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Consider HIV

Testing for HIV and HIV indicator diseases

Background
Since the advent of highly active antiretroviral therapy (HAART), human immunodeficiency virus (HIV) can be considered a treatable condition. In Australia in 2010, 40% of people had their HIV diagnosed late, where late is defined as CD4 <350 cells/mm^3 (CD4 normal range = 450–1 500 cells/mm^3). This late diagnosis can significantly impact on prognosis.

Objective
This article provides examples of late HIV diagnosis and an update of how and when to test for HIV in clinical practice.

Discussion
While HIV is usually diagnosed in those with identifiable risk factors, awareness of indications to test and potential HIV indicator diseases can provide the general practitioner with a cue to offer testing to a patient. Early diagnosis of HIV offers benefits to the patient and the community.

Keywords
HIV infections; delayed diagnosis; risk assessment

Case study 1

A man, 36 years of age, moved to Australia in 2004 from sub-Sahara Africa on a skilled migrant visa. Soon after, he developed new onset severe psoriasis, which was resistant to topical treatment. He was prescribed methotrexate, which led to a resolution of his psoriasis. In 2010, he was diagnosed with human immunodeficiency virus (HIV) after applying for permanent residency. Surrogate markers of disease progression showed the extent of his HIV immune suppression with a CD4 lymphocyte count of <5 cells/mm^3 (normal range = 450–1 500 cells/mm^3).

He was started on antiretroviral (ARV) therapy, but 2 weeks later developed rigors and spiking temperatures of 39.9°C. Investigations revealed a diagnosis of mycobacterium avian intracellae (MAI) infection, which is an acquired immunodeficiency syndrome (AIDS) defining illness. After completing the MAI treatment (three antimicrobials for 12 months) he now has a CD4 count of 480 cells/mm^3 and an undetectable HIV viral load.

If the patient's HIV infection had been diagnosed earlier when he presented with the new onset severe psoriasis, it is unlikely his CD4 count would have fallen so low (as ARV therapy would have been started). It would then have been very unlikely that he would have had the opportunistic infection MAI, which is strongly associated with a very low CD4 count.

Case study 2

A Caucasian man, 33 years of age, was diagnosed HIV positive after his general practitioner (GP) diagnosed an oral candida infection. At diagnosis, his CD4 count was 10 cells/mm^3. He was commenced on ARV therapy and had an excellent response to treatment; his most recent CD4 being 698 cells/mm^3.

The patient had been attending his GP regularly over the preceding 4 years, reporting many non-specific symptoms including fatigue, night sweats and unexplained weight loss of 10 kg. The symptoms had concerned the GP who had investigated him intermittently with a series of bloods tests, including viral serology and checks for disorders of metabolism. The patient had never been offered a HIV test and he did not think he had been at risk of acquiring HIV infection.

Case study 3

A woman, 30 years of age and in her first pregnancy, tested HIV positive during routine antenatal testing at 8 weeks gestation. At diagnosis, her CD4 was 1100 cells/mm^3.

She was started on ARV therapy at 20 weeks gestation, which reduced the risk of mother-to-child HIV transmission. She tolerated treatment well and, by delivery, her viral load was undetectable.

Her baby tested negative for HIV at 48 hours and then at 12 weeks. The patient was unable to identify any risks that had exposed her to HIV infection. Her regular partner was tested and also found to be HIV positive. His CD4 count was 230 cells/mm^3, but he was asymptomatic. He was started on ARV therapy.

Case study 4

A man (patient A), 28 years of age, attended the emergency department (ED) complaining of a 2 day history of a sore throat, fever and rash. Before this, he had been fit and well with no significant past medical history. He was not taking any medications. His temperature was 38ºC. He had a generalised erythematous maculopapular rash and a red inflamed throat. A diagnosis of 'viral illness' was made. After being given paracetamol, he was well enough to go home and advised to be reviewed if his symptoms persisted. His symptoms resolved, so he didn't attend for review.

Eight weeks later, his regular male sexual partner (patient B) was diagnosed as HIV positive. Patient A was tested as part of contact tracing procedure and also found to be HIV positive. Both had tested HIV negative 6 months earlier. The only identifiable risk was that patient A had had sexual intercourse with an ex-partner 2 weeks before his presentation to the ED.

Patient A's presentation to the ED is consistent with an HIV seroconversion illness. During and just before seroconversion, there is uncontrolled viral replication and HIV is readily transmitted by sexual contact. Early diagnosis of primary HIV infection provides a public health opportunity to prevent the onward transmission of HIV.[1]

By the end of 2011, 31 645 cases of HIV infection had been diagnosed in Australia, and an estimated 24 731 people were living with diagnosed HIV infection.[2] People born in Australia accounted for 55% of cases of HIV newly diagnosed between 2007 and 2011. Sexual contact between men remains the most common route of HIV transmission, accounting for 66% of transmissions. In 2002–11 approximately 6% of HIV diagnoses in Australia were in people with a history of injecting drug use, of whom more than half also reported sexual contact with men.[2] Among people born outside of Australia, the rate of HIV diagnosis in heterosexuals has increased. This is particularly so of people born in sub-Saharan Africa and high prevalence Asian countries.[3]

Starting treatment

Treatment of HIV could be considered a medical success story. Before 1996, the majority of people who had HIV died of AIDS. Since the advent and successful use of highly active antiretroviral therapy (HAART), HIV is now regarded as a chronic condition that can be controlled, with patients looking forward to an increasingly normal life expectancy. Treatment has become simplified with one pill once a day, and an expanding array of treatment options. Modelling has indicated that with timely diagnosis of HIV and management with effective antiretroviral treatment, HIV positive individuals, on average, are only likely to lose around 7 years of life.[4]

Despite the optimism treatment has brought to those living with HIV, a large proportion of the HIV diagnosed in Australia is 'late' (where late is defined as a CD4 <350 cells/mm^3). In 2010, 40% of people were diagnosed with HIV late, 20% of which had a CD4 count of <200 cells/mm^3.[3] The late diagnosis of HIV is a worldwide problem, not one unique to Australia.

A late diagnosis is one of the most important factors impacting on the morbidity and mortality associated with HIV.[5] Before the introduction of effective ARV therapy, patients with a low CD4 lymphocyte count were at considerable risk of opportunistic infections or AIDS. With increasing availability of well tolerated and simplified treatment regimens, AIDS and opportunistic infections are rare.

In recent years, there has been a growing awareness that untreated HIV infection is also associated with the effects of ongoing inflammation, with the development of many non-AIDS related conditions including cardiovascular disease, kidney disease, liver disease, cancer and neurocognitive decline.[5] A large international randomised controlled trial demonstrated episodic ARV therapy guided by the CD4 count (compared with continuous antiviral therapy), significantly increased the risk of opportunistic disease or death from any cause.[6]

Currently available ARV regimens are more effective, more convenient and better tolerated than older combinations. To counteract the harmful effects of ongoing immunosuppression, evidence based guidelines have moved in recent years toward starting ARV therapy earlier, and certainly before an individual's CD4 is in the region of 500 cells/mm^3.[7]

Testing for HIV

HIV testing rates in Australia are considered to be one of the highest in the world. However, it has been shown that 'late presenters' have often been seen in the recent past by numerous healthcare professionals, without the diagnosis of HIV having been made.[8] Therefore, there is considerable scope to increase the early detection of HIV, thereby improving the long term prognosis of those infected with HIV, and reducing the onward transmission rate.

The prevalence and the community awareness of many sexually transmissible infections in Australia is increasing. It is important that we encourage health professionals and the community to accept HIV testing, to identify patients at risk and to increase the rate of opportunistic detection by remembering to consider HIV as a diagnosis, even in those not overtly presenting as being at high risk. Health professionals should be able to recognise the signs and symptoms of undiagnosed HIV infection and acute seroconversion illness. It should also be remembered that people who have been infected with HIV may not recognise they have been at risk of acquiring HIV. One example is that of someone who considers that they are in a monogamous relationship, when in fact their regular partner is having high risk sexual intercourse outside the relationship.

Reasons to test for HIV

The early identification of HIV infection has many clear benefits.

HIV is a treatable condition

The prognosis is excellent if an individual is diagnosed early and started on treatment when the CD4 count is still above 350 cells/mm^3.

There is a strong correlation between a low baseline CD4 lymphocyte count when first commencing ARVs and the poor prognosis of an HIV infected individual.[9]

Opportunity to change behaviours

There is clear evidence that once an individual is aware of their HIV status they change their behaviour, and so are less likely to onward transmit HIV.[10] An estimated 49% of HIV transmissions are from 20% of people who are unaware of their HIV infection. Early detection would result in about eight transmissions averted per 100 persons newly aware of their infection.[11]

Reduced risk of transmission

Effective treatment of HIV resulting in HIV viral suppression reduces the risk of HIV transmission. A recent, large randomised controlled trial showed that ARV therapy reduced the risk of HIV transmission in heterosexual couples by 96%.[12]

Health resource implications

People who are diagnosed late with HIV are likely to utilise more healthcare resources than those who are diagnosed early, particularly hospital costs and non-HIV drug therapies. It has been shown that treating those who are diagnosed late (CD4 <200 cells/mm^3) costs twice as much as treating those who are diagnosed earlier.[13]

Prevention of mother-to-child transmission in pregnancy

Many women are diagnosed with HIV antenatally. A 2006 Australian study revealed that many obstetricians do not routinely offer HIV tests to women, as they perceive them not to be at risk.[14] Testing rates in Australia have improved since this time, however, it is important to ensure routine testing continues to be offered to antenatal women, as intervention during pregnancy, delivery and the neonatal period can reduce the risk of mother-to-child transmission from 25–40% to less than 1%.

Who to test for HIV?

There is no doubt that the role of a GP in the early detection and management of HIV is a challenging one. However, people who are unknowingly HIV positive typically visit their healthcare provider with illnesses and unexplained symptoms, which in hindsight, could have been attributed to HIV.

HIV is mostly diagnosed in people who have had an identifiable risk, which has been beneficial for targeted testing and health promotion campaigns. However, this picture may be changing. In the past 10 years, men and women whose exposure to HIV was attributed to heterosexual contact experienced a substantially higher rate (28%) of late HIV diagnosis.[2] Nevertheless, studies have shown that many patients who have recently tested positive for HIV have had evidence of HIV indicator diseases (*Table 1*) for which they should have been offered a HIV test.

Other indications to test (*Table 2*) may be seen more routinely without underlying HIV infection, but are still common in HIV positive individuals and may be used as a trigger to screen for HIV. In addition, there is evidence to show that doctors and other healthcare workers may not challenge assumptions made about the presence or absence of a risk factor for HIV when assessing a patient. HIV testing should always be offered when:

- there has been the possibility or reality of a high risk exposure, ie. unprotected receptive anal sex, and to be able to assess risk, an adequate sexual history must be taken
- there is an unexplained illness or symptoms (especially indicator illnesses), as well as glandular fever-like illness.

Which test should be used?

Australian laboratories are using the fourth generation HIV test (antigen/antibody combination test) which becomes positive 2–6 weeks after exposure.[15] Given the small window period with the fourth generation HIV test, it is recommended to test patients at their initial presentation and 3 months later. As the fourth generation assay is a screening test, laboratories will test any reactive samples with a reference test. The point-of-care test (POCT) has recently been licensed in Australia, and may be of use in harder-to-reach high risk groups where an on-the-spot analysis can help improve testing rates.

The national Australian HIV testing policy was published in November 2011, and more information around HIV testing can be found at http://testingportal.ashm.org.au/hiv.

How to test

The purpose of a pre-test discussion is to establish informed consent, to assess risk, to

Table 1. HIV indicator diseases[16,17]

Any AIDS defining condition
Tuberculosis
Sexually transmissible infection (STI)
Hepatitis B
Hepatitis C
Malignant lymphoma
Castleman disease
Head and neck cancer
Anal and cervical intraepithelial neoplasia grade 2 or above
Unexplained thrombocytopenia, lymphopenia or neutropenia for more than 4 weeks
Shingles (varicella zoster infection) recurrent or multidermatomal
Severe or recalcitrant psoriasis
Severe or recalcitrant seborrhoeic dermatitis
Extensive warts or molluscum contagiosum
Oral candida (absence of dentures, corticosteroids and antibiotics)
Florid and difficult to treat fungal infections
Oral hairy leukoplakia
Acute necrotising gingivitis
Constitutional symptoms with no other apparent cause (eg. pyrexia of unknown origin, weight loss and diarrhoea, lymphadenopathy of unknown cause)
Mononucleosis type syndrome (possible HIV seroconversion)
Any unexplained retinopathy

Table 2. Indications to test for HIV[18]
People diagnosed with an infection with a shared transmission route, such as a sexually transmissible infection and hepatitis B or hepatitis C
Injecting drug users, including the reported re-use of equipment (including water and spoons) used for skin penetration
Partners of the above
People with a change in sexual partner
Men who have sex with other men, and any female partners
People from high prevalence countries and partners
Pregnant women
Recipients of blood transfusions and blood products before 1985
Clinical suspicion of HIV (eg. HIV indicator condition)

explain the benefits of testing to the individual, and to provide details of how and when the result will be given. The pre-test discussion may provide an opportunity to discuss risk reduction and how to access post-exposure prophylaxis for HIV. The discussion may generate questions, and some patients may need more time and support to understand what is proposed and to make an informed decision. If a patient is not legally able to consent, the responsibility for consent rests with the person/agency legally authorised to make such decisions on their behalf.

It is the responsibility of the healthcare professional requesting the test to ensure that appropriate mechanisms are in place for delivering the test result. It may also be necessary to get patients to re-test if they are still within the window period if it is a defined risk event.

A positive test result should always be given in person except for extenuating circumstances (eg. where there is the perception that a patient may not return to the healthcare provider and may continue to engage in high risk behaviour based on the wrong assumption that they are HIV negative).[16] Information should be provided about the next steps of staging the HIV infection and future treatment options, including consideration for the need to refer to support agencies and other specialist services. It is important to ensure that the patient understands how HIV infection is transmitted and to support the patient with partner notification strategies. Where possible, get names of possible contacts or refer the patient to services experienced with contact tracing.

Key points

- Despite high testing rates, HIV infection in Australia is often diagnosed late.
- HIV infection is usually diagnosed in individuals with an identifiable risk. Individuals unaware of risks they have been exposed to, or who classify their risk as small, may not present for testing.
- It is the responsibility of the healthcare provider to assess risk appropriately and to offer HIV testing based on that assessment.
- The prognosis of individuals living with HIV is excellent if HIV is diagnosed at an early stage.
- Testing those at risk of HIV acquisition and those who present to healthcare providers with an HIV indicator condition, may act as part of the overall strategy to optimise our chances of detecting HIV at an earlier stage.

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References

1. Pilcher CD, Eron JJ Jr, Vemazza PL, et al. Sexual transmission during the incubation period of primary HIV infection. J Am Med Assoc 2001;286:1713–14.
2. The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2012. The Kirby Institute, the University of New South Wales, Sydney, NSW. Available at http://www.kirby.unsw.edu.au/sites/hiv.cms.med.unsw.edu.au/files/hiv/resources/2012AnnualSurvReport.pdf [Accessed 20 November 2012].
3. The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2011. The Kirby Institute, the University of New South Wales, Sydney, NSW. Available at http://www.kirby.unsw.edu.au/sites/hiv.cms.med.unsw.edu.au/files/hiv/resources/2011AnnualSurvReport_0.pdf [Accessed 20 November 2012].
4. Nakagawa F, Lodwick R, Smith C, et al. Projected life expectancy of people with HIV according to timing of diagnosis. AIDS 2012;26:335–43.
5. Fisher M. Late diagnosis of HIV infection: major consequences and missed opportunities. Curr Opin Infect Dis 2008;21:1–3.
6. The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med 2006;355:2283–96.
7. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 2013. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf [Accessed 10 April 2013].
8. Sullivan AK, Curtis H, Sabin CA, Johnson MA. Newly diagnosed HIV infections: review in UK and Ireland. BMJ 2005;330:1301–02.
9. The Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet 2008;372:293–99.
10. Marks G, Crepaz N, Senterfitt JW, Janssen RS. Meta-analysis of high risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. J Acquir Immune Defic Syndr 2005;39:446–53.
11. Hall I, Holtgrave D, Maulsby C. HIV transmission rates from persons living with HIV who are aware and unaware of their infection. AIDS 2012;26:893–96.
12. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 Infection with early antiretroviral therapy. N Engl J Med 2011;365:493–505.
13. Krentz HB, Auld MC, Gill MJ. The high cost of medical care for patients who present late (CD4<200 cells/microL) with HIV infection. HIV Med 2004;5:93–98.
14. Giles ML, Garland SM, Grover SR, Lewin SM, Hellard ME. Impact of an education campaign on management in pregnancy of women infected with a blood-borne virus. Med J Aust 2006;184:389–92.
15. Weber B, Fall E, Berger A, Doerr H. Reduction of diagnostic window by new fourth generation human immunodeficiency virus screening assays. J Clin Microbiol 1998;36:2235–39.
16. Gazzard B, Clumeck N, d'Arminio Monforte A,Lundgren JD. Indicator disease-guided testing for HIV - the next step for Europe? HIV Med 2008;9 (Suppl 2):34–40.
17. UK National Guidelines for HIV Testing 2008. Available at www.bhiva.org/documents/Guidelines/Testing/GlinesHIVTest08.pdf [Accessed 11 April 2013].
18. Australian Society for HIV Medicine. 2011. National HIV testing guidelines. Available at http://testingportal.ashm.org.au/hiv [Accessed 20 October 2012].

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