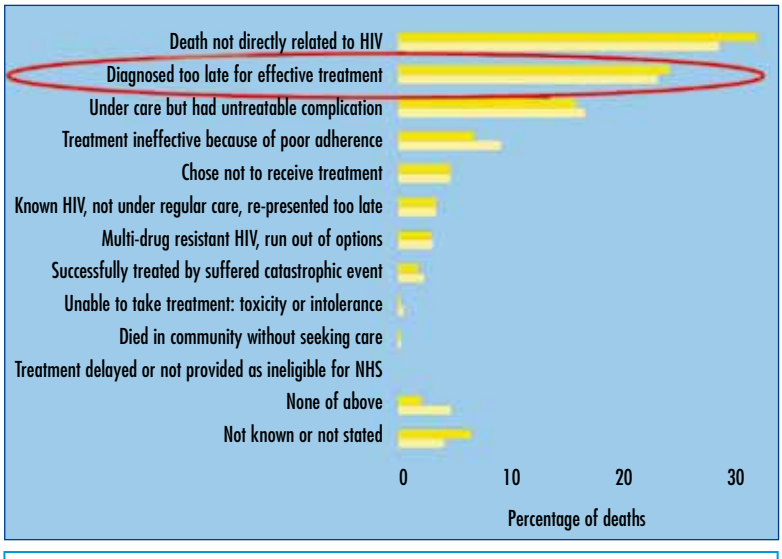
Diagnosis and management of HIV infection

Infection with human immunodeficiency virus (HIV) is now increasingly common in the UK, but the diagnosis is often missed or overlooked. This article summarizes who to test and how best to offer testing to patients in whom HIV testing is clinically indicated.

Human immunodeficiency virus (HIV) infection is no longer a medical rarity, with 86 500 cases diagnosed and under care in the UK by 2010 (Health Protection Agency, 2010a). It has evolved from an untreatable terminal illness to a chronic treatable medical condition with an excellent prognosis following the introduction of highly active antiretroviral therapy. This has brought new challenges for the HIV physican with the care of an ageing cohort of chronically infected patients with emerging comorbidities. The majority of patients who die under our care have been diagnosed too late for antiretroviral therapy be effective (Health Protection Agency, 2010a). Significantly most of these patients have been investigated by their GPs and other physicians and the diagnosis of HIV has been overlooked without being excluded (Roberts et al, 2006).

Figure 1. Scenarios leading to death. Top bars reclassified during audit, bottom bars as initially reported. From Lucas et al (2008). HIV = human immunodeficiency virus.



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In 2008 new national guidelines on HIV testing were launched (Palfreeman et al, 2009) with the intention of reducing the number of patients presenting late with HIV infection by addressing the estimated 26% of patients in the UK who are HIV infected but undiagnosed (Health Protection Agency, 2010a). The guidelines recommend that HIV testing should be normalized and that it should be within the competence of any healthcare professional to obtain consent for an HIV test.

Consequences of late diagnosis

Unfortunately many patients with HIV are diagnosed late in infection (*Figure 1*). In 2009 34% of patients between the ages of 15 and 49 years and 52% of those over 50 years were diagnosed with a CD4 count below 200 cells/mm^3 – well below the recommended threshold for starting antiretroviral treatment (Health Protection Agency, 2010a) and at a level when many would be at risk of opportunistic infection. Many have been living with HIV for years, unaware that they pose a risk to their sexual partners and undiagnosed by the doctors who they have encountered in the interim.

Patients presenting late to care are less likely to mount a good immune response to antiretroviral treatment, more likely to get side effects from treatment and more likely to die of either complications of HIV or other causes (Lucas et al, 2008). Almost all of this is preventable by earlier diagnosis.

Patients diagnosed early in infection not only have better clinical outcomes (Stöhr et al, 2007; Lucas et al, 2008; Health Protection Agency, 2010a), but are less likely to transmit their virus to others both as a result of behavioural changes and of the impact of treatment on infectivity (Marks et al, 2006). The costs of care of patients diagnosed late are significantly higher than those diagnosed early, and these costs would be much less than the costs of HIV treatment which would have prevented a hospital admission (Krentz et al, 2004).

Opportunities to reduce undiagnosed infection

It is known that before late diagnosis many individuals have been seen in health care and the opportunity for diagnosis missed. In a study by Burns et al (2008) 80% had been seen by their GP and 62% had been to hospital

in the 2 years before presentation (Roberts et al, 2006; Burns et al, 2008; Lucas et al, 2008).

If testing were routine in many health-care settings, as the guidelines propose, such missed opportunities would be reduced. This approach has been proven to be highly effective in the antenatal setting.

Before 1999 HIV testing was exceptional in UK antenatal clinics and only those thought to be at risk of infection were offered testing. The unintended consequence of this was that many women only found out their status after unwittingly infecting their unborn infant. This situation was reversed with the introduction of universal opt-out testing in antenatal clinics, and now the offer and acceptance of HIV testing is almost universal with vertical HIV transmission reduced to a handful of cases (Townsend et al, 2008) (*Figure 2*).

The same arguments apply in favour of an opt-out model for HIV testing in general medicine. The recommendations on HIV testing are to offer tests on an opt-out basis to all patients presenting to the following settings:

1. Genitourinary medicine or sexual health clinics
2. Antenatal services
3. Termination of pregnancy services
4. Drug dependency programmes
5. Health-care services for those diagnosed with tuberculosis, hepatitis B, hepatitis C and lymphoma.

Routine HIV testing should also be offered to all patients presenting either to acute medicine or registering in primary care in parts of the country where HIV infection has a particularly high prevalence, i.e. >2:1000. This figure (>2:1000) was derived from cost-effectiveness data in the USA (Walensky et al, 2005). The Health Protection Agency (2010a) have now produced data mapping HIV prevalence by area (*Figure 3*), from the Survey of Prevalent HIV Infections Diagnosed.

In addition to routinely offering HIV testing in certain settings the following should also be routinely offered a test wherever they present for health care:

1. All patients where HIV, including primary HIV infection, enters the differential diagnosis
2. All patients diagnosed with a sexually transmitted infection
3. All sexual partners of men and women known to be HIV positive
4. All men who have disclosed sexual contact with other men
5. All female sexual contacts of men who have sex with men
6. All patients reporting a history of injecting drug use
7. All men and women known to be from a country of high HIV prevalence (>1%)
8. All men and women who report sexual contact abroad or in the UK with individuals from countries of high HIV prevalence.

In 2009 the Department of Health funded eight pilot schemes to evaluate the feasibility of offering HIV testing in a variety of settings including testing in primary care and on acute medical admission units. These reported to a national multidisciplinary conference on HIV testing in December 2010 (Health Protection Agency, 2010b) with preliminary reports indicating that HIV testing is highly acceptable to patients, easy to perform and is effective in detecting patients in whom the diagnosis would have otherwise been missed (Perry, 2010).

In the authors' experience many patients diagnosed as HIV positive were surprised that previous blood tests had not revealed the presence of HIV infection and they assumed they had automatically been tested as part of a routine 'full blood count'.

Of note, many of these pilots excluded older individuals (who are disproportionately represented in late presenter cohorts), and in the one pilot where routine testing was recommended to all adults under the age of 80 years, those aged 60–79 years were less likely to be offered a test and contributed to 50% of missed diagnoses (Perry, 2010).

Figure 2. Estimated proportion of human immunodeficiency virus (HIV)-infected pregnant women diagnosed before delivery and of exposed infants becoming infected with HIV in England 1999–2009. From Health Protection Agency (2010c).

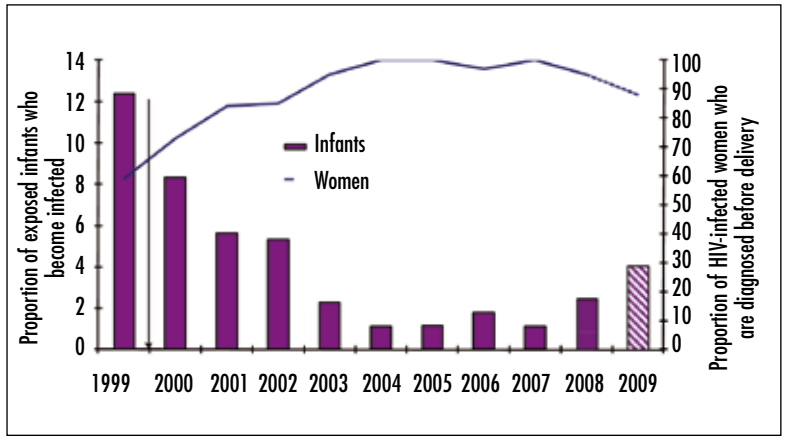
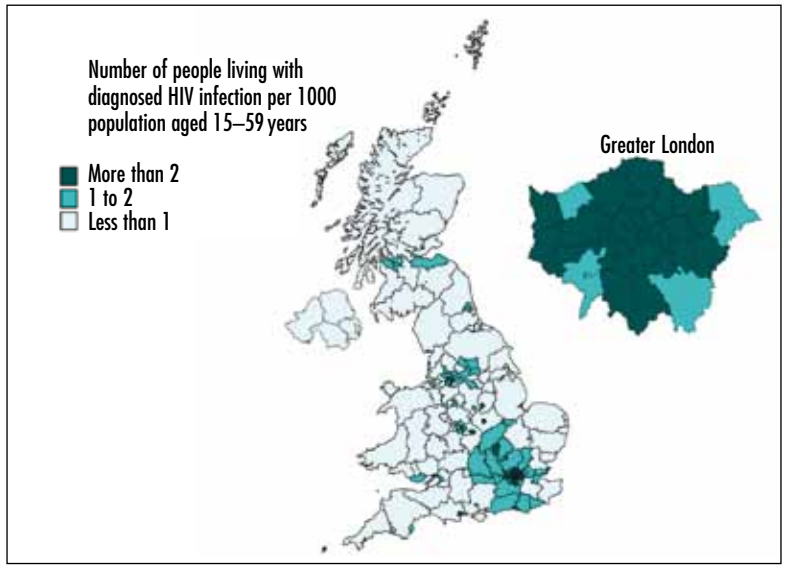


Figure 3. Prevalence of diagnosed human immunodeficiency virus (HIV) infection in the UK, 2009. From Survey of Prevalent HIV Infections Diagnosed, Health Protection Agency (2010a).



Primary HIV infection

One of the most significant opportunities to make a diagnosis of HIV is during primary HIV infection (or seroconversion).

Of infected patients 80% recall having a primary infection, usually a flu-like illness associated with a rash (*Figure 4*), and 80% sought medical attention for it (Sudarshi et al, 2008). This is frequently missed both in primary and secondary care. Up to 15% of seroconverters are hospitalized as a result of the severity of their symptoms (including aseptic meningitis) and again the diagnosis is frequently missed (Schacker et al, 1996). Although flu-like illnesses and rashes are both common presentations, if they occur together HIV infection should be excluded as patients seroconverting are much more infectious to others than patients who are chronically HIV infected, and prompt diagnosis can therefore be both in the individual's and public health interest.

Fourth generation HIV combined antibody/antigen tests should now be offered by all laboratories and will show a positive or equivocal result during a seroconversion illness. If this is strongly suspected referral to local genitourinary medicine or HIV services is recommended.

Most patients presenting late with HIV do not necessarily present with acquired immune deficiency syndrome (AIDS). For example, the commonest clinical event in one of the largest randomized controlled trials involving HIV patients (the 5472-patient SMART trial) was community-acquired bacterial pneumonia (Gordin et al, 2008). No data exist yet on the prevalence of HIV infection in patients with pneumonia but as HIV infection is now becoming more common it is entirely reasonable to exclude this as an underlying cause in anyone presenting to hospital with this or any other diagnosis in the list of indicator diseases (*Table 1*).

The list of clinical indicator diseases to prompt HIV testing was drawn up based on the infections which make up the original set of AIDS diagnoses, in which it is mandatory to exclude HIV infection, together with a set of other diagnoses which are more common in HIV infection and therefore it would be prudent to exclude HIV from the differential diagnosis.

The most important diagnoses where HIV testing should be considered as routine are tuberculosis, hepatitis and lymphoma.

Tuberculosis is especially common in HIV infection, being the commonest AIDS-defining illness in the UK. Despite the clear association and recommendations for universal testing (Pozniak et al, 2005) less than 50% of tuberculosis patients in London are offered HIV testing (Rodger et al, 2010). Hepatitis B and C both share infection routes with HIV and failure to exclude co-infection can potentially compromise future HIV drug therapy as many of the antivirals used are active against both hepatitis B and HIV.

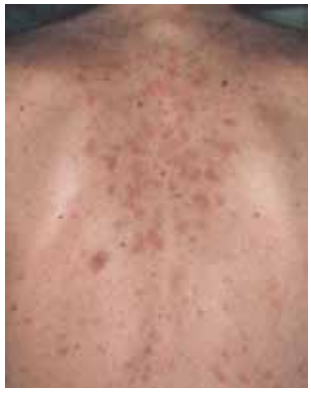
Lymphoma, especially non-Hodgkin's lymphoma, is a frequent malignancy in HIV and failure to exclude this before embarking on cytotoxic chemotherapy can have potentially fatal consequences. Conversely when managed with antiretrovirals the prognosis in many centres is now similar to that seen in the HIV-negative population.

Figure 4. Seroconversion rash. HIV = human immunodeficiency virus.

Primary HIV infection

The typical symptoms include a combination of any of:

- Fever
- Rash (maculopapular)
- Myalgia
- Pharyngitis
- Headache or aseptic meningitis.



These resolve spontaneously within 2–3 weeks and therefore if primary HIV infection is suspected, this needs to be investigated at the time of presentation and not deferred

Obtaining consent for HIV testing

This should now be within the competence of any health-care worker. All that is needed is a brief explanation of why a test is recommended and how the patient will get the result, for example:

'We routinely recommend a number of tests including X, Y Z and an HIV test to everyone coming into hospital with your symptoms or diagnosis in order to rule out this important treatable condition. Is that OK?'

Therefore taking consent for an HIV test is no different for taking consent for any other investigation or procedure, and this advice is consistent with the General Medical Council (2008) guidance *Consent: patients and doctors making decisions together.*

This position has changed significantly over the last few years. Before effective treatment was available for HIV infection some patients who were at risk of being infected chose not to be tested as they believed they would not derive benefit from the knowledge that they were carrying a fatal infection. Some life insurance companies also discriminated against those who had taken an HIV test as they thought this action would make them more likely to become positive in the future. The General Medical Council and Department of Health issued guidance on HIV pre-test counselling (General Medical Council, 1997) which went into some detail about allowing patients to weigh up the pros and cons of accepting a test.

Since the advent of effective antiretroviral treatment the prognosis of patients diagnosed has changed dramatically. The Association of British Insurers have had a clear policy of not discriminating against anyone who

takes a test since 1994 and have recently issued updated guidance (Association of British Insurers, 2005). The previous General Medical Council and Department of Health guidance was finally withdrawn in 2006.

Which test to use

Blood tests

All laboratories in the UK should now be using a fourth generation combined antibody and antigen test which should detect primary infection, i.e. within the first few weeks. All reactive serology will be confirmed by subsequent assays using different methodology to eliminate any false positive reactions before any result is issued. It might be appropriate to repeat the blood test if it is likely that the patient had been infected within the previous month and is therefore within the 'window period'.

Point of care tests

These rely on either serum from finger prick or from a mouth swab and can give the patient a result in a few minutes. The advantage of a rapid result needs to be weighed against the reduced sensitivity and specificity of the test compared to a blood test and therefore these tests should be reserved for clinical situations where a rapid result is needed (for example an untested woman presenting in labour) or where venepuncture is not possible. Only CE kite-marked kits should be used and all positive results should be confirmed by a blood test.

Conclusions

The advent of highly active antiretroviral therapy has transformed HIV infection into a chronic manageable disease with a near-normal lifespan. However, approximately a quarter of individuals are unaware of their infection and are diagnosed late with significant impact on individual and public health.

Many of these individuals have been through hospital settings in the recent past. Increasing the routine offer of HIV testing, normalizing the testing process and improved recognition of clinical indicator diseases by hospital clinicians should significantly improve the current situation and thereby patient care. BJHM

KEY POINTS

- Human immunodeficiency virus (HIV) infection is often overlooked in the differential diagnosis of patients ill in hospital.
- Obtaining consent for HIV testing requires no special skills or counselling.
- It is good practice to exclude HIV infection whenever this enters the differential diagnosis by testing and to offer testing to anyone who might conceivably be at risk.
- The prognosis for HIV infection has been transformed by effective therapy in the last 10 years.

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Conflict of interest: none.

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Table 1. HIV indicator diseases

System	AIDS-defining conditions	Testing recommended
Respiratory	Tuberculosis Pneumocystis	Bacterial pneumonia Aspergillosis
Neurology	Cerebral toxoplasmosis Primary cerebral lymphoma Cryptococcal meningitis Progressive multifocal leucoencephalopathy	Aseptic meningitis or encephalitis Cerebral abscess Space-occupying lesion of unknown cause Guillain–Barré syndrome Transverse myelitis Peripheral neuropathy Dementia Leucoencephalopathy
Dermatology	Kaposi's sarcoma	Severe or recalcitrant seborrhoeic dermatitis Severe or recalcitrant psoriasis Multidermatomal or recurrent herpes zoster
Gastroenterology	Persistent cryptosporidiosis	Oral candidiasis Oral hairy leukoplakia Chronic diarrhoea of unknown cause Weight loss of unknown cause Salmonella, shigella or campylobacter Hepatitis B infection Hepatitis C infection
Oncology	Non-Hodgkin's lymphoma	Anal cancer or anal intraepithelial dysplasia Lung cancer Seminoma Head and neck cancer Hodgkin's lymphoma Castleman's disease
Gynaecology	Cervical cancer	Vaginal intraepithelial neoplasia Cervical intraepithelial neoplasia Grade 2 or above
Haematology		Any unexplained blood dyscrasia including: • neutropenia • thrombocytopenia • lymphopenia
Ophthalmology	Cytomegalovirus retinitis	Infective retinal diseases including herpesviruses and toxoplasma Any unexplained retinopathy
Ear, nose and throat		Lymphadenopathy of unknown cause Chronic parotitis Lymphoepithelial parotid cysts
Other		Pyrexia of unknown origin Any lymphadenopathy of unknown cause Mononucleosis-like syndrome (primary HIV infection) Any sexually transmitted infection

AIDS = acquired immune deficiency syndrome; HIV = human immunodeficiency virus.

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