Recognition and Diagnosis of HIV Infection

July 2019

This resource was first published in 2014 and revised in 2017 and 2019
Introduction

- HIV positive patients attend healthcare with HIV related illness prior to diagnosis
  - HIV infection often not thought of in differential diagnosis
  - Over-reliance on lifestyle risk factors
  - Reluctance on the part of healthcare professional to discuss HIV
- The problem of late diagnosis
  - Risk of advanced disease
  - Failure to get maximum benefit from antiretroviral therapy
  - On-going HIV transmission

There is good evidence to suggest that patients eventually diagnosed with HIV infection have had contact with medical services, with symptoms resulting from HIV, prior to diagnosis. Unfortunately, in many cases, an HIV test has not been included in the investigation of these symptoms resulting in missed opportunities to diagnose HIV.
Antiretroviral therapy has revolutionised the management and prognosis of HIV. Patients diagnosed with HIV are now felt to have a near normal life expectancy. However, even with antiretroviral therapy patients diagnosed with advanced disease have significantly poorer outcomes than those diagnosed earlier in the course of HIV infection. As a result, it is important to diagnose patients as early as possible to allow maximum benefit from treatment.
Aims

• Case histories to illustrate the natural history of HIV
  — Better understanding of common HIV presentations
  — Use of clinical indicator conditions; to indicate the need for HIV testing in symptomatic patients
• How to do an HIV test
  — Increased confidence to test patients

Increased recognition and diagnosis of HIV

This module will work through three cases to look at particular stages in the natural history of HIV infection. By the end of the module you should have an appreciation of the symptoms and common presentations of HIV infection. This should equip you to recognise patients who may have HIV infection and allow you to offer testing.
Case 1
Acute HIV Infection
Learning Outcomes

Case 1

- Recognise the clinical features of acute HIV infection and use these to indicate when to offer HIV testing to patients
A 29 year old man presents to medical receiving with a 48 hour history of myalgia, abdominal pain, diarrhoea, sore throat and fever

**Past medical history**
- Nil

**Drug history**
- No regular medications
- No drug allergies
- No illicit drug use

**Social history**
- Works as a financial adviser
- Non smoker
- Alcohol of around 40 units/wk
- Married with 2 children

**Family history**
- Father with ischaemic heart disease and type 2 diabetes
On examination

- Temp 38.2°C
- Pulse 100/min
- BP 125/78
- Resp rate 18/min
- SpO2 99% on air
- Conjunctival injection

- Cervical adenopathy
- Maculopapular rash over trunk
- Heart sounds pure
- Chest clear with no added sounds
- Abdomen soft and mildly tender
- but with no guarding

Biochemistry

- AST 770 IU/I
- ALT 380 IU/I

Haematology

- Hb 132
- WCC 3.6
- Neut 1.2

Radiology

- CXR normal
- US liver normal

What infections could explain his presentation?
What infections could explain his presentation?

- Streptococcal upper respiratory infection
- Infectious mononucleosis
- Viral upper respiratory tract infection
- Viral hepatitis
- Acute HIV infection
- Secondary syphilis

This gentleman has an acute infection with sepsis as characterised by 2 SIRS criteria. The sore throat and rash would be in keeping with a streptococcal upper respiratory tract infection (URTI). The illness is also characteristic of infectious mononucleosis although he may be a little old for this. Whilst a viral URTI is possible the presence of sepsis makes this less likely. Syphilis is an increasing problem and should always be considered in the context of a patient with rash and fever.

The presence of the hepatitis results in him being tested for hepatitis A, B and C. He is not HIV tested because ‘he has no risk factors’.
He is commenced on intravenous benzylpenicillin to treat streptococcal infection. He has a number of investigations carried out including blood cultures and throat swabs. After 48 hours he continues to be febrile and his antibiotics are changed to ceftriaxone to broaden cover.
Results

• ASOT negative
• Throat swab no growth
• Blood cultures no growth
• Monospot negative
• Hepatitis A IgM negative
• Hepatitis B sAg negative
• Hepatitis C Ab negative/PCR negative

The investigations would go against streptococcal infection as would the failure to respond to benzylpenicillin. Infectious mononucleosis seems unlikely given the negative monospot and there is no evidence of viral hepatitis.

What further investigations do you want to do?
The patient has blood taken for an autoimmunology screen and a CT of his abdomen is requested. As the FY2 on the ward you mention HIV testing to the consultant on their ward round. You are told that he does not have any risk and therefore this cannot be an HIV infection. Having completed this module you point out the epidemiology of HIV infection and that most HIV is acquired sexually. Whilst homosexual spread is more common you are aware that heterosexual spread does occur and that patients do not always declare the full story when giving a sexual history. You appreciate that both these factors mean that the absence of traditional risk factors for HIV cannot be used to exclude the diagnosis and as such an HIV test is required to do this. After some discussion the patient agrees to HIV testing.
This gentleman has acute HIV infection. This is dedicated by his presentation with a glandular fever like illness and by the rise in his CD4 count and fall in his viral load after 4 weeks. This is what happens after acute HIV infection as the patient’s immune system develops an element of control over the virus. This is however variable and some patients are left with low CD4 count and high viral loads. These patients are more likely to develop symptomatic disease sooner going forward making it important to make the diagnosis at this point.

Acute HIV, sometimes called seroconversion illness, is very common in people infected with HIV. Although patients can become critically ill with acute HIV, in the majority the symptoms settle spontaneously and then patient recovers. This therefore represents an opportunity to diagnose HIV.

Failure to diagnose HIV puts this man at risk of progressive disease but also puts his partner at risk of infection. It is known that the high viral loads associated with acute HIV infection substantially increase the risk of sexual transmission. Diagnosing him with HIV at this point allows appropriate precautions to be taken to prevent onward transmission.
Case 2
Symptomatic HIV
Learning Outcomes

Case 2

• Recognise the clinical features of symptomatic HIV infection (also known as ‘clinical indicator illnesses’)
• Be confident in offering an HIV test to patients with clinical indicator illnesses
A 48 year old women is referred to a general medical clinic with a 7 month history of loose stool and 2 stone weight loss. She cites the commencement of her diarrhoea during a 2 week trip to India but empirical antibiotics have failed to improve her symptoms.

### Past medical history
- Multidermatomal shingles 2 years ago
- No history bowel problems
- No regular medications

### On Examination
- Thin (BMI 18)
- No adenopathy
- Abdomen soft and non tender with no organomegaly

### Social History
- 2 children aged 16 and 18
- Primary school teacher
- Widowed

### Family History
- No history of bowel problems

Given the presentation after a trip to India there is concern about enteric infection. She had blood drawn for inflammatory markers and stool examined for bacterial and parasitic organisms.
### Results

<table>
<thead>
<tr>
<th><strong>Haematology</strong></th>
<th><strong>Biochemistry</strong></th>
<th><strong>Bacteriology/Virology</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Hb 103</td>
<td>- AST 100 IU/l</td>
<td>- 3 x stool cultures negative, no ova, cysts or parasites</td>
</tr>
<tr>
<td>- WCC 3.6</td>
<td>- ALT 98 IU/l</td>
<td>- HAV total Ab pos/IgM neg</td>
</tr>
<tr>
<td>- Platelets 98</td>
<td>- Albumin 27</td>
<td>- HBV sAg neg/sAb pos</td>
</tr>
<tr>
<td></td>
<td>- CRP 29</td>
<td>- HCV Ab neg</td>
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<tr>
<td></td>
<td>- TTG negative</td>
<td>- HEV IgM neg/IgG neg</td>
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</tbody>
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At a review in the clinical 6 weeks later her symptoms are unchanged and the following results have returned.

Her viral hepatitis serology confirms previous vaccination against both hepatitis A and B but no evidence of active infection.
Progress

- Outpatient colonoscopy
  - normal
- CT chest, abdomen and pelvis
- Haematology referral
  - pancytopenia
  - mild hepatitis

She progresses to outpatient colonoscopy which is reported as normal. Given the pancytopenia and mild hepatitis there is concern about haematological malignancy and she is referred on for review in haematology and an outpatient CT chest, abdomen and pelvis is requested.
When you review her at Haematology clinic you note the past medical history of multidermatomal shingles and are concerned about her being immunocompromised. She has had her CT scan that shows no abnormality and in particular no evidence of significant lymphadenopathy. When you discuss her case with the consultant you ask about the possibility of HIV infection. It is felt that she does not have any risk factors for HIV and therefore an HIV test is not suggested to the patient. The plan is to admit her as a day case for bone marrow biopsy.
On the day of her bone marrow biopsy she feels unwell. On review on the day ward she is febrile and tachycardic with cough and purulent sputum. A chest X-ray confirms the diagnosis of a bi basal pneumonia and she is admitted to commence intravenous amoxicillin. 24 hours after admission you get a phone call from microbiology to inform you that she has grown gram positive cocci in blood, these are subsequently identified as pneumococci. As you have recently read an article about the increased risk of invasive pneumococcal disease in HIV patients you suggest an HIV test to the patient and she consents to this.
These results show that she has advanced HIV infection and is likely to have had HIV for several years. Her CD4 count is low and had you not made the diagnosis, it is likely that she would soon develop opportunistic infection. The viral load indicates that in every millilitre of her blood there are over 100 000 HIV virus particles. However, by making the diagnosis she has the opportunity to benefit from anti retroviral treatment.
This lady’s case is typical of patients with advanced HIV infection. It is known that there are often numerous missed opportunities to diagnose HIV in these patients as they will present to medical services with illnesses characteristic of HIV and evolving immunocompromise. These illnesses are well recognised and can be thought of in terms of systems.

An objective look at this lady’s case highlights that she has had many of these; shingles, thrombocytopenia, anaemia, diarrhoea and weight loss. The concern is that the absence of lifestyle risk factors for HIV are used as a surrogate for a negative HIV test. With heterosexual acquisition well recognised as a way in which people acquire HIV in the UK, this approach is not logical. It is also accepted that we, as healthcare workers do not often take complete sexual histories and that patients will often not volunteer a full sexual history. Therefore the absence of traditional risk factors should not be used to decide if someone needs an HIV test as part of the diagnosis workup. In a symptomatic patient the indication for HIV testing should be governed by their clinical presentation and the presence of clinical indicators in the presenting complaint and their past medical history.

List of indicator conditions can be found in the BHIVA testing guidelines:
http://www.bhiva.org/documents/guidelines/testing/glinesHIVTest08.pdf
Case 3
HIV Infection with
Opportunistic Infection
Learning Outcomes

Case 3

• Recognise the common opportunistic infections in HIV infected patients
• Recognise the effectiveness of antiretroviral therapy in advanced disease
A 26 year old women presents to medical receiving with progressive dyspnoea. She describes a 4 week history of dry cough and is no longer able to go to the gym because of breathlessness. Her GP has treated her with a course of amoxicillin followed by a 7 day course of clarithromycin with no improvement.

**Past medical history**
- Shingles 4 years ago
- Previous treatment for Crohn’s disease (stopped as unresponsive)
- TB

**Social history**
- Non smoker
- No illicit drug use
- Works in a call centre
- Occasional alcohol

**On examination**
- Thin (BMI 18)
- Oral thrush and cervical adenopathy
- SpO2 91% on air with respiratory rate 26/min
- Bibasal crepitations
Her chest X Ray shows widespread interstitial shadowing. She is commenced on intravenous Co-amoxiclav and Clarithromycin along with 40% oxygen to maintain her saturations around 92%. Despite this, her oxygen demands rise and 48 hours after admission she has a CT scan of her chest.
Her CT scan is reported as showing widespread ground glass changes consistent with an interstitial process. As she has not responded to broad spectrum antibiotics she is commenced on prednisolone to treat pulmonary fibrosis. She proceeds to bronchoscopy to carry out lung biopsy and also has a bronchoalveolar lavage sent for culture and respiratory pathogen PCR.
PCP Pneumonia

- BAL PCR positive for Pneumocystis jirovecii (previously Pneumocystis carinii)
- HIV positive
  - CD4 count = 68
- Co-trimoxazole 1920mg 6 hourly PLUS Prednisolone 40mg 12 hourly

In this case PCR for PCP had not been specifically requested. However as good clinical information had been supplied on the request form the virologists identified this as a possibility and did the test. It can be seen how the diagnosis of PCP could have been missed if not thought about by the requesting physicians. 2 days later the virus laboratory telephone to report that her BAL is PCR positive for pneumocystis jirovecii (previously pneumocystis carinii).

As a result of diagnosis of PCP pneumonia is made and she has an HIV test that is positive. Further testing shows her to have a CD4 count of 68. This lady has advanced HIV with an opportunistic infection (PCP). She is commenced on high dose intravenous co-trimoxazole along with her steroids.
Unfortunately her oxygen demands climb despite this treatment and she requires transfer to ITU for ventilation. 48 hours later she is commenced on antiretroviral therapy in addition to her PCP therapy. She requires to be ventilated for 72 hours and is discharged from ITU back to the ward.

She completes 3 weeks of Co-trimoxazole and steroids and continues on her antiretroviral drugs. She is fit for discharge 4 weeks after admission and on review in clinic 4 weeks later she is doing well. PCP is probably the most common opportunistic infection seen with advanced HIV. The delay in diagnosing it in this lady probably led to the need for ventilation in ITU. Even though she was very ill, antiretrovirals still improve prognosis so it is important to test for HIV.
This lady’s illness is what could be termed AIDS. She has an opportunistic infection in the context of HIV infection. HIV associated opportunistic infections include tuberculosis, cervical cancer and non Hodgkins Lymphoma and all patients with these should be offered HIV testing as routine. Other opportunistic infections and typical presentations include the following. The BHIVA national testing guidelines, which contain a full list of opportunistic and symptomatic syndromes in HIV can be downloaded from the BHIVA website at this address http://www.bhiva.org/documents/guidelines/testing/glinesHIVTest08.pdf
The natural history of HIV should be thought of as a continuum. Most patients will have symptoms of an acute HIV infection (Case 1). This will settle spontaneously and after 5 to 10 years on average they will start to get symptoms of a failing immune system (Case 2). This is often clinically evident through a variety of symptomatic conditions. Eventually ongoing immune dysfunction will result in opportunistic infection (Case 3).
HIV Epidemiology
Who to test
Learning Outcomes

HIV Epidemiology/Who to Test

• Appreciate that a significant number of people living with HIV do not belong to traditional lifestyle groups and therefore the absence of these lifestyle risk factors cannot be used to exclude HIV infection
• Know how to discuss HIV testing with a patient
• Know how to do an HIV test and interpret the results
Public Health England-Progress Towards Ending the HIV Epidemic in the UK -2017 report (Figure 14)

Common perception of HIV infection is that it is a disease associated with certain lifestyles. The figure above shows the proportions of people living with HIV in the UK grouped according to how they are thought to have acquired the illness.

This data shows that men who have sex with men is the most common way in which people acquire HIV. However, you may have been surprised to notice that large numbers of people acquire HIV through heterosexual sex and the large proportions of people in each group who remain undiagnosed.

This is why absence of traditional lifestyle risk factors must never be used as a reason not to offer someone an HIV test. Whilst opportunistic HIV testing in those who belong to high risk groups is encouraged, we also need to think about ‘risk illnesses’ that should prompt HIV testing as part of their investigation. This will allow the large numbers of undiagnosed people to be identified and access treatment and care.
How to do an HIV test
Pre test DISCUSSION not counselling

• Patients’ consent essential
  – Document in notes

• Pre-test discussion
  – No need for lengthy counselling
  – Why you wish to do an HIV test
  – Potential benefits of testing for HIV
  – When will you give the patient the result

• Giving the result
  – Timely manner
  – Preferably in person

The General Medical Council state that you must always obtain consent from the patient in order to do an HIV test. This should not involve a lengthy counselling session but should take the form of a pre-test discussion. The essential components of the pre-test discussion are included above.

It is good practice to give HIV results in a timeous manner and preferably in person.
Many patients and doctors worry about the insurance implications of HIV testing. Whilst a positive HIV test does affect (but not exclude) the availability of insurance, there are no insurance implications of a negative test. Concern over insurance implications of a positive test should not prevent offering HIV testing as clearly this does not stop us testing for other illness associated with high insurance premiums such as diabetes.
The HIV Test

• What about ‘the window period’
  – Time between infection and positive HIV serology?
  – Modern tests look for antigen and antibody i.e. they are positive sooner (often within 4 weeks)

• Mindful of window period
  – The patient with possible acute HIV infection
  – The patient who wishes to test after a particular risk episode
  – The patient with ongoing risk

The modern HIV test is extremely sensitive. It can be falsely negative in early disease, the so called ‘window period’. As we are talking about HIV testing patients with symptoms and therefore established infection this is unlikely to be an issue. However you should be mindful of this in the following circumstances:

• The patient with possible acute HIV infection
• The patient who wishes testing after a particular risk episode
• The patient with ongoing risk

In each of these cases, if the initial test is negative it is good practice to repeat the test in 12 weeks time.

BASHH/BHIVA Statement on window period for Testing:
What do I do with the results?

• A negative test
  – Window period (less of an issue when investigating symptomatic disease)
  – ?Acute infection – repeat in 4 weeks
• A positive test
  – Discuss with local HIV physician ASAP
  – Help in giving result?
  – HIV review (within 2 weeks)
• Patient should not wait longer than 2 weeks to be told the results and within 7 days if positive!
• Third sector organisations available for support and information include:
  Waverly Care
  HIV Scotland
  Terrence Higgins Trust Scotland

If the patient tests negative you should be mindful of the window period. If they have had particular risk then they should be recalled for a test in 3 months time. If the clinical concern is of acute HIV infection the test should be repeated in 4 weeks time. If the test is negative in the context of concern about established HIV infection, the patient can be reassured that they do not have HIV.

If the patient tests positive for HIV you should contact your local HIV physicians as soon as possible to arrange ongoing management. It is good practice for HIV clinicians to see the patient within 2 weeks of diagnosis.

Regardless of the result the patient should be informed within 2 weeks of having the test taken. If the test is positive they should be informed as soon as possible and within 7 days at most.
All you need to know about antiretroviral therapy
Learning Outcomes

Antiretroviral Therapy

• Understand the way in which HIV is treated
• Recognise the effectiveness of antiretroviral therapy and the importance of early diagnosis
HIV is typically treated with 3 antiretroviral agents. These are targeted against different viral components and typical agents would include:

- Nucleoside reverse transcriptase inhibitors (e.g. tenofovir, abacavir, AZT)
- Non nucleoside reverse transcriptase inhibitors (e.g. efavirenz, nevirapine)
- Protease inhibitors (lopinavir, darunavir, atazanavir – ‘boosted’ with ritonavir)
- Newer classes of drugs in the integrase inhibitors and entry inhibitors are now available allowing even resistant virus to be treated effectively

Many of these agents are now co-formulated. A typical antiretroviral regime will involve taking between 1 and 4 tablets once daily. Side effects tend to be minimal and the agents are very well tolerated.
This data shows the effectiveness of combination antiretroviral therapy. This study looked at the life expectancy of people living with HIV who were commenced on antiretroviral therapy between 1996 and 2008. This showed a substantial increase in life expectancy although this still falls short of that of the general population. However this difference in life expectancy is most marked when therapy is commenced at lower CD4 counts. This highlights the need for early recognition and diagnosis so that patients can attain maximum benefit from antiretroviral therapy.
Take home messages
Remember!

- In the years prior to being diagnosed with HIV patients present to doctors with illnesses characteristic of HIV infection.

- Failure to diagnose HIV at the visits represents missed opportunities and puts the patient at risk of disease progression.

- We often use the absence of lifestyle risk factors as a way of excluding HIV infection. As HIV can be acquired in a variety of ways and large numbers of patients remain undiagnosed, this approach is not justified. We should use the identification of indicator illnesses to improve recognition and diagnosis.
Remember! (cont’d)

• The natural history of HIV represents a spectrum of illness ranging from acute infection through symptomatic disease and eventually opportunistic infection

• Antiretroviral treatment confers a near normal life expectancy but is most effective when started early in disease. Therefore it is essential that patients are diagnosed as soon as possible

• The treatment and care of HIV is very effective in preventing onward transmission
Think about including HIV testing in the investigation of ...

- Monospot negative ‘glandular fever’
- Unexplained diarrhoea and weight loss
- Thrombocytopenia
- Recurrent or multidermatomal shingles
- Pneumococcal bacteraemia
- When testing for Hepatitis B or C is thought necessary
- Pyrexia of unknown origin
- Oral candidiasis
- Persistent lymphadenopathy
Questions
Q: Acute HIV infection often presents as ...

1. Sepsis syndrome
2. Glandular fever like illness
3. Can be asymptomatic
4. Cough and fever

Answer: 2. Glandular fever like illness

Acute HIV often presents as a glandular fever like illness with fever; adenopathy, rash, malaise etc. It should always be considered in a patient thought to have glandular fever but has a negative monospot. Whilst sepsis syndrome is possible, this is less common. Acute HIV is usually symptomatic although patients may not remember having symptoms.
Q: Which of the following is a common presentation of HIV infection

1. Invasive pneumococcal infection
2. Diarrhoea
3. Weight loss
4. Cervical adenopathy

Answer: All of the above
Q: Concerning risk factors for HIV infection – which statement is true?

1. In the absence of lifestyle risk behaviour HIV is unlikely
2. HIV is only acquired heterosexually in those from high prevalence countries
3. These are irrelevant when deciding to offer a test to someone with unexplained diarrhoea and weight loss

Answer: 3

The absence of lifestyle risk factors must never be used as a surrogate for a negative HIV test. Heterosexual spread is common and not isolated to countries with high prevalence of HIV infection. In patients with potentially symptomatic HIV they should be offered an HIV test as a work up for that illness. Any perceived lifestyle risk factors do not alter that.
Q: Concerning HIV testing - which statement is true?

1. Only trained counsellors should carry out HIV testing
2. The patient must give consent
3. The test has a high positive rate
4. A negative HIV test must be declared when applying for insurance

Answer: 2. The patient must give consent

Patients should always give consent for HIV testing. This can be verbal consent. Any GMC registered doctor should be capable of consenting a patient for HIV testing. Lengthy counselling is not required a pre-test discussion is all that is needed. There is no need to declare a negative HIV test, this has no use to insurance companies as most pregnant women undergo HIV testing antenatally. In reality most insurance companies are likely to test prospective customers themselves.
Q: HIV therapy – which statement is true?

1. If started early can confer a near normal life expectancy
2. Involves taking many tables several times per day
3. Has high rates of severe side effects
4. Significantly impacts upon daily activities

Answer: 1. If started early can confer near normal life expectancy

HIV therapy confers life expectancy similar to agree matched controls if started early enough. This is why it is so important to test patients, so that they can derive the most benefit from therapy. Typical regimes are once daily and involve taking between 1 and 4 tablets, this is typically less than someone with type 2 diabetes. Therapy tends to be well tolerated and has minimal, if any, impact upon daily activities.
Further Reading


The guidelines give a very clear description of who to test for HIV, how to do it and to give the results.
They also give a list of the indicator conditions that indicate the need to offer HIV testing to a patient. Displayed are the tables listing these indicator illnesses in adults and children.
Recommend HIV testing in the investigation of ...

- Glandular fever type illness with negative EBV IgM
- Unexplained diarrhoea and weight loss
- Pneumococcal bacteraemia
- Oral candidiasis
- Multidermatomal shingles
- Thrombocytopenia
- Diagnosis of any STI
- Diagnosis of Hepatitis B or C
- Lymphadenopathy
- Pyrexia of unknown origin
- Tuberculosis
- Cervical intra epithelial neoplasia grade 2 or above

Although these lists of indicator illnesses are not exhaustive a smaller number of conditions are listed above. This list is based upon UK wide audit that identified that these were the most common conditions that patients subsequently diagnosed with HIV presented with. This slide can be printed out and kept to act as an aide memoire.

BHIVA Testing Guidelines: