

## 20.1 Cardiovascular disease

Adam Jenney

Infectious Diseases Unit, The Alfred Hospital, Melbourne, VIC

Cardiovascular disease has become an important consideration for patients with HIV infection, with increased risk related to HIV itself, antiretroviral medications and their effect on lipids and the metabolic syndrome. People with HIV infection initiating combination antiretroviral therapy (cART) must be monitored for dyslipidaemia, hypertension and diabetes, all of which predispose to the development of coronary artery disease. Cardiac causes of dyspnoea in people with HIV infection include cardiomyopathy, pericardial effusions and pulmonary hypertension. The risk of inducing an arrhythmia should be considered whenever new medications are prescribed.

### 20.1.1 Coronary artery disease Pathogenesis

HIV infection itself can cause marked functional alterations to vascular endothelium including enhanced expression of adhesion molecules, elevated levels of inflammatory cytokines, hypercoagulability and even endothelial cell apoptosis.<sup>1</sup> It may also cause dyslipidaemia, particularly a lowering of cholesterol levels (including both high-density lipoproteins (HDL) and low-density lipoproteins (LDL) and an increase in triglycerides.<sup>2</sup> These changes may contribute to coronary artery disease. However, ischaemic cardiovascular events in people with HIV infection continue to be strongly associated with the traditional risk factors such as cigarette smoking, hypertension, family history and hypercholesterolaemia.<sup>3, 4</sup> Such events are likely to increase as life expectancy improves with cART. Furthermore, antiretroviral agents, particularly the protease inhibitors, can contribute to coronary artery disease by causing derangements in metabolism similar to the metabolic syndrome i.e. impairing glucose tolerance, raising triglyceride and cholesterol levels, causing lipodystrophy syndrome<sup>1,5</sup> and raising blood pressure.<sup>6</sup>

The Data Collection on Adverse events of Anti-HIV Drugs (DAD) study group showed that combination antiretroviral therapy led to a 26% relative increase in the rate of myocardial infarction each year in the first few years of use (although the absolute risk was low).<sup>7</sup> A follow-up analysis revealed protease inhibitors were the most likely agents to have this effect partly explained by the dyslipidaemia they cause. The authors found there was additional risk of myocardial infarction in those taking protease inhibitors versus those taking combination antiretroviral therapy that did not include these drugs.<sup>8</sup> It is important to note that, although significant, the magnitude of the increased risk was not very great (relative risk 1.16) and the benefits of antiretroviral therapy can be very profound and may include cardiovascular health.<sup>9</sup> Indeed in the Strategies for Management of Antiretroviral Therapy (SMART) study, there were significantly fewer fatal and non-fatal cardiovascular events in the viral suppression (treated) group compared with the drug conservation group (episodic treatment according to

CD4 cell count; the majority of whom received no antiretroviral therapy for the duration of follow-up prior to study closure by the Data Safety Monitoring Board).<sup>10</sup>

In 2008, an analysis of the DAD cohort study data, revealed an increased risk of myocardial infarction in patients recently exposed to abacavir (relative risk 1.90) and didanosine (relative risk 1.49) compared to those without such an exposure.<sup>11</sup> In those patients on abacavir- or didanosine-containing regimens with high risk for coronary artery disease, attention should be directed to minimising other cardiovascular risk factors present. Whether patients should be switched to an alternative cART is currently under debate. Cardiovascular risk for tenofovir was not evaluated in the DAD study.<sup>12</sup>

Therefore it is very important to monitor for, and manage, cardiac risk factors as they arise as part of routine HIV care.<sup>13</sup> For example, weight and blood pressure should be recorded regularly, and anthropometry, which may reveal lipodystrophy, should be performed. Fasting lipid (particularly LDLs and triglycerides) and glucose levels should be checked prior to initiation of cART and every six to twelve months thereafter while the patient is on cART.<sup>14</sup> More detailed assessments such as carotid artery studies and stress echocardiograms may be required, depending on symptoms. Routine coronary angiograms, however, are not indicated.

Management should focus on preventive strategies – smoking cessation, hypertension control, dietary assessment and follow-up, weight loss and exercise. Dyslipidaemia treatment may necessitate a change in antiretroviral therapy (e.g. switching from protease inhibitors), although the control of HIV replication dictates what strategy is used. HMGCoA reductase inhibitors (statins) are effective in reducing both cholesterol and triglycerides, but may be associated with rhabdomyolysis (especially in combination with fibrates). In people with HIV infection, pravastatin is safer to use than atorvastatin (which should be used cautiously, commencing with a low dose) and simvastatin (which should be avoided).<sup>15</sup> Ezetimibe can reduce cholesterol levels by decreasing gastrointestinal uptake. Fibrates (e.g. gemfibrozil, fenofibrate) produce greater reductions in triglycerides than cholesterol levels. Both fibrates and most statins interact with protease inhibitors, as both are metabolised by hepatic cytochrome P450 3A4 enzymes. Omega 3 acid ester and nicotinic acid derivatives can reduce triglycerides. Oral hypoglycaemic agents can cause serious side-effects (e.g. lactic acidosis with metformin) and glitazones can interact with protease inhibitors.

### 20.1.2 Dilated cardiomyopathy

Dilated cardiomyopathy is diagnosed when both ventricles are enlarged with an ejection fraction of less than 45% in the absence of coronary artery or valvular disease. Before the advent of cART,

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the estimated annual incidence of dilated cardiomyopathy was 15.9/1000<sup>16</sup> and while much of this was subclinical disease, at the time it was considered the most serious cardiac complication of HIV infection<sup>17</sup> and, comparatively, carried a very poor prognosis compared to other causes of myocarditis.<sup>18</sup> It has been estimated that cART has reduced the incidence of cardiomyopathy by 30%.<sup>19</sup>

### Pathogenesis

Myocarditis, the primary cause of dilated cardiomyopathy, is characterised by an inflammatory infiltrate with destruction of adjacent myocardial cells; it is pathologically distinct from the ischaemic damage of coronary artery disease. Myocarditis may be present without evidence of dilated cardiomyopathy, and was found in up to half of the autopsies performed on a series of HIV patients.<sup>20</sup> The aetiology is usually unknown, but myocarditis has been caused by viral infections, including HIV (which can invade via perivascular macrophages and cause apoptosis in cardiomyocytes<sup>21</sup>), cytomegalovirus, Epstein Barr virus, and Coxsackie B3 virus and other disseminated infections which have involved the myocardium (e.g. *Candida*, *Cryptococcus* and *Toxoplasma gondii*).<sup>17</sup> Opportunistic pathogens are identified in only 20% of cases, usually when cardiomyopathy occurs in the setting of disseminated infection.

HIV may cause dilated cardiomyopathy indirectly through the release of cytokines such as tumour necrosis factor-alpha and interleukin (IL)-6; moreover, cytokines in turn cause the release of immune-modulating factors (e.g. nitric oxide), that are both neurotoxic and cardiotoxic. This may explain the poor prognosis of dilated cardiomyopathy with concurrent encephalopathy.<sup>22</sup> Dilated cardiomyopathy can also result from nutritional deficiency (e.g. from a deficit in individual vitamins and minerals such as vitamin B12, carnitine and selenium, to more generalised deficiencies seen in the generally malnourished), medication (zidovudine, pentamidine, IL-2, interferon and doxorubicin) and drug use (cocaine and metamphetamaine).<sup>17</sup>

### Clinical manifestations and diagnosis

While patients are frequently asymptomatic in the early stages, the signs of dilated cardiomyopathy include a displaced apex beat and, if secondary heart failure ensues, tachypnoea, a raised jugular venous pressure, gallop rhythm, regurgitant murmurs, and pulmonary oedema. An echocardiogram will document the

extent of disease (ventricular and valvular dysfunction), detect raised pulmonary artery pressures and pericardial effusions; it is a more sensitive test than either electrocardiogram or chest x-ray. Endomyocardial biopsy may help to identify the aetiology of dilated cardiomyopathy, particularly if other tests are inconclusive. (Image 20.1)

### Treatment

The standard therapies for cardiac failure apply to people with HIV infection – fluid restriction, diuretics, digoxin, angiotensin-converting enzyme inhibitors and beta-blockers, such as carvedilol, bisoprolol and slow-release metoprolol. Heart transplantation has been successfully carried out in a few otherwise asymptomatic patients with HIV infection with cardiomyopathy, however, the practice remains subject to debate.<sup>1,23</sup>

### 20.1.3 Pulmonary hypertension

Pulmonary hypertension occurs in approximately 0.5% of the population with HIV infection,<sup>24</sup> probably resulting for the most part from the primary effects of HIV infection that is thought to induce apoptosis and abnormal endothelial proliferation of pulmonary endothelium via cytokine activation.<sup>25</sup> Pulmonary hypertension may also occur secondary to recurrent lung infections, left ventricular dysfunction, thromboembolic disease, or chronic hepatitis with portal hypertension. The development of pulmonary hypertension does not appear to be related to the degree of immunosuppression and is associated with poor survival (50% at one year). When patients present with shortness of breath and/or the signs and symptoms of right heart failure, an echocardiogram is useful in diagnosis (although some patients will require a right heart catheter study) and to monitor estimated pulmonary artery pressures.

Aggressive treatment of lung infections and combination antiretroviral therapy may slow progression of the condition,<sup>26</sup> and sometimes improvement has been seen with anticoagulation, high-dose calcium-channel antagonists, diuretics and prostacyclin when indicated. Bosentan, an endothelin-1 receptor antagonist, has delivered benefit to patients in small trials in terms of exercise tolerance and right heart pressures.<sup>27</sup> Sildenafil and epoprostenol have also been used with success.<sup>25,28</sup>

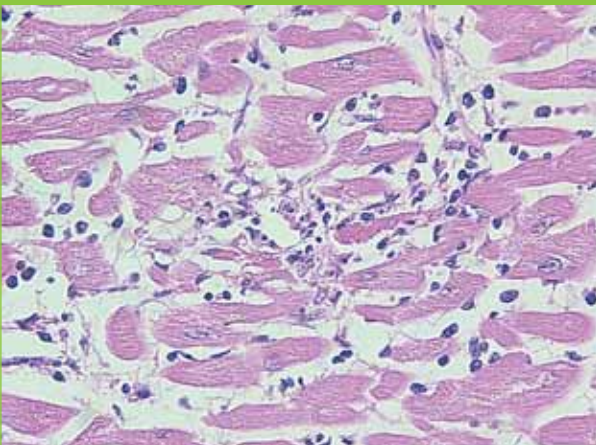
### 20.1.4 Pericardial effusion

A prospective cohort study in the pre-cART era found that pericardial effusions occurred in 11% of patients with AIDS each year. Patients were generally asymptomatic and nearly half the effusions spontaneously resolved.<sup>29</sup> However, survival was significantly shorter in those with an effusion, making the finding a possible marker of poor prognosis.

### Pathogenesis

Pericardial effusions can be spontaneous or secondary to myocarditis, neoplasms, malnutrition and wasting, or myocardial infarction. Many infectious agents have been implicated in pericardial effusions (and pericarditis) including bacteria (*Staphylococcus aureus*, *Streptococcus* spp., *Proteus*, *Nocardia*, *Pseudomonas*, *Klebsiella*, *Enterococcus*, *Listeria* species) mycobacteria (*Mycobacterium tuberculosis*, *Mycobacterium avium* complex, *M. kansasii*), viruses (HIV, herpes simplex virus, cytomegalovirus) and other opportunistic infections (*Cryptococcus neoformans*, *Toxoplasma gondii*).

Images 20.1 Histological section showing viral myocarditis in a man with HIV infection



Source: McLean C, The Alfred Hospital, Melbourne, VIC. Used with permission.

## Diagnosis and therapy

Diagnosis and initial therapy of significant effusions requires pericardiocentesis and drainage, which is usually achieved under local anaesthetic and echocardiographic control.

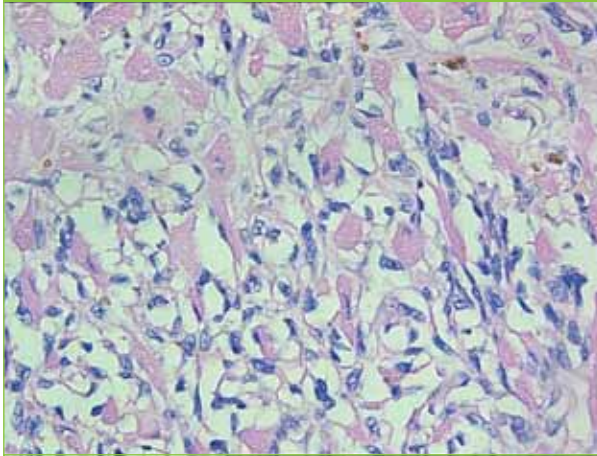
### 20.1.5 Endocarditis

Endocarditis is seen particularly in people with HIV infection who continue to use intravenous drugs. *S. aureus* is the most common organism cultured, although *Candida* spp. and other fungi may be seen. Marantic (non-bacterial thrombotic) endocarditis is less prevalent than initially reported in HIV infection. Investigation and management are as for people without HIV infection.

### 20.1.6 Malignancy

Non-Hodgkin's lymphoma may cause an exudative pericardial effusion (even tamponade) when occurring locally in the mediastinum or as part of widespread disease. When there is infiltration of the heart muscle, atrial or ventricular arrhythmias or heart block may result. Kaposi's sarcoma may similarly be found in myocardium, although is often asymptomatic. (Image 20.2)

Images 20.2 Histological section showing Kaposi's sarcoma of the heart in a man with HIV infection



Source: McLean C, The Alfred Hospital, Melbourne, VIC. Used with permission.

### 20.1.7 Arrhythmias

A prolonged QT interval on electrocardiogram can be due to HIV-associated autonomic neuropathy and can indicate a predisposition to ventricular tachyarrhythmia such as *torsade de pointes*. Certain medications indicated for the treatment of HIV-associated conditions can exacerbate the prolonged QT interval and potential for arrhythmias, including pentamidine (intravenous), cotrimoxazole, amphotericin B, erythromycin, clarithromycin, and ganciclovir. Azole anti-fungal agents (fluconazole, itraconazole, ketoconazole), and all protease inhibitors can increase the QT interval.<sup>30</sup>

## References

- 1 Sudano I, Spieker LE, Noll G, Corti R, Weber R, Luscher TF. Cardiovascular disease in HIV infection. *Am Heart J* 2006;151:1147-55.
- 2 Kamin DS, Grinspoon SK. Cardiovascular disease in HIV-positive patients. *AIDS* 2005;19:641-52.
- 3 David MH, Hornung R, Fichtenbaum CJ. Ischemic cardiovascular disease in persons with human immunodeficiency virus infection. *Clin Infect Dis* 2002;34:98-102.
- 4 Bergersen BM, Sandvik L, Bruun JN, Tonstad S. Elevated Framingham risk score in HIV-positive patients on highly active antiretroviral therapy: results from a Norwegian study of 721 subjects. *Eur J Clin Microbiol Infect Dis* 2004;23:625-30.
- 5 Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, Cooper DA. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS* 1998;12:F51-8.
- 6 Crane HM, Van Rompaey SE, Kitahata MM. Antiretroviral medications associated with elevated blood pressure among patients receiving highly active antiretroviral therapy. *AIDS* 2006;20:1019-26.
- 7 Friis-Møller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, et al. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003;349:1993-2003
- 8 Friis-Møller N, Reiss P, Sabin CA, et al; Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 2007;356:1723-35.
- 9 Stein JH. Cardiovascular risks of antiretroviral therapy. *N Engl J Med* 2007;356:1773-5.
- 10 El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, et al; Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006;355:2283-96.
- 11 D:A:D Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* 2008; 371: 1417-26.
- 12 Stein JH, Currier JS. Risk of myocardial infarction and nucleoside analogues. *Lancet* 2008;371:1391-2.
- 13 Currier JS. Cardiovascular risk associated with HIV therapy. *J Acquir Immune Defic Syndr* 2002;31(Suppl 1):S16-23; discussion S24-5.
- 14 Wanke CA, Falutz JM, Shevitz A, Phair JP, Kotler DP. Clinical evaluation and management of metabolic and morphologic abnormalities associated with human immunodeficiency virus. *Clin Infect Dis* 2002;34:248-59.
- 15 Passalaris JD, Sepkowitz KA, Glesby MJ. Coronary artery disease and human immunodeficiency virus infection. *Clin Infect Dis* 2000;31:787-97.
- 16 Barbaro G. Cardiovascular manifestations of HIV infection. *Circulation* 2002;106:1420-5.
- 17 Sani MU. Myocardial disease in human immunodeficiency virus (HIV) infection: a review. *Wien Klin Wochenschr* 2008;120:77-87.
- 18 Pulerwitz TC, Cappola TP, Felker GM, Hare JM, Baughman KL, Kasper EK. Mortality in primary and secondary myocarditis. *Am Heart J* 2004;147:746-50.
- 19 Barbaro G. Reviewing the cardiovascular complications of HIV infection after the introduction of highly active antiretroviral therapy. *Curr Drug Targets Cardiovasc Haematol Disord* 2005;5:337-43.
- 20 d'Amati G, di Gioia CR, Gallo P. Pathological findings of HIV-associated cardiovascular disease. *Ann NY Acad Sci* 2001;946:23-45.
- 21 Barbaro G. HIV-associated cardiomyopathy etiopathogenesis and clinical aspects. *Herz* 2005;30:486-92.
- 22 Antinori A, Giancola ML, Alba L, Soldani F, Grisetti S. Cardiomyopathy and encephalopathy in AIDS. *Ann N Y Acad Sci* 2001;946:121-9.
- 23 Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. *N Engl J Med* 2002;347:284-7.

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- 24 Limsukon A, Saeed AI, Ramasamy V, Nalamati J, Dhuper S. HIV-related pulmonary hypertension. *Mt Sinai J Med* 2006;73:1037-44.
- 25 Barnett CF, Hsue PY, Machado RF. Pulmonary hypertension: an increasingly recognized complication of hereditary hemolytic anemias and HIV infection. *J Am Med Assoc* 2008;299:324-31.
- 26 Opravil M, Pechere M, Speich R, Joller-Jemelka HI, Jenni R, Russi EW, et al. HIV-associated primary pulmonary hypertension. A case control study. *Swiss HIV Cohort Study. Am J Respir Crit Care Med* 1997;155:990-5.
- 27 Barbaro G, Lucchini A, Pellicelli AM, Grisorio B, Giancaspro G, Barbarini G. Highly active antiretroviral therapy compared with HAART and bosentan in combination in patients with HIV-associated pulmonary hypertension. *Heart* 2006;92:1164-6.
- 28 Carlsen J, Kjeldsen K, Gerstoft J. Sildenafil as a successful treatment of otherwise fatal HIV-related pulmonary hypertension. *AIDS* 2002;16:1568-9.
- 29 Heidenreich PA, Eisenberg MJ, Kee LL, Somelofski CA, Hollander H, Schiller NB, Cheitlin MD. Pericardial effusion in AIDS. Incidence and survival. *Circulation* 1995;92:3229-34.
- 30 Barbaro G. Cardiovascular manifestations of HIV infection. *J R Soc Med* 2001;94:384-90.

## 20.2 Renal disorders

Jeffrey J Post

Department of Infectious Diseases and Albion Street Centre, Prince of Wales Hospital and School of Medical Sciences and Prince of Wales Clinical School, University of New South Wales, Sydney, NSW

HIV-specific renal complications are an uncommon cause of mortality in Australia. More commonly, renal and electrolyte disturbances complicate underlying conditions, or therapy for HIV infection or opportunistic infections. While it has been shown that some antiretroviral agents are associated with systemic hypertension and hyperlipidaemia, it is unclear whether these effects will translate into increased renovascular disease in the cART era.

### Diagnosis

As the differential diagnosis of renal and electrolyte abnormalities in people with HIV infection is wide (Table 20.1), a careful assessment of HIV-related and unrelated disorders, nephrotoxic medications and hydration status needs to be undertaken. Studies have identified potential emerging renal toxicity of licensed antiretroviral drugs. Some cohort studies have suggested that tenofovir<sup>1-4</sup> and indinavir<sup>1</sup> are independently associated with renal impairment although data from clinical trials did not identify significant renal toxicity of tenofovir.<sup>5,6</sup> Renal failure appears to occur uncommonly.<sup>7,8</sup> There have also been recent reports of nephrolithiasis with atazanavir.<sup>9-11</sup> Renal tract obstruction (e.g. nephrolithiasis secondary to indinavir or atazanavir) should be excluded. Urine should be analysed for proteinuria, which should be quantified if present. The indications for renal biopsy are the same as for the general population. Alternative infective causes for renal disease should be considered (e.g. infective endocarditis, chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection and vascular disease).

### Management

Treatment of reversible factors should be undertaken. Dehydration secondary to vomiting, diarrhoea or a reduced oral intake is common in persons with advanced disease, and may also be associated with antiretroviral toxicity. Non-essential nephrotoxic drugs should be ceased. Nucleoside reverse transcriptase inhibitor therapies require dose reduction in the setting of significant renal impairment. Antiretroviral dosing errors in patients undergoing haemodialysis or underexposure in patients with chronic renal failure may be associated with increased mortality.<sup>12,13</sup>

### 20.2.1 HIV-associated nephropathy

HIV-associated nephropathy (HIVAN) is a focal and segmental glomerulosclerosis associated with heavy proteinuria (often with nephrotic syndrome), rapid progression to end-stage renal failure<sup>14</sup> and echogenic kidneys on ultrasound examination. It is reported more commonly in African-American people in the USA and Britain, although it does occur in other populations.<sup>15</sup> Although large, controlled trials are lacking, some therapies may be of benefit in HIVAN. Antiretroviral monotherapy with zidovudine conferred clinical benefit in early reports,<sup>16-18</sup> and more recent case reports and case series suggest that protease inhibitors<sup>19</sup> or cART<sup>20-22</sup> may be beneficial in the management of HIVAN. Prednisone<sup>23</sup> and angiotensin-converting enzyme inhibitors<sup>24,25</sup> may reduce disease progression. Haemodialysis and peritoneal dialysis are effective in persons with HIVAN-related end-stage renal failure. The survival of a renal graft following renal transplantation is similar in the population with HIV infection and the general population.<sup>26</sup> With improved survival of people with HIV infection with cART, renal transplantation may become a more common therapeutic modality.<sup>27</sup>

HIV infection is also associated with other glomerular lesions (Table 20.1) including immune complex glomerulonephritis.

### 20.2.2 Monitoring of patients without established renal disease

Patients without renal disease should be monitored by assessment of serum creatinine, urea and electrolytes, (including serum phosphate, calcium and magnesium), estimated creatinine clearance and urinary protein. Blood pressure measurement should be performed at regular intervals, typically four times each year. A baseline dipstick urinalysis for protein should be performed, and, if proteinuria is detected, should be further evaluated, with an estimated glomerular filtration rate, urine protein/creatinine ratio and a renal ultrasound. Proteinuria is a trigger for detection of common diseases such as diabetes or hypertension, and is a risk factor for cardiovascular disease. Proteinuria may occur as a direct result of HIV infection (e.g. HIVAN), but also occurs in tubular dysfunction such as Fanconi syndrome. Most patients with glomerular proteinuria should be treated with renin-angiotensin blockade e.g. with an

Table 20.1 Causes of renal disease and electrolyte disturbances in people with HIV infection

Electrolyte and acid/base disturbances	Non-HIV-specific causes of renal dysfunction
Hyponatraemia (diarrhoea, adrenal insufficiency, syndrome of inappropriate antidiuretic hormone) Hypernatraemia Hypokalaemia Hyperkalaemia Hypocalcaemia Lactic acidosis (HIV, sepsis, hypotension, antiretroviral therapy)	Acute tubular necrosis Volume depletion (eg. diarrhoea, reduced oral intake) Rhabdomyolysis Tumour lysis Radiographic contrast Cardiomyopathy
Drug toxicity	HIV-related nephropathies
Aciclovir (crystal deposition) Adefovir (renal tubular acidosis) Aminoglycosides (proximal tubular dysfunction) Amphotericin B (tubular dysfunction/acidosis, nephrocalcinosis, hypokalaemia, hypomagnesaemia, hypocalcaemia) Atazanavir (nephrolithiasis) Cidofovir (tubular dysfunction, proteinuria) Ciprofloxacin (interstitial nephritis) Cotrimoxazole(interstitial nephritis) Foscarnet (hyperkalaemia and renal impairment) Indinavir (nephrolithiasis and impaired renal function) Interleukin-2 (capillary leak) Pentamidine (hyperkalaemia, renal impairment) Sulfadiazine (crystal deposition) Tenofovir (proximal renal tubular acidosis, renal impairment) Trimethoprim (tubular dysfunction)	HIV-associated nephropathy Immune complex glomerulonephritis (including Immunoglobulin A nephropathy) Membranous, mesangiocapillary, lupus-like thrombotic microangiopathies (thrombotic thrombocytopenic purpura/haemolytic uremic syndrome)
	Opportunistic processes
	Lymphoma (obstruction or parenchymal) Nephrocalcinosis ( <i>Mycobacterium avium</i> complex or <i>Pneumocystis jirovecii</i> ) Others (rare)
	Co-existing pathology
	Diabetes mellitus Hypertension Atherosclerosis Hepatitis B virus Hepatitis C virus Syphilis Heroin nephropathy Infective endocarditis

angiotensin-converting enzyme inhibitor. Patients treated with potential nephrotoxins should be monitored with at least the same frequency with consideration of more frequent urinalysis.

## References

- Mocroft A, Kirk O, Gatell J, Reiss P, Gargalianos P, Zilmer K, et al. Chronic renal failure among HIV-1-infected patients. *AIDS* 2007;21:1119-27.
- Antoniou T, Raboud J, Chirhin S, Yoong D, Govan V, Gough K, et al. Incidence of and risk factors for tenofovir-induced nephrotoxicity: a retrospective cohort study. *HIV Medicine* 2005;6:284-90.
- Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. *Clin Infect Dis* 2005;40:1194-8.
- Mauss S, Berger F, Schmutz G. Antiretroviral therapy with tenofovir is associated with mild renal dysfunction. *AIDS* 2005;19:93-5.
- Izzedine H, Hulot JS, Vittecoq D, et al; the Study 903 Team. Long-term renal safety of tenofovir disoproxil fumarate in antiretroviral-naïve HIV-1-infected patients. Data from a double-blind randomized active-controlled multicentre study. *Nephrol Dial Transplant* 2005;20:743-6.
- Izzedine H, Isnard-Bagnis C, Hulot JS, Vittecoq D, Cheng A, Jais CK, et al. Renal safety of tenofovir in HIV treatment-experienced patients. *AIDS* 2004;18:1074-6.
- Nelson MR, Katlama C, Montaner JS, Cooper DA, Gazzard B, Clotet B, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. *AIDS* 2007;21:1273-81.
- Gerard L, Chazallon C, Taburet A-M, Girard P-M, Aboulker J-P, Piketty C. Renal function in antiretroviral-experienced patients treated with tenofovir disoproxil fumarate associated with atazanavir/ritonavir. *Antiviral Therapy* 2007;12:31-9.
- Anderson PL, Lichtenstein KA, Gerig NE, Kiser JJ, Bushman LR. Atazanavir-containing renal calculi in an HIV-infected patient. *AIDS* 2007;21:1060-2.
- Pacanowski J, Poirier J-M, Petit I, Meynard J-L, Girard P-M. Atazanavir urinary stones in an HIV-infected patient. *AIDS* 2006;20:2131.
- Chan-Tack KM, Truffa MM, Struble KA, Birnkrant DB. Atazanavir-associated nephrolithiasis: cases from the US Food and Drug Administration's Adverse Event Reporting System. *AIDS* 2007;21:1215-8.
- Tourret J, Tostivint I, Tézenas Du Montcel S, Karie S, Lounay-Vacher V, et al. Antiretroviral drug dosing errors in HIV-infected patients undergoing hemodialysis. *Clin Infect Dis* 2007;45:779-84.
- Choi AI, Rodriguez RA, Bacchetti P, Volberding PA, Havlir D, Bertenthal D, et al. Low rates of antiretroviral therapy among HIV-infected patients with chronic kidney disease. *Clin Infect Dis* 2007;45:1633-9.

## 20 Other diseases or disorders

- 14 Rao TK, Filippone EJ, Nicastrì AD, Landesman SH, Frank E, Chen CK, et al. Associated focal and segmental glomerulosclerosis in the acquired immunodeficiency syndrome. *N Engl J Med* 1984;310:669-73.
- 15 Cantor ES, Kimmel PL, Bosch JP. Effect of race on expression of acquired immunodeficiency syndrome-associated nephropathy. *Arch Intern Med* 1991;151:125-8.
- 16 Ifudu O, Rao TK, Tan CC, Fleischman H, Chirgwin K, Friedman EA. Zidovudine is beneficial in human immunodeficiency virus associated nephropathy. *Am J Nephrol* 1995;15:217-21.
- 17 Michel C, Dosquet P, Ronco P, Mougnot B, Viron B, Mignon F. Nephropathy associated with infection by human immunodeficiency virus: a report on 11 cases including 6 treated with zidovudine. *Nephron* 1992;62:434-40.
- 18 Babut-Gay ML, Echard M, Kleinknecht D, Meyrier A. Zidovudine and nephropathy with human immunodeficiency virus (HIV) infection. *Ann Intern Med* 1989;111:856-7.
- 19 Dellow E, Unwin R, Miller R, Williams I, Griffiths M. Protease inhibitor therapy for HIV infection: the effect on HIV-associated nephrotic syndrome. *Nephrol Dial Transplant* 1999;14:744-7.
- 20 Wali RK, Drachenberg CI, Papadimitriou JC, Keay S, Ramos E. HIV-1-associated nephropathy and response to highly-active antiretroviral therapy. *Lancet* 1998;352:783-4.
- 21 Chemlal K, Nochy D, Kenouch S, Joly V, Carbon C. Dramatic improvement of renal dysfunction in a human immunodeficiency virus-infected woman treated with highly active antiretroviral therapy. *Clin Infect Dis* 2000;31:805-6.
- 22 Kirchner JT. Resolution of renal failure after initiation of HAART: 3 cases and a discussion of the literature. *AIDS Reader* 2002;12:103-5.
- 23 Smith MC, Austen JL, Carey JT, Emancipator SN, Herbener T, Gripshover B, et al. Prednisone improves renal function and proteinuria in human immunodeficiency virus-associated nephropathy. *Am J Med* 1996;101:41-8.
- 24 Kimmel PL, Mishkin GJ, Umana WO. Captopril and renal survival in patients with human immunodeficiency virus nephropathy. *Am J Kidney Dis* 1996;28:202-8.
- 25 Burns GC, Paul SK, Toth IR, Sivak SL. Effect of angiotensin-converting enzyme inhibition in HIV-associated nephropathy. *J Am Soc Nephrol* 1997;8:1140-6.
- 26 Qiu J, Terasaki PI, Waki K, Cai J, Gjertson DW. HIV-positive renal recipients can achieve survival rates similar to those of HIV-negative patients. *Transplantation* 2006;81:1658-61.
- 27 Wyatt CM, Murphy B. Kidney transplantation in HIV-infected patients. *Sem Dialysis* 2005;18:495-8.

## 20.3 Psychiatry and HIV

**Toby Syme**  
**Cassy Workman**  
**Mark Jeanes**

Victorian HIV Mental Health Service, Infectious Diseases Unit, The Alfred Hospital, Melbourne, VIC  
Ground Zero Medical Centre, Sydney, NSW  
Victorian HIV Mental Health Service, Infectious Diseases Unit, The Alfred Hospital, Melbourne, VIC

People with HIV infection suffer high rates of mental disorder. Epidemiological studies have indicated the prevalence of mental disorder in this population to be as high as 47.9% with the most common diagnoses being depressive syndromes, anxiety disorders and substance abuse and dependence.<sup>1,2</sup> Rates of mental disorder are also reported to be high in resource-limited settings.<sup>3</sup> The reasons for this are twofold: firstly, there is an association between risk-taking behaviours linked to HIV transmission, and mental illness,<sup>4</sup> secondly, HIV infection impacts on a person's life and functioning, both directly through neurological injury producing cognitive and behavioural changes and indirectly through the impact of chronic illness on psychological function. Living with a mental disorder has a significant impact on a person's sense of wellbeing and quality of life which may be worsened by the multiple burdens and stigma of living with a mental illness associated with HIV infection. Untreated mental illness can clearly affect person's ability to care for themselves and others, maintain accommodation and employment and to comply with HIV treatment.<sup>5</sup>

People with pre-existing mental disorder are at high risk of contracting HIV infection. The type of predisposing disorders can range from cognitive disorder (intellectual disability, dementia and acquired brain injury) to mood disorder (depression and mania), psychotic disorder (especially schizophrenia) and personality disorder (particularly borderline and antisocial personality disorder). In young people, mental illness can be associated with high-risk behaviours such as lower age for first sexual contact, greater numbers of sexual partners and reduced condom use.<sup>6</sup> Rates of illicit substance and alcohol abuse and

dependence are also higher, exacerbating underlying illness and psychosocial dysfunction and increasing the frequency of HIV risk behaviours. There is evidence that adequately identifying and treating mental illness significantly reduces HIV acquisition risk behaviours.<sup>7</sup>

In people with HIV infection there are a range of mental disorders that may be associated with the stage of illness. Significant illness milestones relate to phases of disease progression such as: the time of initial diagnosis; commencement of antiretroviral therapy; symptomatic illness; antiretroviral failure and the need for salvage therapy; and the later stages of illness that can be associated with the increasing loss of physical functioning combined with the cognitive manifestations of HIV infection. These periods may be associated with periods of stress or normal adjustment, though if severe they can manifest with psychological symptoms such as anxiety or mood symptoms that may be better described as an adjustment disorder or if more severe a major depressive disorder or an anxiety disorder. People with a prior history of mental illness and substance abuse, and with low social support, are more at risk of suffering from major adjustment difficulties, and more likely to come to the attention of clinicians during these periods of change.

In the Australian context, the majority of people currently living with HIV are men who contracted the infection through sexual contact with other men.<sup>8</sup> A large percentage of men who have sex with men present unique psychological issues that come from living in a society often hostile to gender non-conformity, resulting in personal stigma and shame.<sup>9</sup> While societal attitudes to homosexuality have evolved over the last

20 years, the developmental impact of this sense of difference, coupled not infrequently with a history of discrimination and abuse can manifest in adulthood with higher rates of mental illness and substance abuse than in the community in general.<sup>10</sup> Among heterosexuals in Australia diagnosed with HIV infection, migrants especially those from high-prevalence regions such as sub-Saharan Africa are significantly over-represented.<sup>8</sup> This group also presents unique challenges and often has suffered difficult developmental and migration histories, coupled with the challenges of adapting to a new culture and lifestyle. These people are thus at high risk of developing mental disorder which can manifest in differing ways due to the effects of cultural difference.<sup>11,12</sup> Equally, a diagnosis of HIV infection is often highly stigmatised in these communities resulting in secrecy and social isolation for those with the virus. There is a need for culturally sensitive and appropriate practice in order to better engage, educate and treat patients from smaller migrant communities who present with mental illness.

The later stages of HIV infection are commonly associated with the neurocognitive complications of HIV infection and less commonly with severe episodes of psychiatric illness such as manic episodes, psychotic illness and episodes of delirium. These later episodes, though less common, are important to identify and treat early to prevent risks to the patient and potentially others. Antiretroviral medications have also been associated with reported neuropsychiatric symptoms in patients. These can range from mood disturbance to anxiety, sleep disturbance and confusion. The non-nucleoside reverse transcriptase inhibitor, efavirenz, is the most frequently associated with psychiatric symptoms including sleep disturbance, vivid dreams, anxiety, agitation, abnormal thinking and, less commonly, frank manic or psychotic symptoms.<sup>13</sup>

The broad principles of management in this population include a focus on engagement of the person with HIV infection and identification and containment of immediate risks. These may be immediate risks to the person himself (e.g. self harm and suicidal behaviours), or less directly via self-neglect or disturbed behaviour, and also risks to others through direct violence, neglect (e.g. of children) or problem behaviours (e.g. through unsafe sexual practices). All states and territories of Australia have mental health legislation that allows for involuntary treatment of people if there are immediate safety concerns and the person is unable or unwilling to consent to treatment. It is important to have some awareness of the legal structures involved. Treatment of mental illness involves a multifaceted bio-psycho-social approach and often requires the resources of a multidisciplinary team (e.g. psychiatrist, mental health trained nurse, psychologist, social worker and occupational therapist) to adequately assess and deliver treatment. Access to such resources is obviously more difficult in rural and remote regions where many of these functions may be provided by a sole clinician such as a general practitioner or nurse practitioner.

### 20.3.1 Depression

People living with HIV suffer high rates of major depression. A meta-analysis found rates of major depression in HIV-positive people to be twice that of matched HIV-negative controls.<sup>14</sup> Rates may increase with disease progression and symptomatic illness.<sup>15</sup> Certain risk factors are associated with an increased risk of depression: a personal or family psychiatric history of mood disorders, substance use, anxiety disorders, suicidal episodes, being female, low social support, and current medical illness.<sup>16</sup>

Suicidal thoughts and acts are a common reason for psychiatric referral and can occur at times of crisis such as at the time of HIV diagnosis and in the late stages of illness. Depression may adversely affect the outcome of treating HIV infection. There is evidence to support an association between depression and self-neglect, with implications for treatment adherence.<sup>17</sup>

It can be difficult to identify depression in patients with severe medical illness. Depressive symptoms may represent a normal reaction to physical illness, a manifestation of the underlying physical illness (e.g. symptoms of fatigue and anorexia) or a component of a depressive syndrome. As such, depression can be easily missed. Untreated depression in patients is associated with a poor prognosis.<sup>18</sup> Cognitive-affective symptoms (as opposed to somatic symptoms) may be more discriminating in identifying depression in this population. Examples of these would be: a sense of failure, a sense of being punished, indecisiveness, reduced social interest, suicidal ideation, frequent crying and dissatisfaction.<sup>19</sup> In patients with HIV it is always important to consider an organic basis to the depression, especially when there is no personal or family history of mood disorder, there are no obvious precipitants, when the presentation is atypical, when cognitive symptoms appear severe, if the patient is severely immunocompromised or when the patient had failed to respond to treatment. Assessment needs to include a thorough physical examination and medical workup to exclude organic pathology (Table 20.2).

The appropriate treatment approach in the patient with HIV infection with depression depends on the type and severity of the depression (Table 20.3). Once organic illness is excluded or reversed, for mild depression, treatment with short-term psychotherapy alone is usually appropriate and there is evidence to suggest efficacy.<sup>20</sup> This could be supportive, cognitive behavioural or interpersonal psychotherapy and needs to be provided by trained clinicians. For moderate to severe depression, antidepressant medications are recommended, often in combination with psychological therapies. Choice of antidepressant needs to consider the patient's symptom profile and history of prior response. Though there is evidence for good effect with tricyclic antidepressants,<sup>21</sup> given their side-effect profile and risk in overdose, current first-line therapy would be a selective serotonin reuptake inhibitor (SSRI) antidepressant. It is better to choose an agent with less drug-drug interactions such as citalopram, escitalopram or sertraline. Second-line agents include mirtazapine, which aids insomnia and poor appetite, or venlafaxine. For more severe depression associated with melancholic or psychotic symptoms it is advisable to seek advice from a trained psychiatrist as treatment may require the use of augmentation with antipsychotic drugs or mood stabilisers, and, rarely, electroconvulsive therapy.

## Assessment

Psychosocial history	Living environment, employment, finances, relationships
Level of functioning	Activities of daily living Presenting symptoms and relationships to psychosocial factors
HIV status	Duration of illness, recent CD4 cell count, viral load, CD4 cell nadir (Indicates likelihood of CNS involvement, and indicates stage of illness) HIV complications and opportunistic infections Current antiretroviral treatment, recent changes and compliance
Medical and psychiatric history	Other active medical problems and medications Personal and family past psychiatric history Comprehensive drug and alcohol use assessment
Examination	Mental state assessment with focus on cognition and risk assessment Physical examination as indicated to identify and exclude organic illness such as CNS opportunistic infection
Investigations	HIV status (CD4 cell count, HIV viral load if not recently determined) CNS investigation if CD4 cell count <200 cells/ $\mu$ l and clinically indicated, eg CSF (viral load and cryptococcal antigen) and neuroimaging Metabolic screen (renal and liver function), vitamin B12/folate, blood glucose Haemoglobin Endocrine (thyroid function tests, pituitary function, testosterone) Urine drug screen Review past serology (including syphilis)

CNS = Central nervous system; CSF = Cerebrospinal fluid.

## Management

Engagement and therapeutic rapport	Identify and contain risks, consider need for involuntary treatment and notification of children's protective agencies if indicated Consider need for referral to specialist care
Exclusion of organic illness	Further history from family or partner as indicated
Biological	Identify and treat underlying illness e.g. antidepressants, mood stabilisers, antipsychotics as indicated Consider use of short term anxiolytic or hypnotic drug to contain symptoms and aid engagement Consider need for withdrawal regimen if drug or alcohol dependence present Monitor for side-effects and review compliance
Psychological	Educate about identified illness and recovery plan Supportive psychological care Specific psychological approaches as required: short-term cognitive behavioural, or interpersonal and longer term psychodynamic approaches as indicated Partner and or family interventions as identified Motivational interviewing approach to drug and alcohol addictions Consider if neuropsychology assessment is required
Social	Consider role of multidisciplinary team including social worker Role for interventions in housing, financial support, employment, relationships (support groups), home supports to reduce stressors Consider need for drug and alcohol services

### 20.3.2 Anxiety

Anxiety symptoms are common in patients living with HIV, and are likely to be more prominent at times of significant life stresses and at stages of disease progression.<sup>22</sup> Diagnosable anxiety disorders where anxiety is severe and persistent are also common: surveys have estimated the prevalence of generalised anxiety disorder as occurring in up to 15% of patients and panic disorder in as many as 10% of patients.<sup>1</sup> Agoraphobia and social phobia are also common and high rates of post traumatic stress disorder and acute stress disorder have been described.<sup>23</sup> The

presentation of these disorders is often clouded by comorbid mood disorder, substance use and personality disorders making diagnosis more complicated. Effective treatment requires a comprehensive assessment of the presenting symptoms, life stresses and coping style.

Treatment approaches include brief psychological interventions and/or medication. Psychological approaches that may be helpful include behavioural techniques such as progressive

Physical examination	Vital signs Focal neurological signs Signs of focal infection Tremor, asterixis Ophthalmological examination Evidence of head trauma
Initial screen	FBE, ESR, liver function tests, thyroid function tests, blood sugar Urine/serum drug screen: illicit drugs Medication level monitoring: lithium, anticonvulsants Urinalysis Chest x-ray
Investigation of HIV-associated conditions	Serology: toxoplasma, cryptococcus, cytomegalovirus, herpes simplex virus, syphilis
Further investigation	Nutritional deficiency: B12, folate Pulse oximetry and blood gasses: if thought to be hypoxic Sputum culture Blood culture Lumbar puncture: CSF analysis for HIV and opportunistic infections Cerebral imaging: CT, MRI EEG
<small>FBE = full blood examination; ESR = erythrocyte sedimentation rate; CT = computer tomography; MRI = magnetic resonance imaging; EEG = Electroencephalography; CSF = cerebrospinal fluid.</small>	

muscular relaxation, breathing exercises and systematic desensitisation. These may be incorporated within a Cognitive Behavioural Therapy approach<sup>24</sup> and medications are often used concurrently. Benzodiazepines may be helpful for short-term symptom relief, and are usually best used with antidepressant agents and tapered as symptoms improve. Shorter-acting agents with fewer metabolites are preferred such as oxazepam, lorazepam and temazepam, with consideration given to risks such as abuse and dependence. Antidepressants are effective for the longer-term treatment of anxiety, with SSRIs being the first-line choice, again choosing agents that have less hepatic cytochrome p450 interactions. Mirtazapine and venlafaxine can also be effective.

### 20.3.3 Mania

Manic episodes are more common in people with HIV infection than in the general population.<sup>25</sup> An episode of mania is often associated with poor impulse control, impaired judgement and greater risk-taking behaviours, increasing the chance of contracting or spreading HIV infection.

A manic episode may be primary (related to a bipolar disorder) or secondary to a range of causes.<sup>26</sup> Possible secondary causes may be substance-induced mania related to either illicit or prescription medications including antiretroviral agents, mania due to a medical condition such as central nervous system opportunistic infection, a manifestation of a hyperactive delirium, or related to primary HIV infection.<sup>16</sup>

Important clinical features on history include a past or family history of mood disorder, current HIV clinical parameters and stage, current medications and recent changes, substance abuse history and a cognitive assessment. Specific enquiry regarding increased libido or sexual activity should also be made as previously insightful patients may lose their usual judgement, e.g. occasionally develop delusions and believe their HIV is cured. A comprehensive medical examination is required and investigations such as neuroimaging and cerebrospinal fluid analysis undertaken to elucidate central nervous system involvement with HIV.

Manic episodes related to HIV infection tend to be a late manifestation of illness associated with a low CD4 cell count, high viral load and evidence of structural brain damage demonstrable on magnetic resonance image (MRI) or computed tomography (CT) scan.<sup>25</sup> These classically have been associated with cognitive impairment and a poor clinical prognosis, as they have been linked to the development of an HIV-associated dementia.<sup>26</sup> Clinically, patients may present with more irritability, talkativeness, and cognitive slowing and impairment than those with primary bipolar illness. Treatment must be provided in a safe and secure environment which may mean hospitalisation and involuntary treatment.

Evidence suggests the most effective treatment for HIV mania is effective antiretroviral therapy that penetrates the central nervous system.<sup>25</sup> Symptoms may also be controlled with psychotropic medications including mood stabilisers, antipsychotic and anxiolytic drugs. All mood stabilisers have the potential for side-effects and drug interactions. Lithium is reported to be effective but has higher rates of neurotoxicity in this population. Sodium valproate is frequently used but care must be taken to monitor for liver toxicity and the theoretical risk of elevation of HIV viral load. Mood stabilisers are often combined with antipsychotic drugs to treat acute episodes. Current practice suggests that olanzapine, risperidone and quetiapine can be effective in this population though there is an increased rate of extrapyramidal side-effects. Benzodiazepines are also used for short-term sedation.<sup>27</sup>

### 20.3.4 Cognitive disorders

#### Acute changes in cognition

Sudden changes in cognitive function raise the possible diagnosis of delirium. The cardinal signs of delirium are fluctuating conscious state, impaired concentration and disorientation in time or place. As the course of illness is variable there may be periods of lucidity. There may also be associated psychotic symptoms (hallucinations in any sensory modality or delusional ideas) which can be distinguished from other forms of psychotic illness on a temporal basis. Delirium is more likely to occur in the later stages of HIV infection but is not exclusively limited to this period. It is also common in hospitalised patients with rates of up to 22% described in inpatients with HIV infection.<sup>28</sup> A corroborative history of substance abuse or withdrawal may help to clarify the aetiology.

The assessment of delirium includes documentation of cognitive changes both for diagnosis and monitoring progress. Physical examination and investigation should be targeted towards likely causes<sup>29</sup> (Table 20.4).

Treatment will be directed by findings on investigation, but often a specific cause cannot be identified. General management includes measures which increase familiarity with the environment such as adequate lighting, orientation cues and limiting the number of staff involved in interactions with the patient. Medication can be used to decrease agitation and maintain a regular sleep cycle. It is common practice to use antipsychotic medication in these circumstances initially at low doses and titrated accordingly. Occasionally parenteral medication may be required and it should be used judiciously. Benzodiazepine medication is indicated in delirium secondary to alcohol withdrawal but should be used cautiously in other circumstances; there are significant interactions with antiretroviral medications and they have been associated with increased confusion, excessive sedation and ataxia.<sup>30</sup>

### Chronic cognitive disorders

Cognitive difficulties are associated with HIV infection due to the entry of the virus early in the course of infection into the central nervous system. Over time progressive damage to the brain occurs, especially the subcortical regions and frontostriatal pathways. The exact mechanism of this damage is not fully understood but this may occur either due to the direct effect of viral replication, or possibly secondary to inflammatory neurotoxins released over time.<sup>31</sup> There are no specific diagnostic investigations which confirm these pathological processes and so these diagnoses are made on a clinical basis. These cognitive syndromes were defined in 1991 by the American Academy of Neurology AIDS task force as: the HIV-associated dementia complex and the HIV-associated minor cognitive motor disorder<sup>32</sup> (see Chapter 18.2).

The more common and less severe diagnosis is minor cognitive motor disorder. Patients describe difficulty concentrating, increased fatigue, slowness of thinking and impaired memory. On specific assessment these patients may display difficulty in processing speeded information, divided information and sustained effortful processing. There may be mild slowing of motor performance. There is minimal functional impairment and simple behavioural measures should assist. This syndrome remains common despite the advent of cART.<sup>33</sup>

The diagnosis of HIV-associated dementia is reserved for those people with progressive, acquired cognitive changes associated with significant functional impairment. HIV-associated dementia is uncommon until the advanced stages of disease and its incidence has markedly reduced with the advent of cART. HIV dementia follows a subcortical dementia pattern. The main symptoms include lethargy, social withdrawal and psychomotor slowing. There are often movement changes with imbalance, falls and leg weakness. The prominent cognitive symptoms are confusion, mental slowing and memory impairment. Clinically this type of dementia can mimic depressive syndromes. In assessing these symptoms a physical examination may show slowness of eye and limb movements, leg weakness and ataxia. Cognitive examination should focus on tasks involving sustained attention, timed tasks (writing alphabet, copying simple diagram, walking specific distance) and on assessment of frontal/executive function. Progressive cognitive difficulties may be a product of a combination of HIV infection related pathology and host factors such as age, systemic illness, mental illness, alcohol and substance abuse, the neuropsychiatric side-effects of medications used to treat HIV and psychological factors.

Treatment considerations should be sensitive to patient's care requirements and available community supports. Consideration of competence to make medical and lifestyle decisions and discussion of an appropriate proxy should be part of an overall treatment plan. There is some evidence that antiretroviral medication which penetrates the central nervous system can improve some of the cognitive deficits, for example psychomotor speed,<sup>34</sup> associated with this pathology. The improvements may be limited and some patients remain severely impaired despite instigation of treatment.<sup>35</sup>

### 20.3.5 Substance abuse disorders

Substance abuse is a significant risk factor for the development of HIV by direct means, such as sharing of injecting equipment, and indirect means such as risk behaviour associated with impaired judgement while intoxicated. Substance abuse is especially prevalent in people with HIV infection with reported rates ranging from 50-75%.<sup>1</sup> It is important to note that there is a common comorbidity between substance abuse disorders and other psychiatric diagnoses and patients will benefit from a co-ordinated assessment approach. The general approach is to: take a comprehensive history of substance use in an empathic and accepting environment; provide education about harm reduction strategies associated with drug use; and make an assessment of a person's commitment to changing behaviour. This has been classified according to a Stages of Change Model<sup>36</sup> that includes stages of precontemplation, contemplation, preparation, action and maintenance. There are specific psychological therapies that have been shown to be effective in helping people make and maintain changes in behaviour. Psychosocial interventions aimed at stabilising a person's living circumstances can assist and have beneficial effects on maintaining health. There are pharmacological strategies which have been shown to be beneficial particularly when combined with psychological interventions. Initiating some of these pharmacological therapies may require specialist assessment. A person considering abruptly ceasing use, especially of alcohol, should consider a specific detoxification program to prevent the potential complications of withdrawal.

### 20.3.6 Psychotic disorders

There is a complex association between diagnosis of HIV and psychotic disorders, each potentially impacting adversely on the other. The nature of chronic mental illness may significantly impair a patient's capacity to participate in treatment. The diagnosis of chronic psychoses is complex with symptoms divided into disorders of thought, perception, cognition and volition. Deficits in reasoning, impulsivity and impaired capacity to process complex information are often associated with the primary symptoms of psychosis. There is frequently deterioration in psychosocial function that further complicates the provision of effective HIV care. Chronic psychotic symptoms are associated with a diagnosis of schizophrenia and schizoaffective disorder but may also be associated with dementia. Episodic psychotic symptoms may be associated with acute episodes of depression and mania in bipolar affective disorder. The abrupt onset of psychotic symptoms may be secondary to the acute effects of substance use or may be part of a syndrome of delirium.

Any treatment plan for those with psychotic illness involves a risk assessment and consideration of the appropriate environment for treatment to be safely provided. This is facilitated by a close

**Table 20.5 Predicted interactions between psychoactive agents and co-administered antiretroviral drugs.**

Agent (usual adult dose)	Psychotropic metabolism	Interaction and specific adverse effects
<b>ANTIDEPRESSANT</b>		
Escitalopram (10-20 mg/day)	Metabolised by CYP2C19, 3A4 Weak inhibitor of CYP2D6	Inhibitors: possible increase SSRI concentration Inducers: possible decrease SSRI concentration
Citalopram (20-40 mg/day)	Metabolised by CYP2C19, 3A4. Weak inhibitor of CYP3A4 and 1A2	Inhibitors: possible increase SSRI concentration Inducers: possible decrease SSRI concentration
Sertraline (50-200 mg/day)	Metabolised by CYP3A4. Weak inhibitor of CYP2D6	Inhibitors: possible increase SSRI concentration Inducers: possible decrease SSRI concentration
Paroxetine (20-40 mg/day)	Metabolised by CYP2D6	Inhibitors: possible increase SSRI concentration Inducers: no anticipated effect
Venlafaxine (75-225 mg/day)	Metabolised by CYP2D6, 3A4. Weak inhibitor of CYP2D6	Inhibitors: possible increase venlafaxine concentration Inducers: possible decrease venlafaxine concentration
Mirtazapine (30-60 mg/day)	Metabolised by CYP2D6, 1A2, 3A4. Is not an enzyme inhibitor or inducer	Inhibitors: possible increase mirtazapine concentration. Monitor for increased side-effects (somnolence) Inducers: possible decrease mirtazapine concentration
Nortriptyline (25-150 mg/day) Tricyclic antidepressant medication not first-line treatment	CYP2D6	Inhibitors: possible increase TCA concentration Inducers: no anticipated effect
<b>ANTIPSYCHOTIC</b>		
Haloperidol (1-5 mg/day)	CYP2D6 > 3A	Inhibitors: possible increase haloperidol concentration Inducers: possible decrease haloperidol concentration
Olanzapine (5-20 mg/day)	CYP2D6, 1A2, GT. Inhibits CYP1A2, 2D6, 3A4 (weak)	Only minor interaction Monitor for hyperlipidaemia, raised blood sugar and weight gain
Quetiapine (600-900 mg/day)	Metabolised CYP3A4 and 1A2. not an enzyme inducer or inhibitor	Inhibitors: possible increase quetiapine concentration Inducers: possible decrease quetiapine concentration
Risperidone (1-6 mg/day)	Metabolised CYP2D6 more than 3A4	Unlikely to interact with antiretroviral therapy but risperidone levels may be increased with potent ART cytochrome enzyme inhibitors (Ritonavir)
<b>MOOD STABILISER</b>		
Lithium	Renal excretion	No interactions. Narrow therapeutic range, monitor for signs of toxicity
Carbamazepine	Induces CYP3A4 and glucuronyl transferase	Avoid use as may reduce antiretroviral medication levels and compromise treatment
Sodium valproate	Only minor cytochrome P450 metabolism. Ritonavir may induce glucuronidation and lower valproate concentrations	Monitor sodium valproate levels Increases HIV replication <i>in vitro</i>
<b>BENZODIAZEPINE</b>		
Midazolam	Metabolised by CYP3A4 Contraindicated with P4503A4 inhibitors	Increased and prolonged sedation with enzyme inhibitors (protease inhibitors, efavirenz)
Lorazepam, oxazepam, temazepam	Metabolised by glucuronic acid conjugations. Less susceptible to CYP interactions	Preferred choice for those on complex medication regimes
<b>ALTERNATIVE MEDICATION</b>		
St John's Wort	Induces CYP3A4	Potential to reduce antiretroviral levels metabolised by this pathway Avoid co-administration
Adapted from: Tseng AL, Foisy MM. Significant interactions with new antiretrovirals and psychotropic drugs. <i>Ann Pharmacother</i> 1999;33: 461-73. Table of interactions available from <a href="http://www.tthivclinic.com/pdf/psych-int.pdf">http://www.tthivclinic.com/pdf/psych-int.pdf</a> (cited April 2008).		
Note: Mild-Moderate CYP Enzyme inhibitors: fosamprenavir, atazanavir, delavirdine, indinavir, nelfinavir, saquinavir, efavirenz Potent CYP Enzyme inhibitors: ritonavir, lopinavir/ritonavir CYP Enzyme Inducers: nevirapine, efavirenz, tipranavir, etravirine.		
CYP = Cytochrome P450; TCA = tricarboxylic acid cycle; SSRI = selective serotonin reuptake inhibitor.		

## 20 Other diseases or disorders

working relationship between HIV and psychiatric services. Support to encourage compliance with oral medications will have benefits both for psychiatric symptom relief and compliance with antiretroviral medication. Most antipsychotic medications can be safely combined with antiretroviral medications but the potential for interactions should be considered. Due to the effects of HIV on the central nervous system, patients may be more susceptible to extrapyramidal side-effects and these should be monitored. Therefore the atypical, antipsychotic medications are preferred. However some atypical, antipsychotic medications (e.g. olanzapine, quetiapine) have been associated with hyperlipidaemia and abnormalities of blood sugar metabolism, so periodic investigation is warranted in this already susceptible population.

### 20.3.7 Principles of pharmacotherapy

Clinicians require a good understanding of the role of psychoactive medications in the treatment of mental illness and also the high risk of potential drug-drug interactions and side-effects in the population with HIV infection. Certain antiretroviral drugs, in particular protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are metabolised primarily by the cytochrome P450 3A4 and 2D6 hepatic microsomal isoenzymes, which can in turn inhibit or enhance their activity. Most psychotropic medications are also metabolised by, and can affect the activity of, these isoenzymes. Patients may also have serum protein anomalies resulting in an altered free fraction of protein-bound drugs. There is, thus, a high potential for drug interactions when psychotropic agents are used in the setting of antiretroviral therapy making it important to use care and consult up-to-date drug information or an informed pharmacist prior to prescribing. Commonly used agents in this population include antidepressant medications such as SSRIs that are used to treat depression and anxiety disorders. These agents directly affect the CYP 450 enzymes and, thus, SSRIs that have less interaction with these enzymes (e.g. citalopram, escitalopram and sertraline) are preferred for use. Benzodiazepines are commonly prescribed for short-term use in anxiety disorders. However their half lives can be significantly prolonged by treatments: thus agents with shorter half lives (e.g. oxazepam, temazepam and lorazepam) are preferred. Similarly mood stabilisers and antipsychotics can interact with certain antiretroviral drugs and care is required when prescribing<sup>37</sup> (Table 20.5).

## References

- 1 Bing EG, Burnam MA, Longshore D, Fleishman JA, Sherbourne CD, London AS, et al. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. *Arch Gen Psychiatry* 2001;58:721-8.
- 2 Kelly B, Raphael B, Judd F, Perdices M, Kernutt G, Burrows GD, et al. Psychiatric disorder in HIV infection. *Aust N Z J Psychiatry* 1998;32(3):441-53.
- 3 Adewuya AO, Afolabi MO, Ola BA, Ogundele OA, Ajibare AO, Oladipo BF. Psychiatric disorders among the HIV-positive population in Nigeria: a control study. *J Psychosom Res* 2007;63(2):203-6.
- 4 Thompson SC, Checkley GE, Hocking JS, Crofts N, Mijch AM, Judd FK. HIV risk behaviour and HIV testing of psychiatric patients in Melbourne. *Aust N Z J Psychiatry* 1997;31(4):566-76.
- 5 Whetten K, Reif S, Ostermann J, Pence BW, Swartz M, Whetten R, et al. Improving health outcomes among individuals with HIV, mental illness, and substance use disorders in the Southeast. *AIDS Care* 2006;18(Suppl 1): S18-26.
- 6 Di Clemente RJ, Ponton LE. HIV related risk behaviours among psychiatrically hospitalised adolescents and school based adolescents. *Am J Psychiatry* 1993;150 32432-5.
- 7 Smith MD. HIV risk in adolescents with severe mental illness. *J Adolesc Health* 2001;29(5):320-9.
- 8 Guy RJ, McDonald AM, Bartlett MJ, Murray JC, Giele CM, Davey TM, et al. HIV diagnoses in Australia: diverging epidemics within a low-prevalence country. *Med J Aust* 2007;187(8):437-40.
- 9 Friedman MS, Marshal MP, Stall R, Cheong J, Wright ER. Gay-related development, early abuse and adult health outcomes among gay males. *AIDS Behav* 2007; Nov 8. DOI 10.1007/s10461-007-9319-3.
- 10 Cochran SD, Mays VM, Sullivan JG. Prevalence of mental disorders, psychological distress, and mental health services use among lesbian, gay, and bisexual adults in the United States. *J Consult Clin Psychol* 2003;71 (1):53-6.
- 11 Cohen M, Arad S, Lorber M, Pollack S. Psychological distress, life stressors, and social support in new immigrants with HIV. *Behav Med* 2007;33(2):45-54.
- 12 Draguns JG and Tanaka-Matsumi J. Assessment of psychopathology across and within cultures: issues and findings. *Behav Res Ther* 2003;41:755-76.
- 13 Poulsen HD, Lublin HK. Efavirenz-induced psychosis leading to involuntary detention. *AIDS* 2003;17(3):451-3.
- 14 Ciesla JA and Roberts JE. Meta-analysis of the relationship between hiv infection and risk for depressive disorders. *Am J Psychiatry* 2001;158:725-30.
- 15 Atkinson JH, Heaton RK, Patterson TL, Wolfson T, Deutsch R, Brown SJ, et al. Two-year prospective study of major depressive disorder in HIV-infected men. *J Affect Disord.* 2007 Nov 26; doi:10.1016/j.jad.2007.10.017
- 16 Stolar A, Catalano G, Hakala SM, Bright RP, Fernandez F. Mood disorders and psychosis in HIV. In: Citron K, Brouillette MJ, Beckett A. *HIV and Psychiatry*. 2nd rev. ed. Cambridge, 2005:88-109.
- 17 Lima VD, Geller J, Bangsberg DR, Patterson TL, Daniel M, Kerr T, et al. The effect of adherence on the association between depressive symptoms and mortality among HIV-infected individuals first initiating HAART. *AIDS* 2007;21(9):1175-83.
- 18 von Ammon Cavanaugh S, Furlanetto LM, Creech SD, Powell LH. Medical illness, past depression, and present depression: a predictive triad for in-hospital mortality. *Am J Psychiatry* 2001;158(1):43-8.
- 19 Clark DC, Cavanaugh SV, Gibbons RD. The core symptoms of depression in medical and psychiatric patients. *J Nerv Ment Dis* 1993;167:705-13.
- 20 Olatunji BO, Mimiaga MJ, O'Cleirigh C, Safren SA. Review of treatment studies of depression in HIV. *Top HIV Med* 2006;14(3):112-24.
- 21 Rabkin JG, Wagner G, Rabkin R. Effects of sertraline on mood and immune status in patients with major depression and HIV illness: an open trial. *J Clin Psychiatry* 1994;55(10):433-9.
- 22 Sewell MC, Goggin KJ, Rabkin JG, Ferrando SJ, McElhiney MC, Evans S. Anxiety syndromes and symptoms among men with AIDS: a longitudinal controlled study. *Psychosomatics* 2000;41(4):294-300.
- 23 Radcliffe J, Fleisher CL, Hawkins LA, Tanney M, Kassam-Adams N, Ambrose C, Rudy BJ. Posttraumatic stress and trauma history in adolescents and young adults with HIV. *AIDS Patient Care STDS* 2007;21(7):501-8.
- 24 Andrews G, Creamer M, Crino R, Hunt C, Lampe L, Page A. *The Treatment of Anxiety Disorders*. 2nd Edition. Cambridge University Press, 2003.
- 25 Ellen SR, Judd FK, Mijch AM, Cockram A. Secondary mania in patients with HIV infection. *Aust N Z J Psychiatry* 1999;33(3):353-60.
- 26 Cruess DG, Evans DL, Repetto MJ, Gettes D, Douglas SD, Petitto JM. Prevalence, diagnosis and pharmacological treatment of mood disorders in HIV disease. *Biol Psychiatry* 2003;54:307-16.

- 27 Ferrando SJ, Tiamson-Kassab MLA. HIV Disease. In: Blumenfeld M, Strain JJ. Psychosomatic Medicine. Lippincott, Williams and Wilkins: 2006, 277-96.
- 28 Uldall KK, Ryan R, Berghuis JP, Harris VL. Association between delirium and death in AIDS patients. AIDS Patient Care STDs. 2000;14(2):95-100.
- 29 Judd FK. Delirium in the consultation setting. Int Rev Psychiatry 1996;8:259-66.
- 30 Breitbart W, Marotta R, Platt MM, Weisman H, Derevenco M, Grau C, et al. A double blind trial of haloperidol, chlorpromazine and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry 1996;153:231-7.
- 31 Ghafouri M, Amini S, Khalili K, Sawaya BE. HIV-1 associated dementia: symptoms and causes. Retrovirology 2006;3:28.
- 32 Report of a Working Group of the American Academy of Neurology AIDS Task Force. Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus-type 1 (HIV-1) infection. Neurology 1991;41(6):778-85.
- 33 Neuenberg JK, Brodt HR, Herndier BG, Bickel M, Bacchetti P, Price RW, et al. HIV related neuropathology, 1985-1999: rising prevalence of HIV encephalopathy in the era of highly active antiretroviral therapy. J Acq Imm Defic Syn 2002;31(2):171-7.
- 34 Marra CM, Lockhart D, Zunt JR, Perrin M, Coombs RW, Collier AC. Changes in CSF and plasma HIV1-RNA and cognition after starting potent antiretroviral therapy. Neurol 2003;60:1388-90.
- 35 Saktor NC, Lyles RH, Skolasky RL, Kleeberger C, Selnes OA, Miller EN, et al. HIV associated neurological disease incidence changes: Multicenter AIDS Cohort Study, 1990-1998. Neurol 2001;56:257-60.
- 36 Prochaska JO, di Clemente CC. The transtheoretical approach: crossing traditional boundaries of therapy. Homewood ILL: Dorsey Professional Books: 1984.
- 37 Thompson A, Silverman B, Dzung L, Treisman G. Psychotropic medications and HIV. Clin Infect Dis 2006;42(9):1305-10.

## 20.4 Rheumatological disease

Adam Jenney

Infectious Diseases Unit, The Alfred Hospital, Melbourne, VIC

Many rheumatological diseases have been described in people with HIV infection and can appear at any stage of the infection. In some cases rheumatological disease may be the first clue to underlying HIV disease.<sup>1</sup>

### 20.4.1 Articular rheumatological disease

#### Arthralgia

Arthralgia and myalgia occur as part of the 'flu'-like symptoms in more than 50% of people experiencing the HIV seroconversion illness.<sup>2</sup> Arthralgia affects 12-45% of people with HIV and occurs any time during the course of the infection, although it is most common in the setting of advanced immunosuppression (Table 20.6).<sup>3</sup> Episodes last from a few days to several weeks. Symptoms are usually intermittent and polyarticular, and will usually respond to simple analgesics (paracetamol or non-steroidal anti-inflammatory drugs [NSAIDs]).

#### HIV-associated arthritis

Table 20.6 Causes of arthropathy in HIV

HIV-associated arthritis
Painful articular syndrome
Spondyloarthropathy (reactive arthritis, psoriatic arthritis)
Septic arthritis
Drug-related arthropathy
Avascular necrosis

HIV-associated arthritis mainly affects the knees and ankles symmetrically, causing pain and loss of function for a few weeks to six months.<sup>4</sup> Unlike reactive arthritis (see below), patients usually lack the HLA-B27 antigen, there is no preceding infection and the synovial fluid shows only a mild inflammatory response. Simple analgesics are usually sufficient, although severe monoarthritis may benefit from intra-articular glucocorticoids.

#### Painful articular syndrome

Ten percent of people with HIV infection experience severe, acute pain in a particular joint (especially the knee, elbow or shoulder). The intense pain may last two to 48 hours and often requires narcotic analgesics.

#### Spondyloarthropathy

The spondyloarthropathies include Reiter's syndrome, reactive arthritis, ankylosing spondylitis, psoriatic arthritis, and so-called undifferentiated spondyloarthritis. They have clinical features in common with each other, and the patients exhibit the HLA-B27 allele.

#### Reactive arthritis

Reiter's syndrome is the triad of arthritis, urethritis and eye disease (conjunctivitis or uveitis), and is a subset of reactive arthritis. Whether reactive arthritis (including Reiter's syndrome) is more common in people with HIV infection compared with the general population is controversial, with prevalence estimates between 0.1-10%. In Africa, where the HLA-B27 allele is rare, a majority of patients with reactive arthritis have HIV infection.<sup>5</sup>

#### Clinical manifestations

Reactive arthritis is characterised by a non-purulent oligoarthropathy, which complicates a distant, non-articular infection in the preceding one to six weeks. Particularly affecting joints of the lower limbs (Image 20.3), reactive arthritis is asymmetrical and progressive, involving tense effusions of the knee, ankle and foot joints. Wrists and hands may also be affected. Unlike the other spondyloarthropathies, the axial skeleton and sacroiliac joints are rarely involved.<sup>4</sup> The arthritis can be mild and intermittent or take a progressive course evolving over several weeks to months.<sup>6</sup> Entesopathy (inflammation of ligament, tendon, fascia and joint capsule) is a prominent feature and causes bony destruction at the site of the insertion of the connective tissue involved.

Constitutional symptoms such as fever, weight loss, malaise and fatigue are also common. Associated skin conditions such as keratoderma blennorrhagicum (vesicles on the palms and soles that evolve into hyperkeratoses), circinate balanitis and onycholysis may be more common in people with HIV infection with reactive arthritis.

### Diagnosis

Reactive arthritis is usually triggered by urogenital infections (e.g. *Chlamydia trachomatis* and *Ureaplasma urealyticum*) or gastrointestinal infections (e.g. *Yersinia*, *Shigella*, *Salmonella* and *Campylobacter*). A history of an undiagnosed diarrhoeal illness may be an important clue.

The diagnosis of arthritis is clinical. However, it is important to exclude septic arthritis (e.g. staphylococcal or gonococcal arthritis) if just one joint is swollen. Aspiration of an affected joint in reactive arthritis reveals sterile fluid with raised white cells (mainly neutrophils) and is negative for crystals.

### Management

Paracetamol and NSAIDs are standard therapies for mild reactive arthritis. Persistent, debilitating or severe disease may require sulfasalazine, chloroquine and intralesional glucocorticoids. Methotrexate can help recalcitrant disease, but requires careful monitoring of the patient.<sup>7</sup> The triggering infection (particularly chlamydia, which may persist until the arthritis appears) should be looked for and treated whenever it is identified. Monoclonal antibody tumour necrosis factor (TNF)-blocking agents have been occasionally used in people with HIV infection with severe refractory disease but they are not recommended for routine management.<sup>8</sup>

### Psoriatic arthritis

The rheumatological complications of psoriasis are more frequent and more severe in the setting of HIV infection; indeed psoriasis itself is more common in people with HIV infection than in the general population.<sup>4</sup>

### Clinical manifestations

Psoriasis may cause an asymmetrical oligoarthritis (like reactive arthritis) or may manifest as a syndrome of symmetrical arthritis with dactylitis ('sausage digits') and classical spondylitis (morning stiffness, spinal pain and sacroileitis). A severe episode of skin and joint disease may be the first manifestation of HIV infection.

### Management

Treatment for psoriatic arthritis is similar to that for reactive arthritis.

### Septic arthritis

Although uncommon, a single, inflamed joint may indicate septic arthritis. This condition should be considered, particularly in injecting drug users with HIV infection, where *Staphylococcus aureus* is the major pathogen, causing 60% of skeletal infections, followed by *Candida albicans* (20%).<sup>9</sup> However, more than 20 different species of micro-organism have been associated with septic arthritis in people with HIV infection.<sup>3</sup> Cultures of blood and synovial fluid are essential for diagnosis and selection of an appropriate antimicrobial agent.

Particular consideration should be given to opportunistic pathogens (e.g. *Mycobacteria* and *Cryptococcus*), especially when CD4 cell counts have fallen to fewer than 100 cells/ $\mu\text{L}$ .<sup>10</sup> Joint washout during arthroscopy or arthrotomy, and intravenous antimicrobial therapy, are the mainstays of treatment.

### Drug-related arthropathy

Rifabutin has been documented to cause arthropathy in people with HIV infection probably in a dose-related manner.<sup>11</sup> Protease inhibitors (particularly indinavir) have been implicated in conditions such as temporomandibular dysfunction, frozen shoulder, tendonitis and Dupuytren's contracture.<sup>12</sup> The introduction of combination antiretroviral therapy has been associated with a reduction in some rheumatological conditions (e.g. reactive arthritis and psoriasis) but an increase in others (such as osteoporosis, osteonecrosis, urate abnormalities and tubercular bone and joint infections).<sup>9</sup> In addition *de novo* appearance of rheumatic diseases after combination antiretroviral therapy (cART) has been commenced, including sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, reactive arthritis and polymyositis has been observed and probably represents manifestations of immune reconstitution inflammatory syndrome, also often referred to as Immune Restoration Diseases (IRDs) (see Chapter 22).<sup>13,14</sup> IRDs may manifest themselves 3–27 months after initiation of cART and is more likely in those with very low CD4 cell counts starting treatment.<sup>15</sup>

### Avascular necrosis

Avascular necrosis of bone, or osteonecrosis, particularly affecting the femoral head, (but also the tibial plateau, humeral head and talus) has been reported in association with HIV infection and, particularly, protease inhibitor-containing cART.<sup>16</sup> It is thought that the metabolic complications from cART (especially hyperlipidaemia) may cause avascular necrosis, although other important risk factors in the HIV setting include antiphospholipid antibodies, acquired protein S deficiency, vasculitis and corticosteroid use.<sup>10</sup>

Image 20.3 Bone scintigraphy of a 39-year-old HIV-infected man showing severe reactive arthritis of multiple joints and plantar enthesopathy



Source: Adam Jenney, The Alfred Hospital, Melbourne, VIC. Used with permission.

Clinicians should have a high index of suspicion for this condition when a patient presents with severe unexplained shoulder or groin pain.<sup>8</sup> Magnetic resonance imaging is the most reliable method of diagnosis, and treatment requires analgesia and a physiotherapy program. Surgical intervention including joint replacement is sometimes necessary.

## Rheumatoid arthritis

Rheumatoid arthritis is very rarely found with concurrent HIV infection. Remission of the former can occur with progression of HIV infection, probably because the arthritis is mediated by CD4 inflammatory cells. Nonetheless, these conditions can co-exist.<sup>17</sup>

## 20.4.2 Non-articular rheumatological disease

### Myopathies

**Polymyositis** may occur at any stage of HIV infection. The patient typically presents with myalgia, proximal muscle weakness and wasting. The serum creatine kinase is markedly elevated, in keeping with an inflammatory myositis seen on biopsy. High-dose oral glucocorticoids (prednisolone 0.5-1 mg/kg daily) is required, with improvement occurring over one to two months (Table 20.7).

A major differential diagnosis of this condition is **zidovudine myopathy**, which can occur three to 21 months after commencing the drug. The patient presents with proximal muscle weakness, sometimes of insidious onset with the legs more commonly affected than the arms, and a two to six-fold rise in creatinine kinase.<sup>1</sup> Histology and electron microscopy show only limited lymphocyte infiltration, ragged red fibres, accumulation of glycogen and lipids, and abnormal mitochondria. Zidovudine should be ceased and improvement follows in one to two months. It is important to note that other reverse transcriptase inhibitors can cause a similar myopathy.

A wasting myopathy may occur during advanced HIV infection. This condition may cause a mild rise in serum creatinine kinase, but is not associated with inflammatory cells.

Severe **rhabdomyolysis** resulting in renal failure has been reported in association with HIV infection, and can be due to antiretroviral medications, and their interactions with other drugs e.g. protease inhibitors and statins, primary HIV infection and other muscle infections.

**Pyomyositis** may occur as single or multiple abscesses, spontaneously or after trauma (e.g. an intramuscular injection). Gram positive (e.g. *Staphylococcus aureus*, *Streptococcus pyogenes*) and Gram negative organisms (e.g. *Escherichia coli*) may cause this infection, although opportunistic infections such as toxoplasmosis, mycobacteria and *Cryptococcus* should also be considered in more advanced HIV disease.

Other myopathies reported in people with HIV infection include myasthenia gravis, inclusion body myositis, nemaline rod myopathy (a rare disorder causing proximal myopathy and minor elevations of creatinine kinase with rod-shaped nemaline bodies seen in atrophic fibres on electro microscopy), and myopathy associated with malignancies such as non-Hodgkin's lymphoma.

### Sicca syndromes

Diffuse infiltrative lymphocytosis syndrome (DILS) affects 1-2% of people with HIV infection. It causes parotid enlargement, xerostomia and xerophthalmia, and is mediated by CD8 cells.

Unlike Sjogren's syndrome (which is CD4 mediated), auto-antibodies (such as rheumatoid factor, antinuclear, Ro and La antibodies) are not found and extraglandular involvement is common, with lymphocytic interstitial pneumonitis occurring in 50% of cases.

The gastrointestinal tract, liver, kidneys, reticular endothelial system and peripheral nerves may also be affected. High-dose oral glucocorticoids for two to three months with antiretroviral therapy may be required. The Sicca syndrome (dry eyes and mouth, and parotid enlargement) occurs in 25% of affected patients.

Symptomatic relief can be gained with artificial tears and saliva. Combination antiretroviral therapy can reduce parotid swelling and the sicca symptoms and even improve the neuropathy.<sup>8</sup> Zidovudine should be included in cART regimens for its direct effects on this disease (it has been successfully used in primary Sjogren's syndrome).<sup>18</sup>

### Vasculitis

A number of vasculitides have been reported in people with HIV infection, and include systemic necrotising vasculitis (e.g. polyarteritis nodosa), hypersensitivity vasculitis (e.g. Henoch-Schönlein purpura), granulomatous angiitis (lymphatoid granulomatosis), primary angiitis of the central nervous system, and DILS.<sup>4</sup> Vasculitis can be difficult to treat, often requiring immunosuppressive therapy. It is important to exclude other causes such as infection (cytomegalovirus, hepatitis B virus, hepatitis C virus, and varicella-zoster virus) and drug reactions.

Table 20.7 Causes of myopathy in HIV infection

HIV-seroconversion myalgia
Polymyositis
Zidovudine myopathy
HIV-wasting myopathy
Rhabdomyolysis
Pyomyositis
Myasthenia gravis
Inclusion body myositis
Nemaline rod myopathy
Malignancy-associated myopathy (e.g. non-Hodgkin's lymphoma)

## References

- 1 Kaye BR. Rheumatologic manifestations of HIV infections. Clin Rev Allergy Immunol 1996;14:385-416.
- 2 Niu MT, Stein DS, Schnittman SM. Treatment trials for primary human immunodeficiency virus type 1 infection. J Infect Dis 1993;168:1601-2.
- 3 Cuellar ML. HIV infection-associated inflammatory musculoskeletal disorders. Rheum Dis Clin North Am 1998;24:403-21.
- 4 Vassilopoulos D, Calabrese LH. Rheumatologic manifestations of HIV-1 and HTLV-1 infections. Cleve Clin J Med 1998;65:436-41.
- 5 Cuellar ML, Espinoza LR. Rheumatic manifestations of HIV-AIDS. Baillieres Best Pract Res Clin Rheumatol 2000;14:579-93.
- 6 Itescu S. Adult immunodeficiency and rheumatic disease. Rheum Dis Clin North Am 1996;22:53-73.
- 7 Reveille JD. The changing spectrum of rheumatic disease in human immunodeficiency virus infection. Semin Arthritis Rheum 2000;30:147-66.
- 8 Reveille JD, Williams FM. Infection and musculoskeletal conditions: Rheumatologic complications of HIV infection. Best Pract Res Clin Rheumatol 2006;20:1159-79.

## 20 Other diseases or disorders

- 9 Medina F, Perez-Saleme L, Moreno J. Rheumatic manifestations of human immunodeficiency virus infection. *Infect Dis Clin North Am* 2006;20:891-912.
- 10 Mody GM, Parke FA, Reveille JD. Articular manifestations of human immunodeficiency virus infection. *Best Pract Res Clin Rheumatol* 2003;17:265-87.
- 11 Siegal FP, Eilbott D, Burger H, Gehan K, Davidson B, Kaell AT, Weiser B. Dose-limiting toxicity of rifabutin in AIDS-related complex syndrome of arthralgia/arthritis. *AIDS* 1990;4:433-41.
- 12 Florence E, Schrooten W, Verdonck K, Dreezen C, Colebunders R. Rheumatological complications associated with the use of indinavir and other protease inhibitors. *Ann Rheum Dis* 2002;61:82-4.
- 13 Colmegna I, Koehler JW, Garry RF and Espinoza LR. Musculoskeletal and autoimmune manifestations of HIV, syphilis and tuberculosis. *Curr Opin Rheumatol* 2006;18:88-95.
- 14 Calabrese LH, Kirchner E, Shrestha R. Rheumatic complications of human immunodeficiency virus infection in the era of highly active antiretroviral therapy: emergence of a new syndrome of immune reconstitution and changing patterns of disease. *Semin Arthritis Rheum* 2005;35:166-74.
- 15 Louthrenoo W. Rheumatic manifestations of human immunodeficiency virus infection. *Curr Opin Rheumatol* 2008;20:92-9.
- 16 Gutierrez F, Padilla S, Ortega E, García JA, Flores J, Galera C, et al. Avascular necrosis of the bone in HIV-infected patients: incidence and associated factors. *AIDS* 2002;16:481-3.
- 17 Ornstein MH, Kerr LD, Spiera H. A reexamination of the relationship between active rheumatoid arthritis and the acquired immunodeficiency syndrome. *Arthritis Rheum* 1995;38:1701-6.
- 18 Steinfeld SD, Demols P, Van Vooren JP, Cogan E, Appelboom T. Zidovudine in primary Sjogren's syndrome. *Rheumatology (Oxford)* 1999;38:814-7.

## 20.5 Endocrine disorders in HIV infection

**Katherine Samaras**  
**Jeffrey J Post**

Garvan Institute, Sydney, NSW  
Department of Infectious Diseases and Albion Street Centre, Prince of Wales Hospital and  
School of Medical Sciences and Prince of Wales Clinical School, University of New South Wales, Sydney, NSW

Endocrine abnormalities are relatively common in HIV infection, due to specific effects of the virus, HIV-related disease, complications of drug therapy, drug-drug interactions and the effects of restoration of the immune system after the commencement of combination antiretroviral therapy (cART) (Table 20.8).

### 20.5.1 Diabetes mellitus

Disturbances in glucose metabolism (insulin resistance, impaired glucose tolerance and diabetes mellitus) are among the most common endocrine disorders found in treated HIV infection and are mostly due to the effects of cART.<sup>1</sup> Before the availability of cART, most cases of diabetes occurred in patients treated with pentamidine for treatment of *Pneumocystis jirovecii* infection. These cases were characterised by insulin deficiency and ketoacidosis (type 1 diabetes mellitus), since pentamidine destroys pancreatic insulin-secreting beta-cells.<sup>2-4</sup> The most common form of diabetes mellitus in patients with HIV infection in the cART era is type 2 diabetes, occurring in up to 10% of patients.<sup>5,6</sup> It is due to a combination of cART effects on insulin resistance and insulin secretion.<sup>1,7,8</sup>

The symptoms of diabetes mellitus include excessive thirst, polyuria, fatigue, unintentional weight loss, skin infections (such as candidiasis or boils) or blurred vision. Complications of diabetes, such as peripheral neuropathy, may be present at diagnosis. The symptoms of peripheral neuropathy from diabetes include burning or painful dysaesthesia, the sensation of walking on cotton wool or numbness. Neuropathy in treated

HIV infection may also be contributed to by nucleoside reverse transcriptase inhibitors (NRTIs).

The diagnosis of diabetes mellitus is made by testing the random (>11.0 mmol/L) or fasting glucose level (>7.0 mmol/L) in accordance with the criteria of the NHMRC guidelines.<sup>9</sup> Further, pre-diabetes could be considered if the fasting glucose is greater than 5.5 mmol/L. Impaired fasting glucose (5.5-6.9 mmol/L) represents a high risk for conversion to type 2 diabetes and represents a patient group where preventive strategies (including lifestyle change and weight loss predominantly, with the consideration of metformin treatment) can defer the onset of diabetes mellitus.

The treatment of diabetes mellitus in people with HIV infection requires lifestyle changes with an emphasis on healthy weight and, more importantly, healthy waist circumference, with appropriate nutritional and physical activity advice. Since the epidemic of overweight and obesity now affects more than 50% of Australians, this may affect more people with HIV infection in the future. Those with body fat changes due to cART or those in ethnic groups who are more susceptible to diabetes mellitus (e.g. people with South East Asian, South Asian and South American Indian heritage) need particular consideration.

Metformin is one of the main stays of antidiabetic therapy, since it is an insulin sensitiser, reduces abdominal obesity and improves glycaemic control.<sup>10</sup> In HIV infection, its use is contraindicated by severe renal impairment or cardiac failure where it may induce lactic acidosis. Care should be taken in

**Table 20.8** Endocrine disorders due to effects of HIV, HIV-related disease, immune reconstitution and drug therapy

	Direct HIV-1 virus effects	HIV-related disease	Immune reconstitution	Drug effects
<b>Adrenal disease</b>	Adrenalitis (rare)	<b>Infections:</b> Cytomegalovirus Toxoplasmosis Mycobacterial ( <i>M. tuberculosis</i> , <i>M. avium</i> complex) <b>Malignancy:</b> Kaposi's sarcoma	Addison's disease (rare)	Reduced corticosteroid synthesis: Antifungals (ketoconazole)  Pituitary suppression: Cytochrome P450 3A4 drug interactions with inhaled or oral steroids
<b>Thyroid disease</b>			Hashimoto's hypothyroidism Graves' disease	Interleukin-induced Graves' disease Interferon-induced Graves' disease
<b>Diabetes mellitus</b>				Pentamidine-induced insulin deficiency (type 1 diabetes) Protease inhibitor and NRTI-induced insulin resistance Type 2 diabetes mellitus
<b>Calcium metabolism</b>	Osteoporosis			cART-related osteoporosis
<b>Sex hormones</b>		Androgen deficiency		Androgen deficiency

cART = combination antiretroviral therapy.

## 20 Other diseases or disorders

patients receiving NRTIs with impaired renal function and elevated lactic acid levels. Sulfonylurea drugs increase insulin secretion and improve glycaemic control and are generally considered second-line agents. Thiazolidinediones, insulin sensitising drugs, will also improve glycaemia. Insulin therapy is highly effective in achieving glycaemic control and becomes necessary in a proportion of people with type 2 diabetes. Newer drug classes include exenatide and the dipeptidyl peptidase IV inhibitors, sitagliptin and vildagliptin.<sup>11</sup> These drugs act through novel pathways involving gut-derived peptides influencing insulin secretion. The latter are not currently listed on the Pharmaceutical Benefits Scheme.

### 20.5.2 Thyroid disease

Autoimmune thyroid disease can occur in patients with HIV infection, either as a consequence of cART or immunomodulatory therapy. Primary hypothyroidism due to Hashimoto's hypothyroidism (determined by the presence of anti-peroxisomal antibodies) occurs as a consequence of immune reconstitution, as can Graves' disease.<sup>12-15</sup> Immunomodulatory therapy with agents such as interferon-alpha used in the treatment of hepatitis C infection<sup>16</sup> and interleukin therapy for HIV can result in production of stimulatory antibodies that results in Graves' disease and thyrotoxicosis.<sup>17</sup> Clinicians should be alert to the possibility of hypothyroidism or thyrotoxicosis following immune reconstitution.<sup>18</sup>

### 20.5.3 Adrenal disease

Adrenal deficiency is uncommon, but can occur as a consequence of infection (HIV-1, cytomegalovirus, toxoplasmosis, *Mycobacteria*), neoplastic disease (Kaposi's sarcoma or other malignancies) or, very rarely, autoimmune disease (Addison's disease). Adrenal insufficiency is more common in the setting of HIV infection, with abnormal stimulated cortisol responses in 26% of tested subjects.<sup>19</sup>

The symptoms that should alert a clinician to the possibility of adrenal insufficiency include unexplained fatigue, weight loss, nausea, weakness, postural presyncope, myalgias, arthralgias, sweatiness and confusion. Drug therapy can be associated with reduced synthesis of adrenal hormones (e.g. ketoconazole) or induced metabolism of steroids (e.g. rifampicin, phenytoin).<sup>20</sup> A history of recent withdrawal of oral or inhaled corticosteroid drugs should be sought.<sup>21</sup> Clinical features of adrenal insufficiency include cachexia, pigmentation of the skin or oral mucosa, or a postural drop in blood pressure. Pigmentation will not be found in adrenal insufficiency of pituitary origin, due to deficiency of adrenocorticotrophin hormone, which is rare. Biochemistry may show hyponatraemia, hyperkalaemia, or hypoglycaemia. The diagnostic test for primary adrenal insufficiency is the short synacthen test, where a normal stimulated cortisol response would exceed 550 nmol/L. Secondary adrenal insufficiency (due to pituitary disease) will produce a normal response to cosyntropin testing and is diagnosed by an insulin-induced hypoglycaemia test.

Adrenal insufficiency is treated with glucocorticoid and mineralocorticoid therapy. Examples of chronic glucocorticoid therapy are prednisone 2.5-5 mg on waking, with or without 1-2.5 mg early afternoon; or cortisone acetate 25 mg on waking, 12.5 mg early afternoon; or hydrocortisone 15-20 mg on waking, 5-10 mg early afternoon with some patients requiring a third later dose. Most patients will also require mineralocorticoid support with fludrocortisone (0.05-0.1 mg

each day in divided doses, adjusted to clinical response in blood pressure).

Acute adrenal insufficiency may occur in the setting of acute infection, surgery or other physical stress and may manifest with vomiting, hypotension, haemodynamic shock and coma. It must be treated with intravenous glucocorticoids (e.g. hydrocortisone 100 mg every 6-8 hours) in addition to treatment of the underlying cause.

An excess of adrenal hormones (Cushing's syndrome) can occur in patients receiving protease inhibitors that inhibit the cytochrome p450 mediated metabolism of other drugs. Interference with the cytochrome p450 3A4 enzyme system results in the reduced elimination of oral and inhaled steroids. Cushing's syndrome can occur rapidly in patients receiving standard doses of oral steroids, in addition to inhaled steroids, with pituitary-adrenal suppression occurring with long-term therapy.<sup>21</sup> Cushing's syndrome should be suspected on historical and clinical evidence and diagnosed by detection of low or undetectable cortisol levels in a clinically Cushingoid patient. Treatment is by reduction of oral steroid doses or gradual reduction in inhaled steroids, where the underlying respiratory disease permits. For those patients receiving inhaled steroids, simple strategies will reduce steroid exposure and its side-effects. These include using dosing devices with lower oral cavity deposition (e.g. aerosolised rather than inhalers) with spacers and always rinsing/gargling and spitting (not swallowing). Other strategies may include changing the inhaled steroid therapy to agents that are not predominantly metabolised by the specific cytochrome p450 isoenzymes.

### 20.5.4 Disorders of calcium metabolism and osteoporosis

Hypercalcaemia is uncommon in HIV infection. Primary hyperparathyroidism with hypercalcaemia could be expected at the same rate as the general population. If hypercalcaemia is found with low parathyroid hormone levels, underlying infection, malignancy or lymphoma need exclusion.

Bone loss, low bone density and osteoporosis are found in HIV wasting syndrome and patients receiving long-term cART.<sup>22</sup> Multiple factors can contribute including viral effects, drug effects and low androgen levels. In male androgen deficiency/hypogonadism, treatment with androgen supplementation with testosterone has shown benefit.<sup>23</sup> In patients with established osteopenia or osteoporosis, clinicians should ensure an adequate intake of dietary calcium (at least 1000 mg each day) and that serum levels of 25-hydroxy vitamin D exceed 80 nmol/L. Weight bearing physical activity is essential (20 minutes of walking at least thrice weekly and, if possible, a weight training program) in addition to considering other lifestyle factors such as excessive alcohol or caffeine consumption and smoking. Other therapies such as the bisphosphonates or strontium ranelate may also have a role.<sup>24</sup>

### 20.5.5 Disorders of sex steroids Male hypogonadism

Low androgen levels in men with HIV infection appear relatively common, often in the setting of low or normal gonadotrophin levels. The cause is not completely understood, however contributors include the usual causes of hypogonadism in

men. There appears to be an association with HIV wasting and lipodystrophy.<sup>25</sup>

Androgen deficiency in men leads to lean tissue and bone loss, fatigue and mood disturbance. Other symptoms may include a loss of body hair, testicular atrophy, reduced pubic hair and reduced libido. Clinical confirmation includes the findings of gynaecomastia and small soft testicles. Clinical signs that may suggest a secondary cause include the presence of a goitre and thyrotoxicosis, a testicular mass and signs of chronic liver or pituitary disease. Biochemical confirmation is undertaken by measuring an early morning testosterone level (at 8-9am), along with follicle stimulating hormone and luteinizing hormone levels, prolactin and thyroid stimulating hormone levels.

Treatment options include injectable testosterone (testosterone cypionate or tenanthate, 200-250 mg every two to three weeks, or long-acting testosterone undecanoate 1000 mg by intramuscular injection every 10-12 weeks) or transdermal testosterone by patch or gel applied daily.<sup>26</sup> Men receiving androgen supplementation require annual digital rectal examination and prostate specific antigen measures.

## Female hypogonadism

Secondary amenorrhoea is common in women with HIV, affecting about one in four women.<sup>27</sup> The prevalence of amenorrhoea is higher among women who have lost significant amounts of weight in the setting of HIV wasting.<sup>27</sup> Evaluation should exclude pituitary disease (by measuring prolactin, LH and FSH), thyrotoxicosis, premature menopause, polycystic ovary syndrome, in addition to rare causes of hyperandrogenism.

Treatment in women with premature secondary amenorrhoea (i.e. aged less than 45 years) usually takes the form of the oral contraceptive pill or hormone replacement therapy, to alleviate symptoms of oestrogen deficiency and to help maintain bone mass. Therapy should be offered until the age of 50-53 years (i.e. about the usual age of menopause). The presence of a past history of stroke, deep vein thrombosis or pulmonary embolism or current cigarette smoking may alter recommendations for hormonal therapy.

## References

- 1 Samaras K. Metabolic consequences and therapeutic options in highly active antiretroviral therapy in human immunodeficiency virus-1 (HIV) infection. *J Antimicrob Chemother* 2008;61:238-45.
- 2 Wood G, Wetzig N, Hogan P, Whitby M. Survival from pentamidine induced pancreatitis and diabetes mellitus. *Aust NZ J Med* 1991;21:341-2.
- 3 Perrone C, Bricaire F, Lepout C, Assan D, Vilde JL, Assan R. Hypoglycaemia and diabetes mellitus following parenteral pentamidine mesylate treatment in AIDS patients. *Diabet Med* 1990;7:585-9.
- 4 Stahl-Bayliss CM, Kalman CM, Laskin OL. Pentamidine-induced hypoglycemia in patients with the acquired immunodeficiency syndrome. *Clin Pharmacol Ther* 1986;39:271-5.
- 5 Carr A, Cooper DA. Adverse effects of antiretroviral therapy. *Lancet* 2000;356:1423-30.
- 6 Dube MP. Disorders of glucose metabolism in patients infected with human immunodeficiency virus. *Clin Infect Dis* 2000;31:1467-75.
- 7 Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *N Engl J Med* 2005;352:48-62.

- 8 Bradbury R, Samaras K. Anti-retroviral therapy and the human immunodeficiency virus- improved survival but at what cost? *Diab Obes Metabol* 2008; 10(6):441-50
- 9 NHMRC. National evidence based guidelines for the management of type 2 diabetes mellitus. Part 3. Case detection and diagnosis of type 2 diabetes. Approved by the NHMRC 14 December 2001. Available at: [http://www.nhmrc.gov.au/publications/synopses/\\_files/di9.pdf](http://www.nhmrc.gov.au/publications/synopses/_files/di9.pdf) (cited February 2009)
- 10 Mulligan K, Yang Y, Winger DA, Koletar SL, Parker RA, Alston-Smith BL, et al. Effects of metformin and rosiglitazone in HIV-infected patients with hyperinsulinemia and elevated waist/hip ratio. *AIDS* 2007;21:47-57.
- 11 Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2008;368:1696-705.
- 12 Price P, Mathiot N, Krueger R, Stone S, Keane NM, French MA. Immune dysfunction and immune restoration disease in HIV patients given highly active antiretroviral therapy. *J Clin Virol* 2001;22:279-87.
- 13 Sereti I, Sarlis NJ, Arioglu E, Turner ML, Mican JM. Alopecia universalis and Graves' disease after immune restoration with HAART. *AIDS* 2001;15:138-40.
- 14 Jubault V, Penforis A, Schillo F, Hoen B, Izembart M, Timsit J, et al. Sequential occurrence of thyroid autoantibodies and Graves' disease after immune restoration in severely immunocompromised human immunodeficiency virus-infected patients. *J Clin Endocrinol Metab* 2000;85:4254-7.
- 15 Gilquin J, Viard JP, Jubault V, Sert C, Kazatchkine MD. Delayed occurrence of Graves' disease after immune restoration with HAART. *Lancet* 1998;352:1907-8.
- 16 Mandac JC, Chaudhry S, Sherman KE, Tomer Y. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. *Hepatology* 2006;4:661-72.
- 17 Jimenez C, Moran SA, Sereti I, Wynne S, Yen PM, Falloon J, et al. Graves' disease after interleukin-2 therapy in a patient with human immunodeficiency virus infection. *Thyroid* 2004;14:1097-102.
- 18 Hoffman CJ, Brown TT. Thyroid function abnormalities in HIV-infected persons. *Clin Infect Dis* 2007;45:488-94.
- 19 González-González JG, de la Garza-Hernández NE, Garza-Morán RA, Rivera-Morales IM, Montes-Villarreal J, Valenzuela-Rendón J, et al. Prevalence of abnormal adrenocortical function in human immunodeficiency virus infection by low-dose cosyntropin test. *Int J STD AIDS* 2001;12:804-10.
- 20 Eledrisi MS, Verghese AC. Adrenal insufficiency in HIV infection: a review and recommendations. *Am J Med Sci* 2001;321:137-44.
- 21 Samaras K, Pett S, Gowers A, McMurchie M, Cooper DA. Iatrogenic Cushing's syndrome with osteoporosis and secondary adrenal failure in HIV-infected patients receiving inhaled corticosteroids and ritonavir-boosted protease inhibitors: six cases. *J Clin Endocrinol Metab* 2005;90:9394-8.
- 22 Cazanave C, Dupon M, Lavignolle-Aurillac V, Barthe N, Lawson-Ayayi S, Mehse N, et al. Reduced bone mineral density in HIV-infected patients: prevalence and associated factors. *AIDS* 2008;22:395-402.
- 23 Lin D, Rieder MJ. Interventions for the treatment of decreased bone mineral density associated with HIV infection. *Cochrane Database Syst Rev*. 2007; CD005645.
- 24 McComsey GA, Kendall MA, Tebas P, Swindells S, Hogg E, Alston-Smith B, et al. Alendronate with calcium and vitamin D supplementation is safe and effective for the treatment of decreased bone mineral density in HIV. *AIDS* 2007;21:2473-82.
- 25 Grinspoon S, Corcoran C, Lee K, Burrows B, Hubbard B, Hubbard J, et al. Loss of lean body and muscle mass correlates with androgen levels in hypogonadal men with acquired immunodeficiency syndrome and wasting. *J Clin Endocrinol Metab* 1996;81:4051-8.

26 Allan CA, McLachlan RI. Testosterone deficiency in men. Diagnosis and management. *Aust Fam Physician* 2003;32:422-7.

27 Grinspoon S, Corcoran C, Miller K, Biller BM, Askari H, Wang E, et al. Body composition and endocrine function in women with acquired immunodeficiency syndrome and wasting. *J Clin Endocrinol Metab* 1997;82:1332-37.

## 20.6 Ophthalmic diseases

Anthony J Hall

Ophthalmology Department, The Alfred Hospital, and Eye Surgery Associates, Melbourne, VIC

### 20.6.1 Retinal and choroidal disease

#### Cotton wool spots

Aside from its ability to cause retinal infection secondary to immunodeficiency, HIV is associated with a retinopathy in its own right. The retinopathy is characterised by transient nerve fibre layer infarcts (cotton wool spots) and scattered small retinal haemorrhages and rarely causes visual morbidity. It is caused by a combination of local capillary endothelial cell changes (possibly cytomegalovirus induced) and rheological changes and is a sign of established immunodeficiency. It does not require treatment.

#### Cytomegalovirus retinitis

Cytomegalovirus (CMV) retinitis is the most important cause of visual loss in patients with AIDS. The first clinical description of CMV retinitis was made in 1971 in a renal transplant recipient who had widespread systemic CMV disease and subsequently died. Before the AIDS pandemic, CMV retinitis was rare and the treatment of CMV retinitis was poor. None the less, it usually did not present a clinical problem because the immune deficit responsible for the retinitis was often reversible. The original report of CMV retinitis in patients with AIDS was made in 1983.<sup>1</sup>

#### Clinical features

CMV retinitis appears as confluent areas of full thickness necrotising retinitis with haemorrhage. There are usually associated areas of old retinitis with a granular pigmentary change behind the leading border of active retinitis. It is often associated with an accompanying retinal vasculitis (which may

be severe) and only mild overlying vitritis and minimal anterior uveitis. There may be initial involvement at the posterior pole or in the periphery; when the disease occurs in the periphery, it has a more granular appearance than when it occurs at the posterior pole. Occasionally patients with small focal areas of involvement present a diagnostic problem. Visual loss in CMV retinitis may arise from optic nerve or macular involvement with retinitis, rhegmatogenous retinal detachment, serous macular detachment or cystoid macular oedema. Of these causes, only serous or rhegmatogenous detachment are reversible. The degree of visual loss at presentation depends on the site of the retinitis. Peripheral retinitis can be associated with normal vision and no symptoms.

#### Natural history of cytomegalovirus retinitis

The prognosis of untreated CMV retinitis is poor. In patients whose CD4 cell count remains low and who do not receive anti CMV treatment, there is relentless gradual progression and eventual blindness.

#### Diagnosis

CMV retinitis is usually diagnosed clinically without the need for confirmatory tests. CMV retinitis is a disease of the severely immunodeficient and, in patients with AIDS, it rarely occurs with a CD4 cell count of greater than 50 cells/ $\mu\text{L}$ .<sup>2</sup> At a given CD4 cell count, the risk of developing CMV retinitis is increased when other opportunistic infections occur, e.g. *Pneumocystis jirovecii* pneumonia strongly predicts the development of retinitis (relative risk = 5.8), as does *Mycobacterium avium* complex infection (relative risk = 5.3).<sup>3</sup> CMV serology is of little use in the diagnosis of retinitis in patients with AIDS because of the high background degree of seropositivity among sexually-active homosexual men and the lack of a rise in titre of CMV antibody during the development of CMV retinitis.<sup>4</sup> Negative CMV serology may occasionally be useful in excluding CMV as a cause of retinitis in non-homosexual patients with AIDS as these patients have a lower background incidence of positive CMV serology.<sup>5</sup> In patients with CMV retinitis there is usually an associated CMV viraemia detectable by testing the CMV viral load or CMV viral cultures. In patients in whom the diagnosis is in doubt, the most useful confirmatory test is an anterior chamber or vitreous tap for CMV viral polymerase chain reaction. The incidence of CMV retinitis has fallen dramatically since the widespread use of combination antiretroviral therapy (cART).<sup>6</sup> However, there is still a persistent risk of visual loss in patients with HIV infection and CMV retinitis.<sup>7</sup>

#### Therapy

The mainstay of treatment of intra-ocular infections in patients with AIDS is immune restoration with cART. The principles of

Image 20.3 Cytomegalovirus retinitis.



Source: Hall AJ, Ophthalmology Department, The Alfred Hospital, Melbourne, VIC. Used with permission.

treatment of CMV retinitis are to induce remission with induction treatment, maintain remission with ongoing treatment, monitor for progression and complications, and treat these as and when they occur.

In general, treatment should be commenced at diagnosis to limit the extent of progression of the disease, to prevent second eye involvement and to confer the benefit of treatment of systemic CMV infection (Table 20.9). With the exception of ganciclovir implants or intra-ocular injections, the first-line treatments are equally effective at treating the retinitis in the eye targeted for treatment. Where they vary is in the systemic side-effects,

systemic benefits, effect on the second eye and practical difficulties involved in treatment. Local (intra-ocular) therapy for CMV retinitis is generally more effective than systemic therapy at treating the injected eye but has the obvious disadvantages of requiring either regular intra-ocular injections or intra-ocular surgery, and the lack of systemic treatment.

In a well patient with reasonable blood counts and mild-to-moderate CMV retinitis the most common induction regimen would be oral valganciclovir. A patient with more aggressive CMV retinitis may be treated initially with intravenous ganciclovir or intravitreal ganciclovir (repeated injections or implant) with oral valganciclovir.

Drug	Dose	Route of delivery	Advantages	Disadvantages	Side-effects
Valganciclovir	900 mg twice daily for three weeks	Oral	Simplicity of delivery Protects second eye Treats systemic disease	Slightly reduced efficacy over IV or intravitreal treatment	Bone marrow suppression
Ganciclovir	5 mg/kg/12 hourly for 2-3 weeks	IV	Treats systemic disease Protects second eye	Requires IV access	Bone marrow suppression Central line morbidity
Foscarnet	60 mg/kg 8 hourly or 90 mg/kg 12 hourly for 2-3 weeks adjusted for renal function and given with hydration	IV (central venous Catheter)	Confers survival advantage over IV GCV Treats systemic disease - protects second eye	Requires IV access Poorly tolerated	Renal and electrolyte disorders Seizures Penile ulcers Central line complications
Ganciclovir/foscarnet combined	As above	IV	Added effectiveness for aggressive or relapsing disease	Poorly tolerated	As above
Cidofovir	5 mg/kg once weekly with probenecid and hydration for 3 weeks	IV	Added effectiveness for aggressive or relapsing disease Infrequent dosing	Poorly tolerated	Renal and electrolyte disorders Uveitis and hypotony
Ganciclovir	200-400 mg twice weekly	Intravitreal	Excellent systemic tolerance No IV access required	Requires intra-ocular injections No systemic protection No second eye protection	Endophthalmitis Vitreous bleeding Retinal detachment
Foscarnet	1200-2400 mg twice weekly	Intravitreal	Excellent systemic tolerance No IV access required Treats non CMV retinitis	Requires intra-ocular injections No systemic protection No second eye protection	Endophthalmitis Vitreous bleeding Retinal detachment
Ganciclovir implant	4.5 mg slow release device Single device is designed to deliver around 1 µg/hour of GCV for 6-8 months	Intra-ocular device	Excellent systemic tolerance No IV access required Single device used for both induction and maintenance	Requires surgery No systemic protection No second eye protection	Vitreous bleeding Retinal detachment Endophthalmitis

GCV= ganciclovir; CMV = cytomegalovirus; IV = intravenous.

## 20 Other diseases or disorders

Where induction treatment fails or has to be discontinued because of toxicity, the induction regimen can be changed or combinations used. Induction treatment is continued until there is ophthalmoscopic regression of the retinitis, usually between two to four weeks. Regression is diagnosed clinically by the absence of thickening or progression and the replacement of the active lesion with a lightly pigmented scar. The possibility of misdiagnosis should be considered in all patients who tolerate induction therapy but fail to achieve regression of lesions.

After treatment the clinical appearance of the retinitis changes. Healed retinitis is easily recognised by a lack of retinal thickening (seen as a loss of retinal whitening) with disappearance of retinal haemorrhage and vasculitis and halting of progression of the retinitis. Occasionally there is an atypical healing response with persistence of a white flat border of opacification<sup>8</sup> that does not advance for many weeks to months. The risk of progression to bilateral retinitis increase with time. Even on systemic treatment, the incidence of bilateral retinitis in patients who initially presented with unilateral disease is 10% at six months. The incidence of retinal detachment increases with increasing survival of patients with CMV retinitis and with extensive peripheral disease. Detachment occurs due to a combination of multiple small peripheral retinal holes and a mild degree of proliferative vitreoretinopathy.

### Maintenance treatment

All available anti-CMV treatments are virustatic rather than virucidal and, once remission is achieved, maintenance treatment must be used or recurrence will occur (at a median time of 16 days).<sup>5</sup> Maintenance therapy can be discontinued when the CD4 cell count is over 100 cells/ $\mu$ L for six months on cART. All patients should be screened regularly for recurrences and relapses but the frequency of screening should be increased in those at higher risk:

- those who have missed or reduced their maintenance treatment
- those with evidence of systemic CMV activation (including increased plasma CMV viral load)
- those who have had frequent relapses in the past
- those whose CD4 cell count remains below 50 cells/ $\mu$ L.

The advantages, disadvantages and side-effects of these regimens are largely the same as for when they are used as induction (see Chapter 13. 9). Doses and routes of delivery of intravitreal maintenance therapy are listed in Table 20.10.

**Table 20.10** Intravitreal treatment regimens for maintenance treatment of cytomegalovirus retinitis

Drug	Dose	Route of administration
Ganciclovir	200-400 $\mu$ g once weekly	Intravitreal
Foscarnet	1200-2400 $\mu$ g once weekly	Intravitreal
Ganciclovir	Slow release intra-ocular device	Intravitreal

Once the patient is in remission and on maintenance treatment, the eyes should be examined for detection of relapse according

to the following schedule:

- Four-weekly screening for:
  - Standard maintenance patients
- Two-weekly screening if:
  - Missed or reduced maintenance therapy
  - CMV viraemia (or positive equivalent test e.g. CMV viral load).

### Management of relapse of cytomegalovirus retinitis

Relapse of retinitis may take the form of an extension of existing areas of retinitis or the development of new areas of retinitis or the involvement of a previously uninvolved eye. The prevalence of viral resistance increases with time on treatment,<sup>9</sup> but in spite of this there is usually a therapeutic response to re-induction (i.e. an increase in the dose to induction doses) with the same agent as has been used for maintenance treatment.<sup>10</sup> If clinical relapse is accompanied by borderline tolerance of the original maintenance regimen, then re-induction with another regimen is recommended (e.g. a change from oral valganciclovir to intravenous ganciclovir or a change from intravenous ganciclovir to intravenous foscarnet). If the disease is severely vision-threatening or if the patient has relapsed more than once, then a change to intra-ocular therapy (regular intra-ocular injections of ganciclovir or foscarnet or a ganciclovir implant) is usually indicated. If that relapse occurs while on intra-ocular ganciclovir then a change to intra-ocular foscarnet or possibly a combination of ganciclovir and foscarnet is usually indicated. Usually re-induction treatment for relapse requires a shorter course of treatment than does normal induction and ophthalmoscopic monitoring is required to determine when maintenance should be recommenced.

### Immune reconstitution uveitis

Immune reconstitution uveitis usually occurs in patients with previously recognised and treated CMV retinitis (or occasionally in patients with unrecognised and untreated CMV retinitis) who have recently commenced effective cART and who have had a subsequent improvement in their immune function. Patients generally present with a short-lived and benign uveitis. Occasionally the uveitis is accompanied by more severe vision-threatening complications such as macular oedema, neovascularisation or epiretinal membrane formation. Generally the disease is treatable with a simple short (four weeks) course of topical steroids (1% prednisolone acetate 1-2 hourly), occasionally more aggressive treatment with injected orbital steroids (triamcinolone acetonide or methylprednisolone acetate) or oral prednisolone is required. With time, the disease generally burns out of its own accord. Long-term treatment is rarely required. Generally, when the immune reconstitution uveitis is quiet and the CD4 cell count has been greater than 100 cells/ $\mu$ L for six months, it is possible to stop all specific anti-CMV treatment.

### Treatment of retinal detachment

The visual results of detachment surgery for retinitis-related retinal detachment depend on the degree of involvement with retinitis prior to the surgery and the pre-operative acuity. Eyes with extensive macular or disc involvement and those with acuity of less than counting fingers will do worse post-operatively. When surgery is undertaken, it usually entails a vitrectomy, membrane peel, internal drainage, fluid-gas

exchange and injection of silicon oil. The silicon oil should not be removed and hence the eye is rendered variably hypermetropic postoperatively and binocularity is often not achievable if the other eye has normal vision. Some patients with small peripheral detachments can be successfully managed with laser barrage anterior to the detachment. The decision on whether or not to operate depends on the condition of the eye with the detachment, the patient's vision in the other eye and the general health of the patient. The poor median survival of patients post detachment repair cannot be generally extrapolated to all retinitis patients with detachments and treatment decisions should be individualised for all patients.

### Acute retinal necrosis

Acute retinal necrosis is characterised by rapidly progressive peripheral retinitis. Initially there is minimal vitritis but after just a few days the vitreous infiltrate increases dramatically. There are larger areas of retinal whitening than are seen with CMV retinitis and the disease has a much faster tempo (Image 20.4). There is early development of bilateral involvement and early retinal detachment. The disease may occur at any level of immunosuppression and does occur in immunocompetent hosts. Acute retinal necrosis is usually caused by varicella zoster virus but may also be caused by herpes simplex virus and rarely by CMV. The diagnosis is usually made clinically but may be confirmed by anterior chamber or vitreous tap for viral polymerase chain reaction (in particular, this allows differentiation between acute retinal necrosis and CMV retinitis as the treatment of the two is quite different).

Acute retinal necrosis has a worse prognosis than CMV retinitis. Acute retinal necrosis may follow an attack of shingles either in the ophthalmic division of the trigeminal nerve or elsewhere.

Treatment of acute retinal necrosis is usually with high-dose intravenous aciclovir (10 mg per kilogram 8 hourly) or with intravitreal foscarnet (1200 µg) or a combination of the two. Induction treatment is generally continued for two to three weeks until the retinitis appears quiet. After successful induction, maintenance treatment is instituted with oral aciclovir 800 mg five times daily. In immunocompetent patients, maintenance treatment is usually for three to six months but in patients with HIV infection with a low CD4 cell count maintenance treatment is life long.

### Progressive outer retinal necrosis

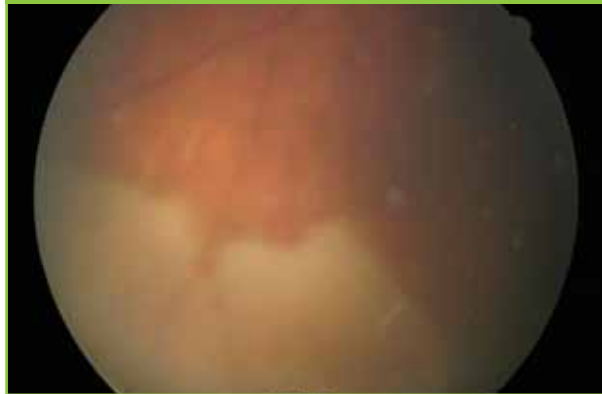
Progressive outer retinal necrosis is a more virulent form of acute retinal necrosis, again caused by varicella zoster virus. Patients present with visual loss from posterior pole involvement. Generally there is minimal vitritis and rapidly progressive multifocal posterior pole retinitis. This is followed by rapid peripheral enlargement of the retinitis and coalescence of the lesions. Again, there is early development of bilateral involvement and early retinal detachment. The untreated prognosis is very poor with almost universal blindness. The disease occurs in patients who are severely immunosuppressed (CD4 cell count less than 20 cells/µL). The diagnosis may be confirmed by an anterior chamber or vitreous tap showing varicella zoster virus.

Treatment is difficult. Generally combination treatment is required with at least one intravenous agent (aciclovir, ganciclovir or foscarnet) and at least one intravitreal agent (usually foscarnet). After induction treatment, long-term combination maintenance treatment is required.

### Toxoplasma chorioretinitis

Retinal or chorioretinal involvement by toxoplasmosis is far less common in HIV patients than is central nervous system involvement (the converse is true in immunocompetent patients). Chorioretinal toxoplasmosis in patients with AIDS

Image 20.4 Acute retinal necrosis



Source: Hall AJ, Ophthalmology Department, The Alfred Hospital, Melbourne, VIC. Used with permission

generally manifests as single or multifocal areas of dense white chorioretinal inflammation: it is less common to have large areas of confluent retinitis. There is usually an associated vitritis. Whether single or multifocal there is usually no adjacent pigmented scar. There is often associated central nervous system disease. The diagnosis may be made clinically if there is associated, confirmed central nervous system toxoplasmosis. The disease may be confirmed by toxoplasmosis serology or by anterior chamber or vitreous tap and PCR for toxoplasma DNA. Treatment is with oral sulphadiazine (4 mg daily) (or clindamycin 300 to 600 mg four times daily), pyrimethamine (50 mg daily) and folinic acid (15 mg daily). If the patient is allergic to sulphur-based antibiotics, then atovaquone may be substituted. For chorioretinal toxoplasmosis without cerebral involvement, oral steroids are usually not required.

### Multifocal choroiditis

Patients with AIDS with multifocal choroiditis generally have only mild, if any visual disturbance. Multifocal choroiditis may be seen in patients with cryptococcal meningitis, especially with associated widespread non-central nervous system cryptococcal disease. In this case, the association with signs and symptoms of cryptococcal meningitis may make the diagnosis. Multifocal choroiditis may also be seen in patients with widespread pneumocystis infection, especially in patients having inhaled pentamidine as prophylaxis for *Pneumocystis jirovecii* pneumonia. Less commonly, multifocal or unifocal choroiditis is seen in patients with disseminated *Mycobacterium avium* complex infection. In each case the clinical features are very similar with small (500 to 1500 µm) creamy white/yellow outer retinal/choroidal lesions. There is rarely associated haemorrhage and the associated vitritis is minimal.

Patients do not require specific ocular treatment but respond to systemic treatment of the associated systemic infection. The visual prognosis is good unless there is subfoveal involvement of the choroiditis.

Table 20.11 Causes of uveitis without retinitis or choroiditis in patients with HIV infection

Disease	Associated fundal features	Uveitis	Progression	Systemic association	CD4 cell count cells/ $\mu$ L	Treatment
Syphilis	May have papillitis, retinitis or choroiditis	Anterior or posterior		Secondary syphilis	Any	As for neurosyphilis
Drug induced uveitis	Nil	Anterior		Cidofovir Rifabutin	Any	Topical steroids and cessation of causative drug
Intra-ocular lymphoma	May have diffuse or multifocal choroiditis	Posterior	Slow	Usually associated cerebral lymphoma	<50 cells/ $\mu$ L	Radiotherapy plus chemotherapy
Reactive arthritis	Nil	Anterior		Arthritis	Normal	Topical steroids

### 20.6.2 Other ocular conditions

#### Uveitis without retinitis or choroiditis

Patients with AIDS with intra-ocular inflammation generally have an associated retinitis or choroiditis. Sometimes patients present with intra-ocular inflammation (uveitis or vitritis) without any focal areas of retinitis or choroiditis. In such cases there is a small number of possible underlying causes (Table 20.11). It is necessary to fully investigate these patients before making appropriate treatment decisions. It is unwise to treat these patients with steroids without determining the underlying cause.

#### Optic neuropathy

Optic neuropathy in patients with AIDS rarely occurs as an isolated phenomenon. CMV optic neuritis is usually seen with adjacent CMV retinitis. *Cryptococcal* optic neuropathy is usually seen with associated *cryptococcal* meningitis. Syphilitic optic neuropathy is usually seen with secondary syphilis and associated syphilitic uveitis. Optic nerve swelling with good optic nerve function may be seen from any central nervous system space occupying lesion in patients with AIDS but the most common causes of papilloedema in patients with AIDS are toxoplasmosis and central nervous system lymphoma.

#### External infections and tumours

##### *Blepharitis and sicca syndromes*

Surface ocular irritation and dryness is common but usually not visually significant. Blepharitis may be associated with facial seborrhoeic dermatitis. Treatment with simple topical lubricants or eyelid hygiene is generally sufficient. Occasionally, long-term, low-dose topical steroids (fluoromethalone) may be needed.

##### *Molluscum contagiosum.*

Eyelid molluscum may cause a chronic conjunctivitis or simply be of cosmetic concern. It can be treated with local anaesthetic and curettage or cryotherapy.

##### *Herpes simplex virus keratitis*

Herpes simplex virus keratitis in patients with AIDS may be peripheral and prolonged. Even so, treatment with a simple longer-term topical acyclovir is generally sufficient. Acyclovir resistance may occur. Systemic therapy is rarely warranted.

##### *Herpes zoster ophthalmicus*

Herpes zoster ophthalmicus may be the presenting feature of HIV infection in young people in at-risk groups. Standard therapy with oral or intravenous aciclovir, valaciclovir or famciclovir is generally effective. Long-term suppressive aciclovir may be required.

##### *Lid and conjunctival Kaposi's sarcoma*

Lid or conjunctival Kaposi's sarcoma are deep red/purple lesions which may be flat or only slightly raised. They may look like a subconjunctival haemorrhage. Lid or conjunctival Kaposi's sarcoma are treated with local anaesthetic and cryotherapy.

##### *Microsporidial keratoconjunctivitis*

Microsporidial keratoconjunctivitis presents with a chronic conjunctivitis with characteristic fine superficial punctate keratopathy and subepithelial infiltrates. The diagnosis is usually made on corneal scrapes or biopsy. The patients usually respond to topical fumagillin.

## References

- Holland GN, Pepose JS, Pettit TH, Gottlieb MS, Yee RD, Foos RY. Acquired immune deficiency syndrome. Ocular manifestations. *Ophthalmol* 1983;90(8):859-73.
- Crowe SM, Carlin JB, Stewart KI, Lucas CR, Hoy JF. Predictive value of CD4 lymphocyte numbers for the development of opportunistic infections and malignancies in HIV-infected persons. *J Acquir Immune Defic Syndr* 1991;4(8):770-6.
- Finkelstein DM, Williams PL, Molenberghs G, Feinberg J, Powderly WG, Kahn J, et al. Patterns of opportunistic infections in patients with HIV infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996;12(1):38-45.
- Lazzarotto T, Dal Monte P, Bocconi MC, Ripalti A, Landini MP. Lack of correlation between virus detection and serologic tests for diagnosis of active cytomegalovirus infection in patients with AIDS. *J Clin Microbiol* 1992;30(4):1027-9.
- Jackson JB, Erice A, Englund JA, Edson JR, Balfour HH Jr. Prevalence of cytomegalovirus antibody in hemophiliacs and homosexuals infected with human immunodeficiency virus type 1. *Transfusion* 1988;28(2):187-9.
- Kedhar SR, Jabs DA. Cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Herpes* 2007;14(3):66-71.

- 7 Thorne JE, Jabs DA, Kempen JH, Holbrook JT, Nichols C, Meinert CL; Studies of ocular complications of AIDS Research Group. Incidence of and risk factors for visual acuity loss among patients with AIDS and cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Ophthalmol* 2006;113(8):1432-40.
- 8 Keefe KS, Freeman WR, Peterson TJ, Wiley CA, Crapotta J, Quiceno JI, Listhaus AD. Atypical healing of cytomegalovirus retinitis. Significance of persistent border opacification. *Ophthalmol* 1992;99(9):1377-84.
- 9 Drew WL, Miner RC, Busch DF, Follansbee SE, Gullett J, Mehalko SG, et al. Prevalence of resistance in patients receiving ganciclovir for serious cytomegalovirus infection. *J Infect Dis* 1991;163(4):716-9.
- 10 SOCA research group. The Studies of Ocular Complications of AIDS Research Group in Collaboration with the AIDS Clinical Trials Group. Combination foscarnet and ganciclovir therapy vs monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS. The Cytomegalovirus Retreatment Trial. *Arch Ophthalmol* 1996;114(1):23-33.

## 20.7 Haematological problems and HIV infection

**Sam Milliken**

Immunology/HIV/Infectious Diseases Clinical Services Unit, St Vincent's Hospital, Sydney, NSW

Despite significant reductions in all complications of HIV infection since the introduction of highly active antiretroviral therapy (cART), haematological problems remain common.<sup>1</sup>

### 20.7.1 Anaemia

Anaemia is a common problem and increases in frequency with stage of HIV infection, ranging from 3% of asymptomatic patients to 12% in people with CD4 lymphopenia (CD4 cell count <200 cells/ $\mu$ L or CD4 percentage <14%) and 37% of patients with AIDS in one large surveillance study.<sup>2</sup> Anaemia has been associated with reduced survival in a number of studies independent of other risk factors such as CD4 cell count and viral load.<sup>2,3</sup> This relationship is more pronounced in patients who remain anaemic after commencing antiretroviral therapy.<sup>4</sup> Common causes of anaemia include anaemia of chronic disease, drugs such as zidovudine, cotrimoxazole, amphotericin B, ganciclovir and dapsone, and infections. Other causes are malignancy (lymphoma and Kaposi's sarcoma involving the gastrointestinal tract) and hypersplenism (often associated with liver disease such as chronic viral hepatitis). Rarer, important causes include Castleman's disease, human parvovirus B19 infection, thrombotic thrombocytopenic purpura and haemophagocytic syndrome. Anaemia of chronic disease may be due to HIV infection, other infections or cancer. Zidovudine and lamivudine may cause a macrocytosis.<sup>1,5</sup> Low B12 levels are not uncommon but true B12 deficiency is rare.<sup>6</sup> Similarly, while direct antiglobulin tests are often positive, ranging from 18 to 43% of people with HIV infection,<sup>7</sup> autoimmune haemolytic anaemia is rare.<sup>8</sup>

The best treatment for anaemia is to identify and manage the underlying cause (e.g. treat infections or remove causative drugs). Human parvovirus B19 infection is a rare but interesting cause of pure red cell aplasia in severely immunosuppressed patients; it responds to cART and intravenous immunoglobulin therapy.<sup>1</sup> If the cause of anaemia cannot be corrected, then exogenous erythropoietin may improve haemoglobin levels and quality of life.<sup>9,10</sup> Treatment with erythropoietin may reduce the risk of mortality while blood transfusion therapy may increase this risk.<sup>11</sup> Consequently, only patients with symptomatic anaemia without a correctable cause should be considered for transfusion.

### 20.7.2 Thrombocytopenia and immune thrombocytopenic purpura

Thrombocytopenia is commonly observed in association with HIV infection; immune thrombocytopenic purpura (ITP) is the most common cause. It may occur in 30% or more of patients with AIDS<sup>12</sup> and can occur at any time during HIV infection. It may be seen before other clinical manifestations.<sup>13</sup> As such, HIV antibody testing is recommended in cases of idiopathic ITP. ITP may be mediated by immune complexes generated by HIV glycoprotein (GP) 120 that are directed against the platelet membrane GPIIb/IIIa complex<sup>12</sup> and it appears megakaryocytes may be directly infected by HIV.<sup>1</sup> While platelet survival is decreased, especially in patients with higher CD4 cell counts, platelet production is also decreased.<sup>1</sup> Other common causes are drugs, such as ganciclovir, cotrimoxazole and rifabutin, infections such as *Mycobacterium avium* complex (MAC), lymphoma and hypersplenism. Rarer causes that appear directly related to HIV infection are the thrombotic microangiopathies, thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome.

Bleeding is uncommon in ITP unless the platelet count is less than  $30 \times 10^9$  cells/L. However, patients with co-existing haemophilia or other coagulopathies should be treated if platelet counts fall below  $50 \times 10^9$  cells/L.<sup>13</sup> The treatment of choice for ITP is cART. Corticosteroids are effective but long-term use is not desirable due to immunosuppression. Other drugs such as dapsone and danazol can be effective. Intravenous immunoglobulin is very effective in increasing platelet counts in the short term but is expensive. Splenectomy may be successful for refractory cases and does not increase risk of progression to AIDS.<sup>13</sup> For other causes of thrombocytopenia, treatment of the underlying cause is usually effective. Support with platelet transfusions should only be considered for patients at immediate risk of bleeding as the effect of transfusion is short lived and platelet allo-antibodies rapidly develop, limiting the effectiveness of future transfusions.

### 20.7.3 Neutropenia, pancytopenia and myelodysplasia

Neutropenia may be due to HIV infection itself, autoimmune neutropenia, infections such as MAC and tuberculosis (TB), marrow infiltration by malignancy (commonly lymphoma), hypersplenism and drugs. Treatment is directed at the underlying cause: cART for immunosuppression; antibiotics for

## 20 Other diseases or disorders

infection; and the withdrawal of potentially causative drugs. Granulocyte colony stimulating factor (G-CSF) will usually correct severe neutropenia in refractory cases and may allow marrow suppressive drugs such as ganciclovir to be continued until infection has resolved. Infection or undiagnosed fever associated with severe neutropenia (neutrophil count  $<0.5 \times 10^9$  cells/L) should be considered a medical emergency with immediate commencement of broad spectrum antibiotics and supportive therapies such as G-CSF.<sup>1</sup>

All of the causes of individual cytopenias may produce a generalised pancytopenia. Late HIV infection commonly causes a myelodysplasia-type syndrome with impaired bone marrow function. Pancytopenia with severe lymphopenia and eosinophilia are commonly observed in the blood. Examination of the bone marrow commonly demonstrates normal or increased cellularity suggesting the impaired marrow function is due to inhibition of cellular maturation and production. Marrow plasmacytosis, lymphoid aggregates, granulomata and fibrosis are common.<sup>14</sup>

### 20.7.4 Lymphadenopathy and splenomegaly

Lymphadenopathy and splenomegaly are commonly seen in association with HIV infection, particularly with acute infection and persistent generalised lymphadenopathy seen with latent infection. Both tend to regress in late stages of infection. Other causes are infections (such as CMV, Epstein Barr virus, hepatitis B and C, MAC, TB, syphilis and Cryptococcus), lymphoma, Kaposi's sarcoma and rarer causes such as haemophagocytic syndrome and Castleman's disease.

### 20.7.5 Paraproteinaemia

A polyclonal increase in globulin occurs as part of the immune response to HIV infection and monoclonal paraproteins have been reported in as many as 7% of people with HIV infection. They do not appear to be clinically significant and may persist despite cART.<sup>15</sup> Similarly, cryoglobulinaemia has been reported in HIV infection, again without clinical significance. Over 90% of cases of cryoglobulinaemia are co-infected with hepatitis C and HIV infection does not appear to be a causative factor.<sup>16</sup>

### 20.7.6 Thromboembolic disease

Thrombosis has been reported in up to 2% of people with HIV infection. Risk factors for this group are age over 45 years, advanced stage of HIV infection, co-existing opportunistic infections, hospitalisation, and therapy with indinavir and megestrol acetate.<sup>17</sup> A number of potentially pro-thrombotic abnormalities have been reported in association with HIV infection including: decreased levels of antithrombin (seen in HIV nephropathy), free protein S, protein C and heparin cofactor II, lupus anticoagulant and anticardiolipin antibodies, co-existent malignant, inflammatory and autoimmune disorders, as well as vascular damage due to injecting drug use, vascular catheters and CMV infection.<sup>18</sup> The presence of lupus anticoagulant or anticardiolipin antibodies are weakly associated with venous thrombosis but cerebrovascular accidents, bone and skin necrosis and brachial artery thrombosis have been reported.<sup>1</sup>

### 20.7.7 Investigations

Lymph node biopsy should be considered for any symptomatic lymphadenopathy or asymptomatic lymph node enlargement over 2 cm, persisting for more than one month, where an

infective cause cannot be determined, or for any persistently enlarging lymph nodes. Fine needle biopsy has a good diagnostic yield but excision biopsy should be considered if it is non-diagnostic and lymphadenopathy persists or progresses.

Bone marrow examination should be undertaken for any unexplained moderate-to-severe anaemia or isolated cytopenia or pancytopenia and for pyrexia of unknown origin where initial tests are unhelpful.

Specimens should be sent for special microbial cultures, such as MAC, flow cytometry to examine cell populations to help exclude lymphoma, as well as for morphological examination.

## References

- 1 Volberding PA, Baker KR, Levine AM. Human immunodeficiency virus hematology. *Hematology* 2003;2003:294-313.
- 2 Sullivan PS, Hanson DL, Chu SY, Jones JL, Ward JW, and the Adult/Adolescent Spectrum of Disease Group. Epidemiology of anemia in human immunodeficiency virus (HIV)-infected persons: results from the multistate adult and adolescent spectrum of HIV disease project. *Blood* 1998;91:301-8.
- 3 Mocroft A, Kirk O, Barton SE, Dietrich M, Proenca R, Colebunders R, et al. Anaemia is an independent predictive marker for clinical prognosis in HIV-infected patients from across Europe. *AIDS* 1999;13:943-50.
- 4 Kowalska JD, Mocroft A, Blaxhult A, Colebunders R, van Lunzen J, Podlekareva D, et al. Current hemoglobin levels are more predictive of disease progression than hemoglobin measured at baseline in patients receiving antiretroviral treatment for HIV type 1 infection. *AIDS Res Hum Retroviruses* 2007;23:1183-8.
- 5 Kawcharoenporn T, Shikuma CM, Williams AE, Chow DC. Lamivudine-associated macrocytosis in HIV-infected patients. *Int J STD AIDS* 2007;18:39-40.
- 6 Remacha AF, Cadafalch J. Cobalamin deficiency in patients infected with human immunodeficiency virus. *Semin Hematol* 1999;36:75-87.
- 7 De Angelis V, Biasinutto C, Pradella P, Vaccher E, Spina M, Tirelli U. Clinical significance of positive direct antiglobulin test in patients with HIV infection. *Infection* 1994;22:92-5.
- 8 Koduri PR, Singa P, Nikolinakos. Autoimmune haemolytic anemia in patients infected with human immunodeficiency virus-1. *Am J Hematol* 2002;70:174-6.
- 9 Henry DH, Beall GN, Benson CA, Carey J, Cone LA, Eron LJ, et al. Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy: overview of four clinical trials. *Ann Intern Med* 1992;117:739-48.
- 10 Abrams DI, Steinhart C, Frascino R. Epoetin alfa therapy for anaemia in HIV-infected patients: impact on quality of life. *Int J STD AIDS* 2000;11:659-65.
- 11 Moore JD, Keruly JC, Chaisson RE. Anemia and survival in HIV infection. *J Acquir Immune Defic Syndr Hum Retroviral* 1998;19:29-33.
- 12 Nardi M, Karpatkin S. Antiidiotype antibody against platelet anti-GPIIIa contributes to the regulation of thrombocytopenia in HIV-1-ITP patients. *J Exp Med* 2000;191:2093-100.
- 13 Coyle TE. Management of the HIV-infected patient. Part II. *Med Clin North Am* 1997;81:449-70.
- 14 Bain BJ. The haematological features of HIV infection. *Br J Haematol* 1997;99:1-8.

- 15 Jacobsen MA, Khayam-Bashi H, Martin JN, Black D, Ng V. Effect of long-term highly active antiretroviral therapy in restoring HIV-induced abnormal B-lymphocyte function. *J Acquir Immune Defic Syndr* 2002;31:472-7.
- 16 Fabris P, Tositti G, Giordani MT, Romanò L, Betterle C, Pignattari E, et al. Prevalence and clinical significance of circulating cryoglobulins in HIV-positive patients with and without co-infection with hepatitis C virus. *J Med Virol* 2003;69:339-43.
- 17 Sullivan PS, Dworkin MS, Jones JL, Hooper WC. Epidemiology of thrombosis in HIV-infected individuals. *AIDS*. 2000;14:321-4.
- 18 Saif MW, Bona R, Greenberg B. AIDS and thrombosis: retrospective study of 131 HIV-infected patients. *AIDS Pt Care STDS* 2001;15:311-20.

