B and syphilis with repeat syphilis testing at three months. The same STI tests are appropriate after any sexual risk exposure including sexual assault²⁰ (also refer to National/State guidelines regarding management of sexual assault). The use of post-exposure prophylactic antibiotics against STIs like chlamydia is not recommended after risk exposure, although they may be indicated after some types of sexual assault.¹⁹

Summary

The primary care clinician has a key role in identifying cases of primary HIV infection and facilitating the clinical monitoring and management of infected individuals. Following diagnosis of primary HIV infection, referral to an HIV-experienced clinician is recommended for consideration of antiretroviral therapy, preferably in the context of clinical trials. To reduce the risk of infection after a high-risk exposure to HIV, post-exposure prophylaxis may be taken within 72 hours of the exposure. Reported exposure provides an opportunity to review risk behaviours, safe sex practices, harm minimisation strategies and assessment for other STIs. Provision of information and psychosocial support are key elements of management following a possible HIV exposure or diagnosis with primary HIV infection.

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