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HIV seroconversion illness

Latest HIV assays may still be negative

Human immunodeficiency virus (HIV) seroconversion illness occurs in up to 80% of patients who newly acquire the virus. It is hoped that the new fourth generation HIV assay will have improved sensitivity for diagnosis. This article describes the case of a patient who presented with typical symptoms of HIV seroconversion illness but who had a negative initial test with the new assay. Current management of HIV seroconversion illness is also outlined.

Case study

Mr D, a homosexual man aged 34 years, presented with a 3 day history of painful ulcers in the mouth and on the penis associated with high fever and night sweats, malaise, myalgia, headache, and a sore throat. He had unprotected anal intercourse with a HIV positive casual partner 10 days previously. Four days after this casual contact he presented to his general practitioner with a profuse urethral discharge which was diagnosed as urethral gonorrhoea. This responded well to intramuscular ceftriaxone.

Mr D was previously very well with no medical problems or allergies and reported a negative HIV test 3 months earlier. On examination he appeared very unwell with a temperature of 38°C and mild dehydration. There was no rash. Examination of the mouth revealed tender ulceration of the hard palate (*Figure 1*) and a diffuse erythematous pharyngitis. Genital examination revealed one large, slightly tender ulcer (1.5 cm) on the shaft of the penis. Inguinal nodes were not enlarged or tender and there was no other lymphadenopathy. The ulcer was deep and without induration.

Syphilis and HIV serology were performed and a swab from the penile ulcer was sent for herpes simplex virus (HSV) polymerase chain reaction (PCR). HIV screening utilised a fourth generation assay for combined HIV antibody and p24 antigen detection. The result, available later that day, was negative.

The patient was seen 2 days later for clinical review, repeat HIV serology, and full sexually transmitted infection (STI) screening. He showed improvement systemically but had additional oral discomfort. Examination revealed some additional ulceration of the oral labial mucosa as well as the hard palate, but the penile ulceration was much improved. Posterior cervical nodes were now palpable bilaterally and Mr D had developed a faint pink truncal macular rash (*Figure 2*).

The repeat fourth generation assay that day was reactive. Additional tests, including western blot, revealed one reactive band (p24) and the isolated p24 antigen assay (a more specific test) was reactive, confirming HIV seroconversion illness.

The patient was counselled appropriately and initiated on a short course of antiretroviral (ARV) therapy that day with lopinavir/ritonavir, tenofovir and 3TC.¹ Herpes simplex virus PCR from the penile ulcer was negative. Syphilis serology at presentation and at weeks 4 and 12 were also negative, excluding syphilis and indicating genital ulceration was occurring in the context of HIV seroconversion. Repeat HIV serology in subsequent weeks revealed evolving reactivity on the western blot, and a viral load taken with symptoms was more than 750 000; both results consistent with seroconversion.

Basic blood tests including full blood count (FBC), electrolytes, urea, creatinine (EUC), and liver function tests (LFTs) taken at the initial visit revealed a transient thrombocytopenia and lymphopenia, and mild hepatitis,



Figure 1. Ulceration of the hard palate
Photo courtesy Mark Nelson, The Chelsea and Westminster Hospital, London

with LFTs no more than twice the upper limit of normal. Hepatitis B status previously recorded in the notes indicated the patient was a hepatitis B exposed noncarrier (natural immunity).

Discussion

Human immunodeficiency virus seroconversion illness (or primary HIV infection) is thought to occur in up to 80% of patients who newly acquire the virus.^{2,3} It typically occurs 10–14 days after infection. Symptoms last approximately 1 week. Classic symptoms include:

- fever
- rash
- malaise
- sore throat, and
- generalised lymphadenopathy.^{4,5}

Because these symptoms are transient and influenza-like, seroconversion illness often goes unrecognised by both the patient and doctor. Other known manifestations are oral and genital ulceration. Potential neurological complications include meningitis, encephalitis, and Guillain Barre syndrome.⁶ The transient drop in CD4 count that may occur during seroconversion may also push the patient into the realm of well known HIV related disease (eg. oral candidiasis or pneumocystis carinii pneumonia).

The differential diagnosis of a febrile illness with generalised rash and lymphadenopathy could include:

- HIV seroconversion
- secondary syphilis
- Epstein Barr virus (EBV)
- cytomegalovirus (CMV)
- acute toxoplasmosis
- acute hepatitis B, and
- rubella.⁶

In this patient, however, only HIV and syphilis



Figure 2. Patient displaying truncal macular rash
Photo courtesy Mark Nelson, The Chelsea and Westminster Hospital, London

serology was requested. Syphilis serology is essential in all men who have sex with men presenting with the above syndrome.

Testing for seroconversion illness

Experience with third generation (antibody only) HIV enzyme immunoassays (EIA) in recent years suggests these tests become positive around the time of seroconversion illness. This makes sense because as the name suggests, seroconversion illness is the time of seroconversion to HIV antibody. Therefore these EIAs may be negative on a sample taken 1 day during the illness but positive on a sample taken the following day.

The fourth generation assay (that combines p24 antigen) should prove a more sensitive test for HIV seroconversion because p24 antigen typically appears 5 days before antibody.^{7,8} This test is the same test now used for general HIV screening by all reference laboratories in Australia.

Overall the fourth generation combined antibody/antigen assay is the best first line test for the diagnosis of suspected seroconversion. However, as this case suggests, this assay may still be negative with peak symptoms. A repeat sample and test in 2–3 days is recommended when there is an index of suspicion.

Other tests are sometimes used for diagnosing seroconversion (eg. PCR). However, HIV RNA PCR (viral load) assays are quantitative tests and cannot be relied upon for diagnosis because of poor specificity in the form of low level false positives.³ Proviral DNA is a HIV DNA PCR test that is more sensitive and more specific than a viral load assay making it a good second line test or useful adjunct to the fourth generation assay. A proviral DNA requires a whole blood sample. It is important to indicate on the request form, or telephone the reference laboratory, if seroconversion illness is suspected.

Management of seroconversion illness

Patients confirmed or suspected of HIV seroconversion illness should be referred immediately to a HIV specialist general practitioner or sexual health service (Table 1).

Prompt treatment of confirmed HIV seroconversion with a short course of ARV therapy (usually 3–6 months) is an option. This is not standard of care but is at the discretion of the treating physician and patient. Treating seroconversion illness with a short course of ARV drugs has the potential to slow disease progression by preserving HIV specific cytotoxic T-lymphocyte responses.⁹ However, the evidence base is small and it remains an important unanswered study question.¹⁰ Further data is expected from SPARTAC, a large international multicentre trial rolled out last year by St Mary's Hospital, London, currently randomising seroconverters to treatment or not.

Other potential advantages of treating seroconversion include reduction of symptoms and reduced risk of HIV transmission. Potential disadvantages include toxicity, financial cost, and the potential to foster or potentiate a drug resistant virus. Studies indicate that treatment with ARV drugs requires more than 95% compliance to guard against developing drug resistance.¹¹ Such compliance could be undermined by the trauma of the new HIV diagnosis, thereby fostering drug resistant virus. In addition, the transmission of drug resistant virus is a real entity and such virus can be potentiated by an immediate course of ARV therapy.⁹ In this

Table 1. Management algorithm for HIV seroconversion illness**Could this be seroconversion illness?**

- Was there a substantial risk (eg. unprotected anal intercourse)?
- What is the time course (10–14 days)?
- Are typical symptoms present (eg. fever, rash, sore throat, malaise, generalised lymphadenopathy)?

HIV test

- Provide patient with pretest counselling
- Indicate suspected seroconversion on the request form, or telephone the reference laboratory
- Fourth generation assay (ask if same day result is available)
- Consider proviral DNA if available (requires a whole blood sample)
- Undertake full STI screening

Positive result

Refer immediately to HIV specialist GP or sexual health service

Negative result

Repeat test in 2–3 days, or refer

setting, short course therapy fails to control the virus and drug options for the long term treatment of the more established chronic infection are potentially reduced.

The problem of resistant virus transmission necessitates a viral genotype at baseline in all patients with seroconversion illness to look for drug resistance mutations. This test is considered by the author to be standard of care (Mr D's genotype revealed wild type virus, ie. no drug associated mutations).

Conclusion

Seroconversion illness following HIV infection has the potential to go unrecognised because it is transient and influenza-like. Recognition and prompt treatment with a short course of ARV therapy could potentially improve the prognosis of chronic HIV infection – we await more data. The fourth generation combined antigen/antibody assay is the best first line test for diagnosis of suspected seroconversion illness,

but still may initially be negative, necessitating a repeat sample in 2–3 days. Patients confirmed or suspected of HIV seroconversion illness should be referred immediately to a HIV specialist GP or sexual health service.

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