

Medical Emergencies in Human Immunodeficiency Virus (HIV) Infection

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Abstract

With increasing awareness, earlier diagnosis, and aggressive use of anti-retroviral therapy, more people with HIV are living longer so that the average survival time from diagnosis is now significantly better than what it was 10 years ago. As a consequence of this, more patients with HIV are now presenting to hospitals and emergency departments as acute medical emergencies either directly related to their HIV infection, or their treatment.¹ An awareness of the potential problems with which these patients can present to hospital, plus guidance on their management is essential to all acute care physicians. In this article we outline the general management of patients with HIV presenting as emergencies to hospital, and then systematically focus on some of the more common clinical problems which may arise.

Keywords

HIV, AIDS, infection, medical emergencies.

Key Points

1. Medical emergencies in patients with AIDS usually result from opportunistic infection, which are most common when the CD4⁺ count falls below 200 cells/ul.
2. Infection can often be caused by mixed / multiple pathogens
3. Common diseases still affect HIV positive individuals, but may present in unusual ways.
4. Recurrent infection with the same infecting organism is common

Introduction

HIV was identified as the causative organism of AIDS in Paris, 1983. It is now estimated that over 30million people worldwide are infected with HIV. In the UK there has been a 20% increase in total HIV prevalence since 2001.² A recent study by the Health Protection Agency places the number of infected individuals at just under 50,000. There has been a 101% increase in the demand for HIV care since 1997, and 54% of all cases are in London. In the UK, as in most developed countries, there has been a change in epidemiology, with increasing infection rates noted in heterosexuals, particularly amongst recent migrants.³ Despite this, gay men and

intravenous drug abusers still account for a substantial number of new infections.

The introduction of HAART (highly active anti- retroviral therapy), which usually comprises two nucleoside analogues and a protease inhibitor, has resulted in a 75% drop in deaths due to AIDS related diseases since 1995.⁴ This longer life expectancy may have contributed to an increase in the numbers of patients infected with the virus presenting as emergencies to hospital.

Although patients with HIV can experience many problems constituting a medical emergency, by far the most common are those relating to opportunistic infection. Opportunistic infection can happen at **any time** in a patient with HIV, but occur most frequently when the CD4⁺ count falls below 200 cells/mm³. Co-infections in HIV positive patients are not uncommon. For example, many patients with HIV also have co-infection with hepatitis B or C or syphilis, which may have common risk factors for acquisition of infection. Less common although well documented is the finding of simultaneous infection with two opportunistic pathogens.⁵ The physician should also bear in mind that although 'exotic' infections are often the first to be thought of in patients with HIV, conditions more commonly seen in non-HIV positive patients do also occur, and may present in atypical ways.

Clinical assessment: general points

Given the changing epidemiology of HIV infection in the U.K. a high index of suspicion should be given to any patient from sub-Saharan Africa, South East Asia and Eastern European countries presenting either acutely or chronically unwell, especially those with fever. There is usually no urgency to perform a HIV antibody test and discussion about HIV preferably takes place at a time when the patient is able to give appropriate consideration to the implications of the test. There is no absolute requirement for patients to be counselled by specialist advisors; all doctors should have the ability to obtain informed consent for an HIV test.

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All known HIV positive patients or those suspected of being HIV positive presenting acutely unwell to hospital should undergo a thorough history and examination. Particular points to be considered include:

1. Ethnic origin and travel: certain co-infections/opportunistic infections are more likely in those from different geographical areas e.g. HIV positive individuals from the Africa and S.E. Asia are at a much higher risk of tuberculosis, while those from the mid west states of the U.S.A. are at greater risk of histoplasmosis.
2. Length of time since diagnosis.
3. Whether the patient is aware of their recent CD4 counts/viral load.
4. Any previous opportunistic infections.
5. Which antiretrovirals they are taking, as drug side effects can be serious and drug interactions are common.
6. Route of acquisition of HIV, as, for example, ongoing injecting drug users are at greater risk of infective endocarditis.

Investigations to be performed in all HIV positive patients presenting as emergencies
• Full blood count • CD4+ count (May help predict the type of infection, although can be unreliable in acute infection.) • Renal function (Na, K, urea, creatinine) • Liver function tests • Coagulation screen (PT, APTT) • Chest X-ray • Blood culture (x2 if possible), also for mycobacteria • Atypical serology for legionella and mycoplasma • Urinalysis and culture

Figure 1 Initial investigations in HIV positive patients presenting as emergencies

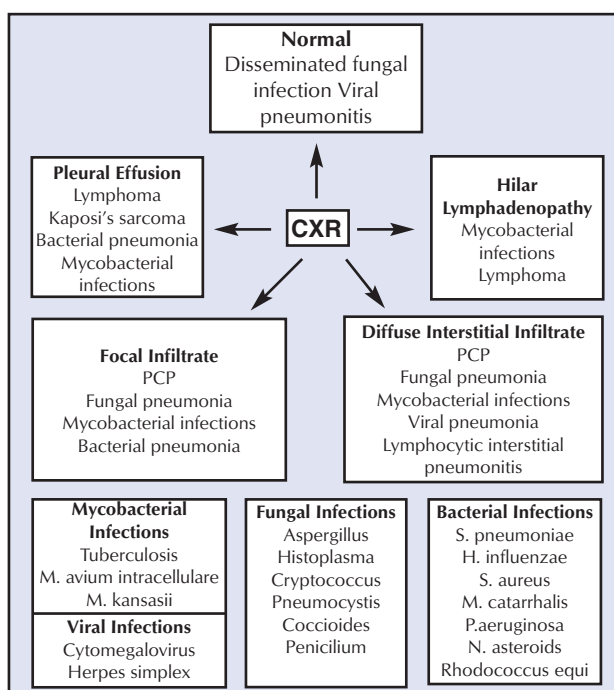


Figure 2 Interpretation of the chest x-ray in patients with HIV

Initial Investigation

The initial investigations recommended for all HIV positive patients presenting as medical emergencies are outlined in Figure 1. More specialist investigations will need to be tailored to the individual's specific presentation and will be discussed later.

1. Respiratory emergencies

Respiratory emergencies constitute the majority of problems experienced by patients with HIV. Indeed, pneumonia is the most common reason for acute hospital admission in a patient with HIV.⁶ Pulmonary complications can occur at any stage of the illness, but in general the type of complication is related to the CD4 count of the patient at the time.

As the CD4 count decreases, the risk of developing *Pneumocystis pneumonia* (PCP), or bacterial pneumonia, especially due to *S. pneumoniae* rises. The use of prophylactic antibiotics has reduced the risk of PCP. Cotrimoxazole is particularly useful in this setting, although albeit rare, breakthrough infections do occur.

Neutropenia is unusual in HIV infection and is more likely to occur as an adverse reaction to therapy, for example to high dose Co-trimoxazole. In this situation disseminated fungal infection should not be overlooked. The re-emergence of TB in patients with HIV is proving a major health issue, especially amongst migrants.

Investigating the HIV patient with respiratory symptoms

In HIV positive patients presenting with fever, cough, sputum production, breathlessness or pleuritic chest pain, the clinical history together with a few simple investigations can usually establish a working diagnosis. Following initial tests as outlined in Figure 1, arterial blood gas analysis should be performed. Any sputum produced should be sent for Gram staining, culture for mycobacteria, and staining for *P. jiroveci* (the causative organism of pneumocystis pneumonia). If tolerated by the patient, exercise oxygen saturation should also be measured especially if resting saturations are normal, as significant desaturation (>5% drop) can be very suggestive of a diffuse pneumonitis. The chest x-ray is often the starting point in establishing a diagnosis (see Figure 2 & Figure 3) however it should be noted that 10-20% with PCP will have a normal chest x-ray.

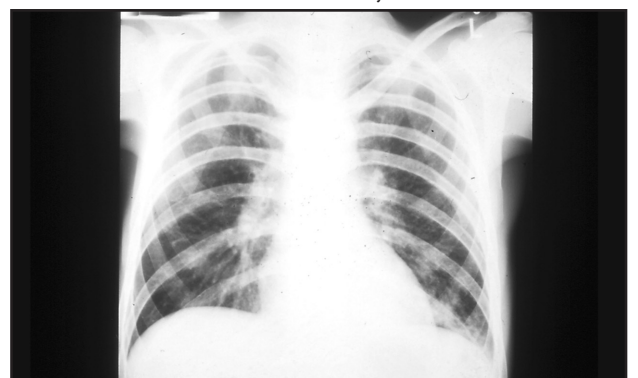


Figure 3 Chest X-Ray of a patient with PCP

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Empirical Therapy (Figure 4)

In most HIV patients with diffuse pulmonary disease a definitive diagnosis is usually preferred over empirical therapy, however in the acute setting empirical therapy is often required until further information becomes available.⁷ This therapy should be initiated as soon as possible, and ideally after blood and sputum samples have been collected. Therapy is primarily directed at treating the common bacterial pathogens and PCP.

If the CD4 count is known to be low ($<200/\text{mm}^3$ or if PCP is suspected clinically, then high dose co-trimoxazole (trimethoprim 20mg/kg/day, plus sulphamethoxazole 100mg/kg/day) should be prescribed. The adjunctive use of corticosteroids in patients with suspected or confirmed PCP infection is now well established.⁹ Prednisolone 40mg PO 12h or, if the patient is unable to swallow, Methyl Prednisolone 1gm IV daily should be initiated.

If bacterial infection is suspected and empirical therapy instituted this should consist of: Co-amoxiclav 1.2g IV 8h, (or cefuroxime 750mg IV 8h), plus erythromycin 500mg IV/PO 6h, (or clarithromycin 500mg IV 12h).⁸ In patients who are intolerant of these antibiotics, expert microbiological advice should be sought. In the rare situation of severe neutropenia in the setting of HIV infection, sepsis or presumed sepsis should be managed following local guidelines.

Further investigation

Should the patient not improve on empirical therapy or if positive identification of the infecting organism is unsuccessful, then the patient should undergo bronchoscopy and bronchoalveolar lavage (BAL). Multilobar BAL is usually sufficient for the diagnosis of PCP, and avoids the additional complications of

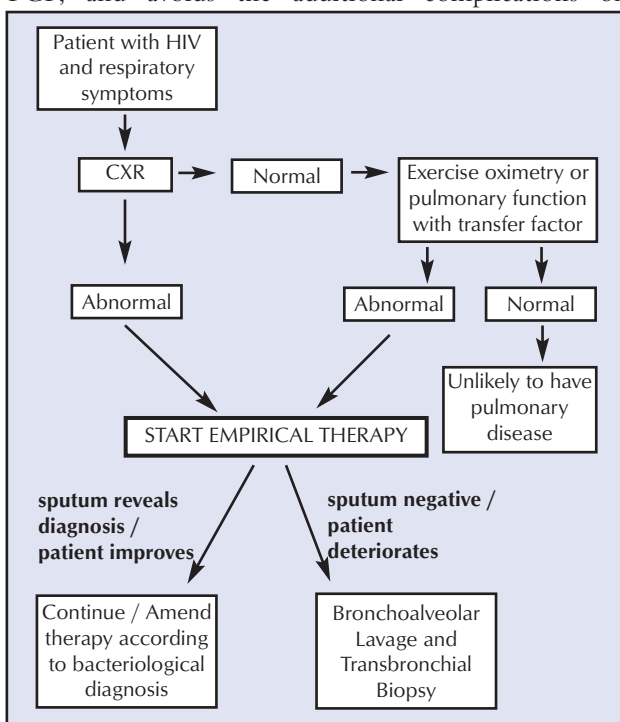


Figure 4 Investigation and treatment for HIV patients with respiratory symptoms.

haemorrhage and pneumothorax associated with transbronchial biopsy (TBB).¹⁰ However TBB improves the sensitivity for the diagnosis of Tuberculosis and fungal pneumonia. This combination will yield a diagnosis in 95% of lower respiratory tract infections in patients with AIDS, and is important in tailoring present, and future antibiotic therapy.¹¹ High resolution CT scanning can also help in the diagnosis of PCP and can be used to distinguish this from other infectious pulmonary processes.¹² Newer tests for the detection of PCP include the estimation of plasma S-adenosylmethionine levels.¹³ The utility of this test however remains to be fully evaluated.

Tuberculosis

It is now becoming clear that the incidence of TB and other Mycobacterial infections is on the increase. Amongst patients from sub-saharan Africa it should be considered the most likely diagnosis in any patient presenting with an abnormal CXR. Investigation of these patients should proceed as above, and an early respiratory opinion is recommended to advise regarding the initiation of anti-tuberculous treatment. This is especially important when considering the rise of multi-drug-resistant strains of TB. Care should also be taken with the isolation of these patients, and the protection of members of staff from infection.

Other respiratory conditions

Pleural effusions should be aspirated or drained, with analysis of the pleural fluid as outlined in Table 3. Pneumothorax is common in patients with PCP, and intercostal drainage is usually required.

2. Central Nervous System (CNS) emergencies

HIV infection can cause a multitude of CNS pathologies, including cerebellar disease, peripheral neuropathy and dementia, as well as severe life threatening infection and malignancy. Patients with HIV may also present as a psychiatric emergency.¹⁴ It is estimated that neurological disease is the primary manifestation in 10-20% of patients with HIV, and that over 70% of patients with HIV infection will develop some form of neurological disease. There are, however 6 neurological conditions affecting HIV patients that may commonly present as an emergency (see Figure 5).

Common neurological emergencies in patients with HIV infection

- Cryptococcal meningitis
- Cerebral toxoplasmosis
- Tuberculous meningitis
- Cerebral lymphoma
- Viral encephalitis
- Paraparesis

Figure 5 Common neurological diagnoses in HIV positive patients

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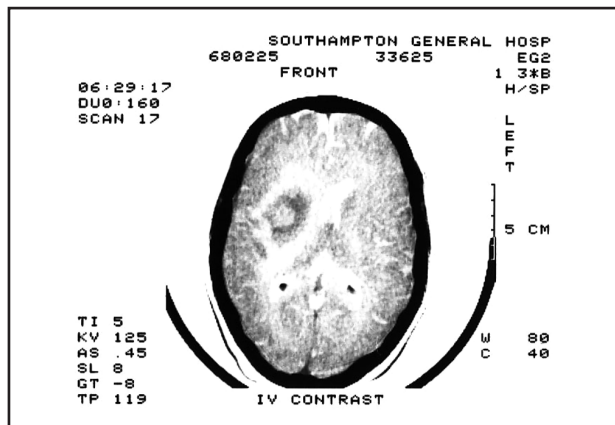


Figure 6 CT head scan: ring-enhancing lesion likely to be cerebral toxoplasma

Fluid should be sent for the following analysis:

- Protein
- Glucose
- White cell count
- Ziehl-Nielsen stain (TB)
- Gram Stain
- India Ink stain (Cryptococcus)
- Cytology
- Bacterial culture
- Viral culture incl. EBV
- VDRL / TPHA

Figure 7 CSF / pleural fluid / pericardial fluid / ascitic fluid investigations

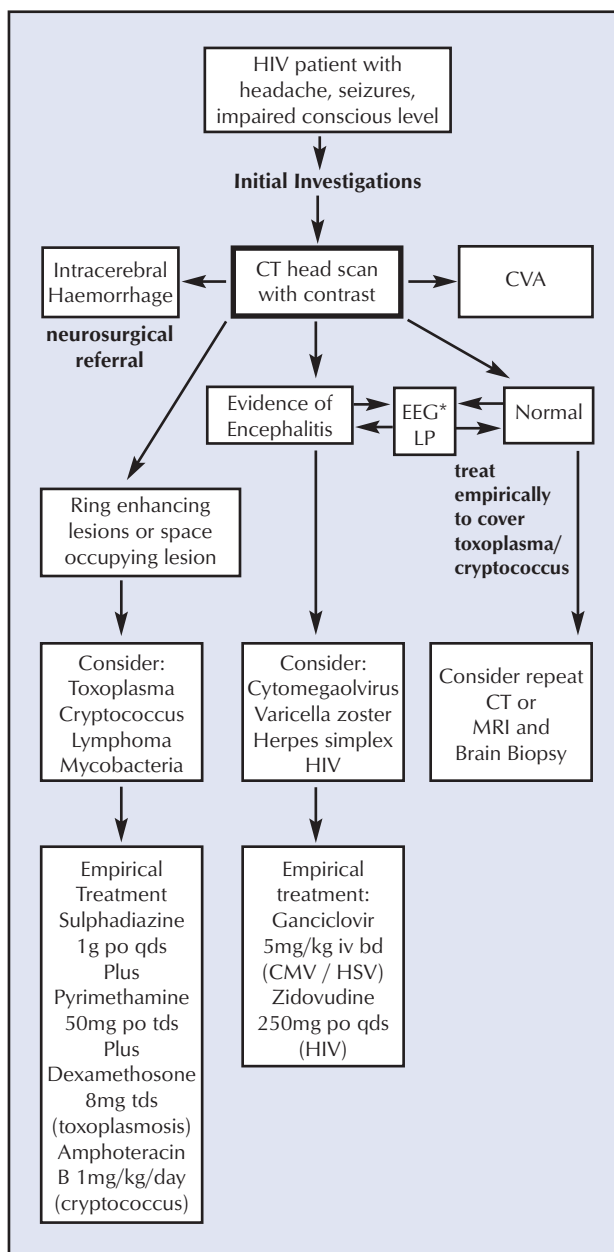


Figure 8 Investigation of neurological symptoms in HIV positive patients. *EEG: Electroencephalogram; LP: Lumbar puncture.

It should also be noted that patients with HIV are also at an increased risk of intra-cerebral haemorrhage secondary to HIV induced coagulopathy, and an increased risk of TIA and CVA due non-atherosclerotic occlusive disease.

The neurological presentation of patients with HIV is often non-specific and can be very variable. As a result, all HIV positive patients presenting to hospital require a detailed neurological examination including fundoscopy. In addition, any HIV patient presenting with acute confusion, seizures, severe headache, focal neurology or an impaired conscious level should be investigated as a matter of urgency.

Investigations

A CT head scan with contrast should be performed in **all** these patients (see Figure 6). If the diagnosis remains uncertain, provided there is no radiological or haematological contraindication, lumbar puncture should then be performed.¹⁵

Specific tests to be carried out on the CSF are listed in Figure 7. It should be noted however that in AIDS the inflammatory response can be muted, and therefore the absence of white blood cells in the CSF does not necessarily preclude meningeal infection.⁷ If a diagnosis remains elusive, then MRI may be more sensitive than CT in detecting various pathologies, including toxoplasma cysts. Lack of availability of MRI often precludes this from being a first line investigation.

In addition to the CSF, serum should also be sent for toxoplasma and cryptococcal antigen.

Management should then be based around the results of investigations as outlined in Figure 8.

Once the results of the lumbar puncture and other investigations are available the treatment can be modified accordingly. Cerebral tuberculosis may take weeks to diagnose and one must have a high index of suspicion to treat initially. Cerebral lymphoma in association with HIV infection can be treated with cranial radiotherapy, it is however associated with an extremely poor prognosis. A biopsy is usually required to diagnose lymphoma and it is usual to treat for toxoplasmosis until proven otherwise.

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In addition to the above algorithm, seizures or signs of a rising intracranial pressure should receive standard therapy.

The HIV positive patient with paraparesis (see Figure 9)

This condition is mentioned separately as it requires different investigation and management. As in the non-HIV patient this represents a medical emergency as without rapid treatment there is a risk of permanent paralysis.

In a patient with paraparesis imaging must be employed first to exclude extrinsic compression, either from a tumour, abscess, or mass. Once this has been excluded antiviral therapy can then be commenced. Although ganciclovir is the preferred agent, good results have been achieved through the use of aciclovir.¹⁶ Newer agents such as Valganciclovir have the advantage of being orally administered. Their place in the treatment of CMV myelitis has yet to be established

Peripheral neuropathy

The patient classically presents with nocturnal painful, burning sensations in their hands and feet, although it may occur throughout the day. It is often caused by anti-viral drugs, such as didanosine or zalcitabine, however the incidence of this is lower than in the past due to lower doses of drug employed and use of drugs before there is profound immune dysregulation. Neuropathy may also be caused by anti-TB drugs such as isoniazid although this is unusual if the patient is taking supplements of Pyridoxine. Prescribing alternative anti-virals may bring some relief, and may prevent progression, but persistence of symptoms is not uncommon. Amitryptiline and / or gabapentin can provide some relief of pain; higher doses than normal sometimes have to be employed. HIV itself can also cause a peripheral neuropathy, and is indistinguishable from drug induced neuropathy. It tends to occur at low CD4 counts and is best treated by improving the patients immune status. Recovery can be slow and incomplete. Other causes such as diabetes and alcohol abuse should not be overlooked as both are more common in HIV positive patients.

3. Cardiac emergencies

As survival amongst HIV individuals improves so the number of patients presenting with cardiac disease

increases. Many studies have demonstrated that cardiac disease is more common in patients with HIV.¹⁷ However in only a small percentage does this prove to be clinically significant.¹⁸ The most common cardiac manifestations of HIV infection are dilated cardiomyopathy, myocarditis, pericardial effusion, and drug-related cardiotoxicity.¹⁹ The number of HIV patients who have a cardiac cause for mortality has been estimated at 1% – 6%.²⁰

Acute coronary syndrome / myocardial infarction

Until recently coronary artery disease was not a recognised complication of HIV infection. The current increase in prevalence has in part been attributed to accelerated atherogenesis.²¹ More recent studies now suggest that this may be due to the use of HAART, specifically protease inhibitors. These have been independently associated with a 26% relative increase in the risk of myocardial infarction per year of exposure in the first 6 years of use.²² The exact mechanism underlying this is not entirely understood, but HAART may be associated with dyslipidaemia and the metabolic syndrome.²³

HIV patients presenting with chest pain and a good clinical history, or ECG changes suggestive of an acute coronary syndrome should be managed in the same way as patients without HIV. If required, this would also include the use of thrombolysis and coronary angiography. The presence of CMV retinitis is considered a relative contraindication to thrombolysis. No guidelines exist at present regarding the continuation or optimisation of HAART in patients following a cardiac event; dyslipidaemia should be treated, with diet and drug therapy as required.

Pericardial disease

Disease of the pericardium is one of the most common cardiac findings at autopsy of HIV individuals. It is estimated that although most patients are asymptomatic, one in five individuals will have evidence of pericardial disease. Asymptomatic effusions are usually non-specific in nature and are often related to the 'pro-inflammatory environment' found in patients with HIV, especially in those who have advanced disease. These require no specific investigations.

Large, symptomatic effusions or pericardial tamponade clearly warrant further investigation and treatment.²⁴ In nearly two thirds of cases a specific identifiable cause can be found. Infection and neoplasia account for most of these cases, with tuberculosis being the most common. In one series it was found that mycobacterial infection accounted for over 30% of all cases of pericardial effusion. Other infectious agents such as bacteria, viruses, or cryptococcus have also been implicated, but result in fewer infections. Lymphoma or Kaposi's sarcoma was identified in 10% of cases.²⁵

The presentation of patients with HIV and pericardial disease will be the same as with non-HIV infected patients, namely breathlessness, pleuritic pain, elevated JVP, or evidence of right-sided heart failure. Two-

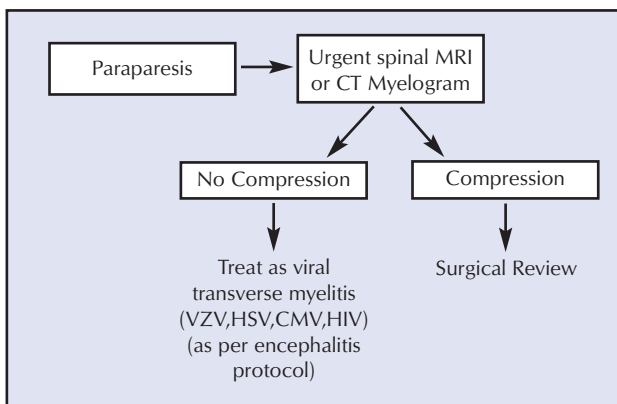


Figure 9 Management of paraparesis in patients with HIV.

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dimensional echocardiography and a 12 lead ECG are usually sufficient to reveal the diagnosis, and if required pericardial drainage is also indicated. Any pericardial fluid aspirated should be investigated (see Table 3).

Symptomatic pericarditis should be managed initially with NSAIDs; if symptoms fail to settle then anti-virals should be considered.

Myocardial disease

The effect of immunosuppression on the myocardium is unknown. However there is a positive correlation between low CD4 count and development of dilated cardiomyopathy.²⁶ Intravenous immunoglobulin infusions have been demonstrated to improve left ventricular (LV) dysfunction in children with HIV induced cardiomyopathy,²⁷ and in areas where HAART is readily available, the incidence of HIV cardiomyopathy is significantly lower. Opportunistic infection may also lead to cardiomyopathy or myocarditis, and in cases of LV dysfunction with no obvious cause, endomyocardial biopsy should be considered. Left ventricular dysfunction should be treated with diuretics and ACE inhibitors; multivitamin supplementation should also be considered.

In addition to the above presentations, the clinician should also be aware that patients with HIV, especially those who have contracted the disease through intravenous drug abuse, are at a higher risk of developing infective endocarditis. This tends to present in the same manner as non-HIV infected individuals, and in the acute setting should be managed in the same way.

4. Renal Emergencies

Acute Renal Failure

In the emergency setting, infection and dehydration are the most common reasons for an individual infected with HIV to develop acute renal failure. Provided the baseline renal function was normal, appropriate use of antibiotics and fluid resuscitation should lead to the complete restoration of normal renal function. Should the patient become anuric or fail to respond to fluid replacement therapy, then imaging should be employed to exclude an obstructive uropathy.

Drug induced renal impairment can occur with a variety of antiretrovirals. Tenofavir renal toxicity is well documented albeit rare. Improvement in renal function following withdrawal of the drug is often slow and incomplete

Chronic Renal Failure

HIV itself has a direct toxic effect on the kidney which can lead to a rapid deterioration in renal function. HIV associated nephropathy (HIVAN) is a focal segmental glomerulosclerosis and is the most common cause of chronic renal disease in HIV patients. Success in the management of this condition has been achieved with steroids and ACE inhibitors, but by far the best results have occurred through the use of HAART.²⁸ Over the past two decades the experience in the management of HIV

patients with chronic renal failure and end-stage-renal-disease has accumulated, with both CAPD and haemodialysis proving effective. The once abysmal outlook for these patients would appear to be changing, with some centres even beginning to perform renal transplantation.²⁹

Gastro-intestinal emergencies

The most frequent GI presentations in HIV positive individuals are gastroenteritis, dyspepsia/dysphagia, and abdominal pain.³⁰ Once again infective processes are the most common pathologies encountered, with cytomegalovirus (CMV) perhaps the most troublesome organism. It should also be borne in mind that good advice regarding care with food and water should be considered indispensable.³¹

Upper GI Symptoms

HIV positive individuals presenting with dysphagia, or painful swallowing should undergo upper GI endoscopy and biopsy. The most likely diagnoses are candidiasis, Herpes simplex, CMV, or simple idiopathic ulceration. Empirical treatment with an oral anti-fungal agent (eg fluconazole 100-200mg daily) is a good first step, especially if plaques are visible in the oral cavity, but relapse is common. If upper GI endoscopy is not possible, then barium swallow is also useful (see Figure 10). Generalised dysmotility of the upper GI tract without any underlying pathology is also a well recognised finding in this group of patients.³²

Simple dyspeptic symptoms in an otherwise well HIV positive individual can generally be treated in the same manner as non-infected patients.³³ Rarely, Toxoplasma, CMV, or Kaposi's Sarcoma may affect the upper GI tract. Kaposi's sarcoma affecting the GI tract is even less common in the absence of cutaneous lesions and therefore careful inspection of the skin is mandatory. Any HIV positive patient not responding to the standard therapy should undergo upper GI endoscopy plus biopsy. Upper GI bleeding may result from vascular tumours such as Kaposi's sarcoma. Factors such as coagulopathy, or portal

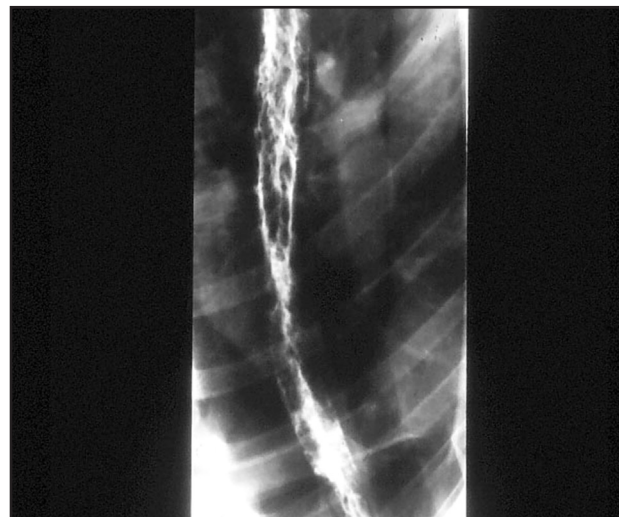


Figure 10 Barium swallow, showing oesophageal candidiasis.

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hypertension due to co-existent chronic hepatitis should be considered.

Diarrhoea

Probably the most common GI complaint to afflict patients with HIV, diarrhoea may also become a longstanding chronic problem. A detailed travel and drug history is important. As with non-HIV positive patients the first step is to assess electrolyte and fluid status, and resuscitate / rehydrate as required. Following this, blood cultures for bacterial pathogens including *Mycobacterium avium* intracellulare, and stool samples for culture, microscopy, and examination for protozoal pathogens should be obtained. If there is a history of recent antibiotic use stools should also be examined for *C.difficile* toxin. Acutely unwell patients should be treated empirically with ciprofloxacin and metronidazole until culture results become available. Salmonella, Shigella, campylobacter, and Giardia should respond rapidly to this therapy. If the stools are found to contain *C.difficile* toxin then oral Vancomycin or metronidazole should be prescribed.

More difficult pathogens to eradicate are Cryptosporidia and microsporidia. Apart from improving the immune status with anti-retroviral agents no treatment works well. Some response may be achieved with use of Paromomycin, Nitazoxanide or high dose Azithromycin.

Any patient in whom cultures are negative, or who fails to respond to empirical therapy should proceed to colonoscopy. Colonoscopy is preferred over flexible sigmoidoscopy, which may miss over 1/3 of cases of CMV colitis.³⁵ Colonoscopy should also include visualisation and biopsy of the terminal ileum if possible. If lower GI endoscopy and biopsy is normal, then upper GI endoscopy plus duodenal biopsy can be considered as a next step. If this also proves to be fruitless in elucidating a diagnosis, then it may be worth considering whether the problem is an HIV enteritis. This often responds to treatment with HAART.

Drug induced diarrhoea is common especially with protease inhibitors, but usually responds to empirical measures. Nelfinavir induced diarrhoea is very common and can be severe and occasionally result in dehydration. Use of calcium supplements is particularly useful in dealing with Nelfinavir induced diarrhoea, although this is less successful in abating diarrhoea induced by other protease inhibitors.

Hepatitis / pancreatitis

These problems both occur with an increased frequency in patients with HIV. Co-infection with Hepatitis B and/or C is common in some groups such as Haemophiliacs and injecting drug users.

Many antiretroviral agents are metabolised via cytochrome P450 and therefore are potentially hepatotoxic. In particular Nevirapine can cause significant hepatic dysfunction and usually occurs within the first 1-2 months of treatment. Women appear to be more susceptible to the side effects of this drug especially if initiated at CD4 counts above 250/ μ L. Stopping the drug is usually all that is required, although due in part to its relatively long half life recovery can be slow.

Conclusion

HIV infection is, for many people, no longer the 'early death sentence' it once was. Although a cure for HIV infection has not yet been found, HAART has changed the landscape and markedly altered the natural progression of the disease. HIV infection is not a 'static state' however, and these patients are prone to a multitude of pathologies and presentations. Physicians must therefore be prepared to meet this ever-increasing problem, and be aware of these patients' specific needs.

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