Diagnosing HIV infection

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Highly active antiretroviral therapy (HAART) has transformed the quality of life and life expectancy of patients with HIV infection. An HIV-related opportunistic disease is more likely to develop with a CD4 count less than 200 cells/μl, and immune recovery with HAART may be slower and less complete if started at a low CD4 count.[1] Early diagnosis is therefore vital. Antenatal diagnosis of HIV infection and correct management can reduce the risk of vertical transmission from 25% to less than 5%.[2] Other benefits of early identification of HIV infection are listed in Table 1.

Is HIV infection diagnosed sufficiently frequently?

It is estimated that in the UK a third of those living with HIV infection are currently undiagnosed.[3] A recent national audit showed that only about a quarter of patients were started on treatment in the recommended CD4 count range, in most cases (82%) because the patients were diagnosed late.[4] There are three main reasons for this:

1 Patients do not present for medical care until they become ill with HIV-related symptoms, because of:
   - lack of education about the benefits of early diagnosis
   - lack of awareness that they have been put at risk, or
   - fear.
2 Patients present with symptoms, but a diagnosis of HIV is not considered, particularly if the patients do not admit to being at high risk.
3 Patients arrive in this country from overseas already severely immunosuppressed.

Primary HIV infection

Over 50% of patients experience an acute febrile illness shortly after infection with HIV[5] at the time of seroconversion. Symptoms usually develop at 2–12 weeks (Table 2) and resolve within two weeks. There are potential advantages in detecting HIV at this stage. Epidemiological studies suggest that individuals are particularly infectious within the first few weeks of contracting HIV and there is thus a high risk of onward transmission. Occasionally, patients with primary infection can become seriously ill with pneumonia or other opportunistic illness. The viral load reaches very high levels shortly after infection, and then falls to a 'set point' which may be useful in guiding future treatment decisions.[6]

The place of treatment in acute HIV infection is controversial. Trials are currently underway to determine the benefits of using HAART, and whether these outweigh the risks of drug toxicity and the possible development of viral resistance. HAART may be indicated both to treat symptoms and to improve the prognosis. Patients suspected of having primary HIV infection should be referred for specialist advice, even if their initial HIV antibody test is negative.

Who should be offered an HIV test?

Patients at high risk should be tested, and all patients with sexually transmitted diseases should be offered screening (this has become routine practice in genitourinary medicine (GUM) clinics). All pregnant women are now tested for HIV infection in the UK unless they choose to opt out; high-risk patients should be offered repeat testing at least once during their pregnancy. HIV should always be considered in those who have come to the UK from countries with a high prevalence, or those who have worked in or visited those countries. Many common clinical conditions occur more frequently in HIV infection (Table 3); even if the risk seems low, testing should be encouraged because of the important advantages of knowing the diagnosis.

How is HIV infection diagnosed?

Screening tests

The usual screening test for HIV infection, which has been in widespread use since 1985, is the detection of antibodies formed against specific HIV antigens by an enzyme-linked immunosorbent assay (ELISA).[7] These automated tests allow large batches of samples to be screened

Table 2. Common manifestations of primary HIV infection.

- Sore throat
- Lymphadenopathy
- Rash (erythematous, maculopapular, non-pruritic)
- Myalgia, arthralgia, headaches
- Mucosal ulceration (oral and/or genital)

Table 1. Benefits of establishing a diagnosis of HIV infection.

- Early medical intervention with HAART
- Education about reducing the risk of infecting others
- Contact tracing
- Access to help from social services, drugs agencies, support groups etc
- Ability to make important life decisions
- Treatment of pregnant women can dramatically reduce the risk of their baby being born with HIV infection (from 25% to 5% or less)
- Prophylaxis against Pneumocystis pneumonia and other opportunistic infections
- Vaccination
- Many symptomatic patients may be suffering inappropriate (and expensive) investigations
- Relief of anxiety about knowing the result

HAART = highly active antiretroviral therapy.

Table 3. Some common clinical problems where HIV infection should be considered.

- Tuberculosis
- Lymphoma
- Shingles, particularly if severe, multidermatomal or recurrent
- Recurrent bacterial pneumonia
- Thrombocytopenia, neutropenia, normochromic anaemia
- Diffuse hypergammaglobulinaemia
- Persistent generalised lymphadenopathy
- Oral candidiasis

relatively cheaply, but produce both false-positive and false-negative results. More recently developed 'third generation' ELISAs have greatly improved sensitivity and specificity. False-positive reactions may occur due to cross-reacting antibodies, for example following multiple transfusions, autoimmune diseases or other infections. Rarely, results will be wrong due to simple human error. For this reason, patients should never be told they have HIV infection until the results of the screening ELISA have been confirmed, usually by a second ELISA, Western blot and/or immunofluorescence. All positive results should, in addition, be confirmed using a second sample.

The Western blot test allows identification of specific HIV antigens, using a polyacrylamide gel on which HIV antigens have been separated electrophoretically. Positive bands from two or three of the major antigen groups are usually needed to confirm a diagnosis. False-positive results can also occur with Western blots. Immunofluorescence and radioimmunoprecipitation are useful additional confirmatory tests, particularly with difficult sera.

The commonest cause of a false-negative result is the 'window period' – most individuals do not become positive until 4–12 weeks after infection, occasionally longer. Any condition affecting the ability to produce adequate antibody levels may also produce a false-negative result (eg bone marrow transplantation).

Most laboratories return confirmed positive or negative results of their HIV screening tests within a week, but results can be requested urgently by arrangement, for example for screening of donors for transplantation, needlestick injuries[8] where screening of the source patient may indicate the need for post-exposure prophylaxis, or where urgent clinical decisions are to be made.

Rapid assays will give a result in 30 minutes, and can be performed in situations where there is no access to laboratory facilities. They are considerably more expensive than ELISAs. When performed properly they are accurate and may have important uses, for example in the third world or in situations where only a small number of specimens are to be tested.

There are occasionally indeterminate results that cannot be resolved with the usual confirmatory tests. These may suggest acute seroconversion, and tests should be repeated perhaps with a viral load test. In these cases, the patient needs careful counselling and follow-up from an expert who understands the implications of the tests.

Key Points

Highly active antiretroviral therapy (HAART) has had a dramatic impact on morbidity and mortality in HIV-infected patients

Identification of HIV infection before significant immunosuppression develops improves outcome

Currently one-third of those living with HIV infection in the UK are undiagnosed

A high index of suspicion is required when patients present with symptoms compatible with HIV infection even if such patients do not admit to high-risk behaviour

KEY WORDS: AIDS, diagnosis, highly active antiretroviral therapy (HAART), HIV

Viral load estimation

Quantitative polymerase chain reaction, branched DNA, and nucleic acid sequence-based amplification are ways of assessing the viral load of a patient. They are currently used to determine the relative risk of disease progression (together with CD4 counts and clinical data) to help assess the best time to start HAART, and to monitor a patient's response to HAART.

The viral load is not routinely used diagnostically, as it is labour intensive and there is a significant risk of false-positive results, but it may sometimes be useful, for example in:

- newborn babies, where there is passive transfer of antibody from the mother to the baby
- acute HIV infection, where the viral load may become positive before the antibody test
- helping to resolve indeterminate results.

A diagnosis of HIV infection should never be made on the basis of one viral load assay alone; depending on the clinical context, at least two positive results, confirmed by antibody testing as soon as possible, are required. Because of concerns around false positivity and viral load fluctuations, these tests should be used only with the help of a colleague experienced in HIV infection.

P24 antigen assay

The P24 antigen assay has been largely superseded by viral load estimations but is still used in certain situations. It tends to become positive early in the course of HIV infection, and then negative,

re-emerging as the disease progresses, although it may be present at all clinical stages of infection.

Informed consent for HIV testing and the need for counselling

Patients have a right to information about any investigation they undergo, and need more information about a condition that may have serious implications for their employment, social or personal life.[9] However, the amount of information given to each patient will depend on the apparent risk of infection and the reason for performing the test. For patients at low risk of infection, basic core information and advice can be given – much of it in the form of a good information leaflet. This should include:

1 Information about HIV, its transmission and how to reduce the risk of infection.
2 The significance of positive and negative results, including false-positive and false-negative results.
3 The benefits of testing and the implications of a positive test for themselves, their families and partners.
4 How the results will be given, what will happen if the test is positive, access to expert care and treatment etc.
5 Where to get further information: local contacts such as the GUM clinic, helplines and websites.
6 Confidentiality.

The patient's consent should be sought before sharing information about the test with other healthcare professionals or the family, and disclosures should be kept to a minimum. Patients who appear more at risk of HIV will need more detailed counselling, preferably from an expert. The local GUM clinic or HIV team should be able to help. Patients do not need to sign a consent form, but a note should be made in the patient's file that informed consent has been obtained. It is important to use interpreters if necessary, but preferably not a spouse or other relative. Local guidelines should be in place for how to deal with a positive result. A specialist in HIV medicine should be contacted before the results are given and a follow-up appointment arranged, preferably within 24 hours.

FURTHER INFORMATION

www.gmc-uk.org
Advice about HIV testing, confidentiality and consent.

www.aidsmap.co.uk
An excellent website covering all aspects of HIV infection.

www.tht.org.uk
The Terence Higgins Trust, a charity which can provide information, support and legal advice for patients with HIV infection.

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