

Key opportunistic infections

13.1 *Pneumocystis jirovecii* pneumonia

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Pneumocystis jirovecii (previously *Pneumocystis carinii*¹ is a fungus² that is ubiquitous. It is unclear whether infection occurs as a primary event³ or as a result of colonisation with reactivation⁴, although antibodies against the organism are present in more than 85% of children under three years of age, suggesting that reactivation with immunosuppression occurs. *P. jirovecii* pneumonia (PJP), is still the most common AIDS-defining condition, and is usually seen in people presenting late in the course of HIV infection⁶ or in people with poor adherence to PJP prophylaxis or combination antiretroviral therapy (cART). PJP occurs uncommonly in persons with a CD4 cell count greater than 200 cells/ μ L, or 14% of the total lymphocyte count, although cases have been reported in individuals with more preserved immune function.⁷

13.1.1 Clinical presentation Immunodeficient persons

The major manifestation of *P. jirovecii* infection is that of PJP. The presentation of PJP is subacute with fever, a non-productive cough, chest tightness and dyspnoea. Symptoms may be present for two to six weeks or more before the diagnosis is made. Extrapulmonary manifestations are rare, and require tissue biopsy for diagnosis.⁸ The typical clinical scenario of a patient with PJP is an immunodeficient person (with a CD4 cell count <200 cells/ μ L or a CD4 cell percentage <14%), not taking cotrimoxazole prophylaxis, presenting with fatigue and fevers. The patient may not necessarily have noticed cough or dyspnoea, yet a non-productive cough is commonly apparent during the clinical assessment. Respiratory examination may reveal no signs aside from tachypnoea and oxygen desaturation on exertion, although crackles may be present on auscultation of the chest. Pneumothorax may complicate PJP.

Immune reconstitution features

Pneumonitis may be seen with immune reconstitution, and immune reconstitution with PJP has been reported infrequently. Distinguishing a pneumonitis secondary to immune reconstitution from undiagnosed PJP may be difficult.

13.1.2 Diagnosis

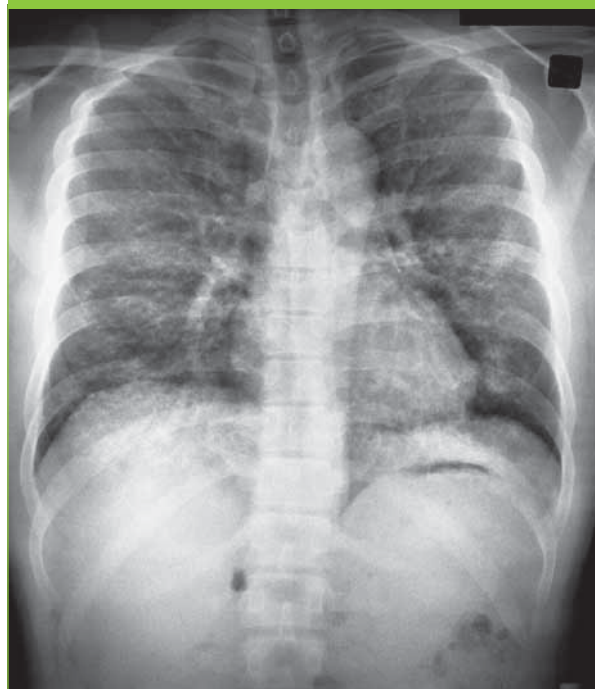
The initial diagnostic approach to PJP includes consideration of the clinical likelihood of disease. People with advanced immunodeficiency who present with fever, fatigue and a dry cough have a high likelihood of PJP if they are not taking PJP prophylaxis, although other infections may present in such a manner. Other pathogens may cause respiratory disease (e.g. *Mycobacterium tuberculosis*, *Mycobacterium avium* complex, *Streptococcus pneumoniae*, *Rhodococcus* spp., *Nocardia* spp. and *Cryptococcus neoformans*) and these need to be considered in the differential diagnosis of any pulmonary presentation. It is especially important to consider

the possibility of tuberculosis, as infection control and public health issues need to be considered.

The initial recommended investigation is a chest radiograph, which may reveal perihilar interstitial infiltrates or diffuse alveolar shadowing (Image 13.1). The chest radiograph may be normal in more than 10% of cases.⁹ Additional focal pathology is suggestive of an alternative diagnosis. PJP may be complicated by pneumothorax and pleural effusions are rare. If pleural effusions are detected, other diagnoses should be considered. Even in cases with a normal chest radiograph, high resolution computed tomography (CT) of the chest (Image 13.2) may reveal the typical 'ground glass' changes seen in the alveolitis due to PJP.¹⁰

An induced sputum specimen is obtained by the induction of a deep cough after the inhalation of hypertonic saline.^{11,12} Pneumothorax should be excluded before sputum induction is undertaken. The procedure should be performed in an appropriately ventilated room, in case other pathogens are present. Induced sputum enables lower respiratory tract sampling, which is suitable for analysis for the presence of *P. jirovecii* cysts.

Image 13.1 Chest radiograph showing bilateral infiltrates



Source: Jeffrey J Post, University of NSW, Sydney, NSW. Used with permission.

Image 13.2 CT scan showing ground glass appearance consistent with *Pneumocystis jirovecii* pneumonia



Source: Jeffrey J Post, University of NSW, Sydney, NSW. Used with permission.

Diagnosis is made by immunofluorescence staining of the sample using monoclonal antibodies,¹³ which typically takes two hours to process. Other stains, including silver stains, have a lower sensitivity. Investigation of induced sputum is not warranted in asymptomatic immunodeficient individuals.¹⁴ Highly sensitive polymerase chain reaction (PCR) diagnostic assays have been developed, but their role in the diagnostic evaluation of PJP is yet to be defined, with one meta-analysis suggesting that induced sputum with immunostaining is the preferred diagnostic approach in low-prevalence settings.¹⁵⁻²¹

Other investigations infrequently used in the diagnosis of PJP include the following:

- Rapid clearance of technetium in lung scans indicates altered alveolar permeability that is consistent with PJP^{22,23}
- Pulmonary diffusing capacity for carbon monoxide is also typically impaired in persons with PJP^{24,25}
- Although lactate dehydrogenase is often elevated in PJP, it is insufficiently specific to exclude other pathology or determine disease severity²⁶
- More recently, there has been significant interest in serum markers of PJP, with low S-adenosylmethionine levels (a molecule that *P. jirovecii* must scavenge) seen in cases with PJP that recover in association with effective treatment^{27,28}
- Other non-invasive markers such as beta-D-glucan have been of interest, but may not be sufficiently specific for PJP²⁹

In people with a high clinical likelihood of PJP, presumptive therapy is sometimes undertaken if the induced-sputum specimen is not diagnostic and other features are consistent with PJP, but bronchoscopy with bronchoalveolar lavage is generally indicated, as the differential diagnosis is broad.³⁰ Bronchoscopy with bronchoalveolar lavage is also indicated in cases of presumptive PJP that do not respond to therapy. Bronchoscopy may be preferred where there is a high likelihood of other infectious agents such as *M. tuberculosis*³¹. Open-lung biopsy is usually unnecessary as induced-sputum examination and bronchoscopy with bronchoalveolar lavage have a high sensitivity (approximately 97%). The pathology of PJP consists of an eosinophilic alveolar exudate with organisms present.³² Blood gas analysis should be undertaken to assess disease severity. Arterial blood hypoxaemia (while breathing room air), with a PaO₂ <70 mmHg, an Alveolar-arterial (A-a) oxygen

gradient of >30 mmHg or oxygen saturation of <94% indicates moderately severe or severe disease. Lesser impairment of gas exchange indicates mild disease. Therapeutic studies of mild-to-moderate disease have included those with a PaO₂ >50 mmHg.

13.1.3 Management

The management of PJP depends on the degree of severity of disease.

Severe disease

People with severe disease should be managed in hospital, as ventilatory support may be required. Those who are not allergic to sulphur-containing drugs or hypersensitive to cotrimoxazole should receive high-dose intravenous cotrimoxazole (trimethoprim 15-20 mg/kg/day and sulfamethoxazole 75-100 mg/kg/day in four divided doses for 21 days). Persons who are allergic to sulphur compounds, or unresponsive to cotrimoxazole, or who develop hypersensitivity during therapy should be treated with intravenous pentamidine (3-4 mg/kg/day for 21 days).³³ Third-line intravenous regimens include clindamycin (600 mg intravenously every eight hours) with primaquine (15 mg orally daily). Supplemental oxygen, non-invasive ventilation (e.g. continuous positive airways pressure or bilevel positive airways pressure),³⁴ or intubation and ventilation may be required. It is not uncommon for patients to deteriorate during the first 48 hours after commencement of therapy. Patients with significant hypoxaemia (PaO₂ < 70 mmHg) should receive corticosteroids prior to the commencement of antimicrobial therapy to reduce the risk of this complication and improve prognosis (prednisone 40 mg orally twice a day for five days, then 40 mg daily for five days, then 20 mg/day until completion of treatment).³⁵⁻³⁹ If oral corticosteroid therapy is not possible then hydrocortisone (100 mg intravenously every six hours) may be used. Corticosteroid therapy may be complicated by central nervous system toxicity (e.g. psychosis, mania), oral candidiasis and other opportunistic infections. Patients who respond well to initial intravenous therapy may complete the 21-day course with oral therapy (see below).

Moderate disease

If disease severity is moderate (e.g. dyspnoea on minimal exertion, PaO₂ 50-70 mmHg) or adherence to or tolerance of an oral regimen is not likely, then initial inpatient management is recommended. Otherwise, oral regimens may be considered (see below). Patients with moderately severe PJP should also receive corticosteroids (if PaO₂ <70 mmHg).

Mild disease

People with mild disease may be treated with oral cotrimoxazole (two double-strength tablets three times daily –one double-strength tablet contains trimethoprim 160 mg and sulfamethoxazole 800 mg) for 21 days. Oral therapy should only be considered where adherence is likely. Adjunctive anti-emetic therapy is commonly prescribed. Alternative regimens in cases of non-severe disease include clindamycin (450 mg orally four times daily) with primaquine (15 mg orally daily); dapsone (100 mg orally daily) with trimethoprim (300 mg orally every eight hours; 15 mg/kg/day),⁴⁰ or atovaquone (750 mg orally twice daily).⁴¹

Salvage therapy

Salvage therapy of PJP with caspofungin has been reported in the non-HIV setting although the role of this agent in the initial treatment of PJP has not been studied and there are case reports of failure of this agent in the HIV setting in people thought to have multiple infective pathologies.^{45,46} Further data are needed before caspofungin can be recommended.

13.1.4 Cotrimoxazole hypersensitivity

The most common toxicity of cotrimoxazole is hypersensitivity. This reaction is not a type 1 allergic reaction, although true allergy may occur. The hypersensitivity reaction typically manifests as a maculopapular rash with recrudescence of fever after initial resolution of fever due to PJP. There may be associated haematological and liver function abnormalities. This may progress to a life-threatening systemic reaction if the drug is not ceased. Secondary PJP prophylaxis with cotrimoxazole following a hypersensitivity reaction may be considered under certain conditions. PJP therapy should be completed and hypersensitivity fully resolved before cotrimoxazole desensitisation is undertaken (Table 13.1).⁴²⁻⁴⁴

Desensitisation should not be undertaken if true allergy occurs. If immune reconstitution is unlikely to occur with cART or is likely to be delayed (e.g. very low nadir CD4 cell count or unlikely adherence to cART) then desensitisation should be undertaken, as PJP prophylaxis will be needed for this period.

13.1.5 Prognosis

Early in the HIV epidemic, patients with PJP had a poor prognosis; with better management of respiratory failure and the introduction of cART, prognosis has improved. The prognosis

of people with severe PJP requiring ventilation has improved, with one recent study reporting a 47% overall survival rate.⁴⁷ Factors associated with a poor prognosis include the degree of hypoxaemia, neutrophilia, high numbers of organisms in bronchoalveolar lavage fluid and severe radiological abnormalities. Point mutations in the dihydropteroate synthase gene which confers resistance against sulphur drugs have been suggested to worsen the prognosis.^{48,49}

13.1.6 Prophylaxis

Primary

Prophylaxis against PJP is recommended in patients with CD4 cell counts <200 cells/ μ L or <14% of lymphocytes, or oral candidiasis or unexplained fever of more than two weeks duration. The institution of prophylaxis (without cART) reduces the risk of PJP in susceptible populations by nine fold.²⁴ Mutations in dihydrofolate reductase may be associated with failure of prophylaxis.⁵⁰

The optimal regimen is cotrimoxazole: one double-strength tablet orally once per day, although half a tablet daily is efficacious and may have a lower rate of toxicity. The risk of acquiring PJP while taking cotrimoxazole prophylaxis is extremely low. Cotrimoxazole is also active against toxoplasmosis and some bacterial pathogens. The most common toxicity is cotrimoxazole hypersensitivity (see above). Alternative regimens include double-strength cotrimoxazole (orally twice daily on two or three days per week), nebulised pentamidine (300 mg once per month, with salbutamol pre-treatment to reduce bronchospasm), dapsone (100 mg orally daily) or atovaquone (750 mg orally twice daily) (Table 13.2).^{51,52}

Table 13.1 Outpatient oral cotrimoxazole desensitisation protocol

Day	Time	Dose number	Amount ¹	Dose ²	Venue
1	0830	1	0.10 mL A	10 μ g	Clinic
	1200	2	0.25 mL A	25 μ g	Clinic
	1600	3	0.50 mL A	50 μ g	Clinic
	2000	4	1.00 mL A	100 μ g	Home
	2330	5	2.50 mL A	250 μ g	Home
2	0830	6	5.00 mL A	500 μ g	Home
	1200	7	10.00 mL A	1 mg	Clinic
	1600	8	20.00 mL A	2 mg	Home
	2000	9	0.40 mL B	4 mg	Home
	2330	10	0.80 mL B	8 mg	Home
3	0830	11	1.50 mL B	15 mg	Home
	1200	12	3.00 mL B	30 mg	Clinic
	1600	13	5.00 mL B	50 mg	Home
	2000	14	10.00 mL B	100 mg	Home
	2330	15	20.00 mL B	200 mg	Home
4	0830	16	Half DS tablet	400 mg	Clinic
1 Solution A = 100 μ g/mL of sulphamethoxazole component; Solution B = 10mg/mL of sulphamethoxazole component.					
2 Doses are expressed as per sulphamethoxazole component.					
DS = double strength; mL A = mL of solution A; mL B = mL of solution B.					
Note: At each clinic visit the patient is checked for the presence of itch, rash and fever.					
Source: Albion Street Centre, Sydney. Used with permission.					

Table 13.2 Common toxicities of agents used in treatment or prophylaxis of *Pneumocystis jirovecii* pneumonia

Agent used in treatment or prophylaxis of PJP	Common toxicities
Atovaquone	Hypersensitivity Gastrointestinal Biochemical hepatitis
Clindamycin	Hypersensitivity Diarrhoea Pseudomembranous colitis Haematological
Cotrimoxazole	Hypersensitivity – typically fever and maculopapular rash; dose-related; may develop into Stevens-Johnson syndrome Nausea, vomiting Bone marrow toxicity – neutropenia, thrombocytopenia Biochemical hepatitis
Dapsone	Hypersensitivity Haemolysis in G6PDH-deficient persons
Pentamidine	Renal tubule dysfunction – renal impairment, hyperkalaemia Pancreatic toxicity – hypoglycaemia, hyperglycaemia Arrhythmias Hypotension

G6PDH = glucose 6-phosphate dehydrogenase; PJP = *Pneumocystis jirovecii* pneumonia.

Secondary

Secondary prophylaxis after an episode of PJP is recommended to prevent relapse or recurrence until immune reconstitution has occurred.

13.1.7 Discontinuing prophylaxis

Cohort studies have demonstrated the safety of discontinuing both primary and secondary PJP prophylaxis after the CD4 cell count has risen above 200 cells/ μ L and 14% of the total lymphocyte count for longer than three months, in the setting of viral suppression and immune reconstitution with cART.⁵³⁻⁵⁹

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13.2 Kaposi's sarcoma

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Kaposi's sarcoma (KS) was one of the earliest, most visible manifestations of HIV infection. In 1981, the Centers for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report published an article about KS and *Pneumocystis carinii* pneumonia; this report is generally accepted as the first description of what came to be known as AIDS.¹ There are four distinct KS variants: the classical or sporadic form, the endemic African form, the iatrogenic immunosuppression-related form, and the epidemic or HIV-related form.

KS is an endothelial cell malignancy and the result of co-infection with human herpesvirus type 8 (HHV8)² (alternatively referred to as Kaposi's sarcoma-associated herpesvirus).³ HHV8 has also been associated with primary effusion lymphoma and multicentric Castlemans disease. Although there is some evidence that circulating growth factors, such as HIV Tat protein, basic fibroblast growth factor and numerous cytokines (including interleukin 1, tumour necrosis factor and interleukin 6) play a role in the pathogenesis of HIV-related KS, infection with HHV8 is necessary for KS to develop.

The KS variants are now thought to represent different manifestations of the same pathological process. Studies using increasingly specific and sensitive assays against HHV8 have shown that the prevalence of HHV8 infection matches the rate of KS in different populations. Low rates (0.2-10%) have been demonstrated in the general populations of the USA.⁴ Asia⁵ and many parts of Europe; high levels (50% or higher) occur

in central Africa, and intermediate levels in Mediterranean countries. The background rate of HHV8 prevalence in patients with HIV infection differs considerably according to the mode of transmission of HIV infection, with rates being high for males who have acquired HIV through homosexual transmission and low for those who have acquired HIV through intravenous drug use, blood or factor concentrate infusion, or heterosexual contact.⁶ Current debate still surrounds the exact nature of transmission of this virus. However, there is general agreement that, in endemic areas, transmission occurs through saliva, similar to the transmission of Epstein Barr virus, whereas in epidemic KS, sexual transmission is thought to be the major mode of acquisition.⁷ The exact sexual activity which leads to acquisition of HHV8 is not yet determined,⁸ although HHV8 has been detected in both the saliva⁹ and semen¹⁰ of people with HHV8 infection. Transmission has also been documented following organ transplantation.¹¹ The risk of transmission via blood products is thought to be low, particularly for highly refined plasma products. Reports of the development of new KS after autologous bone marrow transplant are thought to originate from the cellular products necessary as clinical support through the transplant process rather than the immunosuppressive effects of the induction process.¹²

13.2.1 Clinical presentations Immunodeficient people

Primary infection with HHV8 appears to be asymptomatic. Immunosuppression is a cofactor for the development of

disease in most patients.¹³ KS generally manifests as pigmented lesions involving the skin or the mucous membranes lining the mouth, nose, eye and anus. Skin lesions occur as plaques, patches or nodules. These are reddish or purple in fair-skinned individuals and bluish or brown in darker-skinned individuals. Although the skin lesions are usually painless, they can cause painful swelling, particularly when the lower limbs are affected. Internal organs may also be affected, with the gastrointestinal tract and the lung most commonly involved. Lymph node disease is also common. Nausea, vomiting and bleeding may occur with gastrointestinal tract involvement, and shortness of breath with lung involvement.

The clinical presentation of KS differs according to the KS variant.¹⁴ Epidemic KS occurs commonly in advanced immunosuppression, but may occur at any CD4 cell count. Presentation usually features multiple skin lesions often occurring in the lines of skin cleavage (Langer's lines) – a phenomenon not seen in other KS variants. These skin lesions may rapidly multiply and progress to involve internal organs. The classical form of KS presents as skin lesions in localised clusters on the lower extremities and usually runs an indolent course over several years, with those affected usually dying from other causes. There is an association, however, with another primary malignancy, and clinicians should consider the possibility of other malignancies in individuals with KS lesions. Endemic African KS and iatrogenic immunosuppression KS usually present as skin lesions. These generally remain localised to the skin, but may spread in some patients and affect other organs. A particularly aggressive lymphadenopathic form of endemic KS occurs in young children and is rapidly fatal.

Immune reconstitution features

Control of HIV replication has led to stabilisation or regression of KS disease in most patients. A paradoxical immunoinflammatory reaction brought about by the improvement in immune status on combination antiretroviral therapy (cART) occurs occasionally resulting in the development of KS. This is termed the immune reconstitution inflammatory syndrome or IRIS. Such KS may require a short course of systemic chemotherapy.¹⁵

13.2.2 Diagnosis

In a patient with HIV or risk factors for HIV, the diagnosis of KS should be considered for any skin lesion. However, diagnosis should rarely be made on appearance alone. Even the most experienced clinician will sometimes be fooled by a lesion mimicking the classical appearance of this disease and, for this reason, the diagnosis is best confirmed by a biopsy. The differential diagnosis of KS includes vascular lesions such as purpura, necrotising vasculitis, haemangiomas, angiokeratoma and venous lakes; inflammatory lesions such as pityriasis rosea, granuloma annulare, erythema multiforme, lichen planus and pyogenic granulomas; naevi, malignant melanomas and other cutaneous tumours such as basal cell carcinomas and mycosis fungoides. Other infective causes, such as secondary syphilis and bacillary angiomatosis, should always be considered.

The histological features of KS parallel the clinical appearance of the lesion. In the nodular form a well-circumscribed, non-encapsulated nodule is seen comprising tightly packed, spindle cells. These cells form a vascular-slit pattern with extravasated erythrocytes. In the patch and plaque forms, the spindle cells are less tightly packed and form cleft-like

arrangements between collagen bundles at all levels of the dermis. Haemosiderin-laden macrophages are seen in all types. In early lesions, spindle cells may be relatively few, but a striking perivascular infiltrate of plasma cells is often present. The histological appearance of KS may be easily confused with other conditions and should be assessed by an experienced pathologist.

Serological assays confirm past or current infection with HHV8 and have little clinical utility in the diagnosis of KS. The potential relationship of HHV8 viral load to the development or progression of KS is poorly understood and requires further investigation.¹⁶

13.2.3 Management

Therapies used to treat classical KS have proven effective in both endemic and epidemic forms of the disease. The response in epidemic KS is often less durable. In the vast majority of cases of epidemic KS, control of HIV replication itself through effective antiretroviral therapy will lead to quiescence of KS disease, and often, spontaneous regression of lesions already present.

There are, however, some circumstances when consideration should be given to immediate initiation of specific KS therapy. For example, extensive cutaneous disease and lesions causing discomfort or significant cosmetic problems (such as lesions on the face, over a joint, in the oropharynx or visceral lesions). Additionally, a case could be made for immediate therapy in patients who develop initial lesions while having an undetectable viral load, and in patients with uncontrolled viral replication due to multidrug-resistant virus.

A variety of local and systemic treatment options exist for KS. There are few definitive KS treatment guidelines so management is recommended in consultation with an expert in the area.

Local treatments include radiotherapy and intralesional injections of chemotherapy. Intralesional chemotherapy is rarely used because of side-effects and the difficulties of administration. Radiotherapy to one area may be effective but needs to be reserved for urgent cases where systemic therapy is either inappropriate or has failed.¹⁷

Systemic treatment in addition to cART may be necessary. Cytotoxic chemotherapy forms the mainstay of this approach. Better efficacy and less toxicity have made liposomal doxorubicin or daunorubicin the most useful single agents used to treat HIV-related KS. If required, they are generally given at a dose of 20 mg/m² every two weeks with or without granulocyte colony stimulating factor support. The treatment tends to be well tolerated with the main side-effects related to infection secondary to neutropenia. Hypersensitivity reactions during the infusion and the hand-foot syndrome also occur, as with most liposomal compounds. Cardiomyopathy, neuropathy and alopecia are rare. There are six randomised trials using single agent liposomal anthracyclines (LA) as a comparator versus alternative combinations and the single agent had superior overall response rates of about 80% and duration of response at 30 weeks. Quality of life was also better in the LA group. In a small study, the combination of cART and LA had a superior response rate to cART alone in a highly selected series of patients.¹⁸

Paclitaxel, at a low dose of 100-135 mg/m² every two to three weeks, is associated with response rates of around 71%. In

13 Key opportunistic infections

patients who have failed other KS therapy, the response rate to paclitaxel is reduced to about 60%. Unfortunately the studies were not controlled for the use of cART. Side-effects include myelosuppression and neuropathy. Hypersensitivity is usually abrogated by the use of dexamethasone before infusion.¹⁹

Combination therapy using ABV (adriamycin, bleomycin and VP16) is generally only appropriate when the two first-line agents are not available. Interferon alpha or beta have activity against KS, but can be toxic so are essentially outmoded therapies in the Australian setting.²⁰

New and experimental therapy

A variety of promising KS-specific agents such as retinoic acid were in development before the widespread introduction of cART. Retinoic acid inhibits interleukin (IL-6) production, an important cofactor in the pathogenesis of KS. There is evidence that anti-angiogenic agents such as thalidomide, matrix metalloproteinase inhibitors and imatinib have activity against HIV-related KS.²¹

Antiviral agents such as ganciclovir and foscarnet may prevent the development of or treat KS in patients receiving them for cytomegalovirus infection.²²

Trials of many of these agents have been abandoned because of the dramatic decline in the incidence of KS, leading to difficulties in trial recruitment and therefore evaluation of the efficacy of treatment.

13.2.4 Prognosis

Studies examining both progression and survival in epidemic KS in the pre-cART era found that progression of KS is best determined by markers of KS severity, whereas survival is best determined by markers of immunodeficiency (previous and concomitant opportunistic infections and low CD4 cell count).²³ Even in the pre-cART era, fewer than 10% of AIDS patients with KS died as a direct consequence of their malignancy. In the post cART era, it is generally understood that cART itself improves the outlook of those with KS-complicating HIV infection. If KS is rapidly progressive or symptomatic, systemic chemotherapy with or followed immediately by cART maintenance therapy is indicated. The mainstay of systemic therapy is LA followed by paclitaxel as salvage. Other therapies are not often necessary but include possible interferon or one of many available angiogenesis inhibitors.

KS is not a curable condition. It tends to run a waxing and waning course reflecting the status of the immune system in the natural history of HIV disease progression and treatment. It is not uncommon for patients to require intermittent systemic treatment for years. They tend to re-respond to the same treatments although resistance to treatment can develop necessitating second and subsequent lines of therapy.

There is a paucity of randomised trial evidence evaluating the use of systemic therapies and cART. It is thought that protease inhibitor (PI)-containing regimens are not more superior to non-PI-containing regimens.¹⁶

13.2.5 Prophylaxis

All the drugs studied so far have clinically significant systemic side-effects and are generally unsuitable for long-term prophylactic use.

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13.3 Oesophageal candidiasis

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13.3.1 Epidemiology

Oesophageal candidiasis (OC) is the third most common AIDS-defining infection in Australia.¹ It accounts for 10% of all Australian AIDS cases. The incidence of OC has reduced dramatically since the introduction of combination antiretroviral therapy (cART). More than 100 cases per year were reported in 1993-1994 in Australia whereas there were approximately 20 cases per year reported in 2004-2006. Similar decreases in the incidence of OC have been reported in the USA since the introduction of cART.² Most patients with OC have CD4 cell counts less than 100 cells/ μ L. Less than 15% of cases occur in patients with CD4 cell counts above 200 cells/ μ L.³ Oral candidiasis and OC often accompany the antibiotic and corticosteroid treatment for *Pneumocystis jirovecii* pneumonia (PJP) and central nervous system (CNS) toxoplasmosis.

13.3.2 Microbiology

Candida species are ubiquitous yeasts and commensal agents found in the gastrointestinal tract, female genital tract and oropharynx. *Candida albicans* is the most common cause of OC and accounts for more than 90% of cases.³ Non-*albicans* isolates are often present with *C. albicans*. These include *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei* and *Candida glabrata*. The pathogenicity of non-*albicans* isolates in this context is unknown as most patients respond to standard doses of fluconazole.³

13.3.3 Clinical presentation

Patients with OC present with dysphagia, odynophagia or retrosternal discomfort. Characteristically the pain is diffuse, unlike the focal pain which is more common in patients with non-*Candida* oesophagitis. Weight loss is common. Oral thrush is present in up to 80% of cases of OC.⁴ The diagnosis of OC should be reassessed if oral candidiasis is not present. Fever and oral ulceration are uncommon.

13.3.4 Diagnosis

The clinical diagnosis of OC is usually made in immunodeficient patients who present with dysphagia and oral candidiasis.⁵ Endoscopy is indicated only in those patients who fail to respond to an empirical trial of fluconazole. Macroscopically, the oesophageal lesions typically comprise both

pseudomembranous and ulcerative elements. Speciation of *Candida* isolates assists in identifying non-*albicans* isolates that may be inherently resistant to fluconazole.

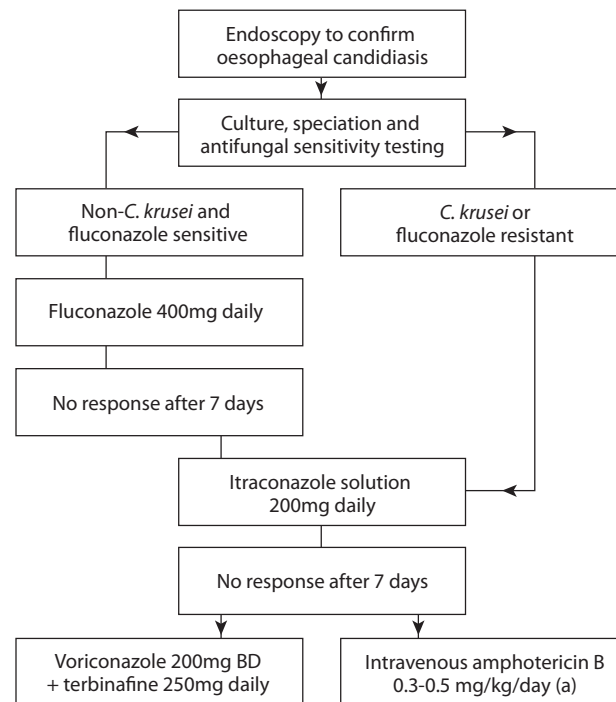
13.3.5 Management

Many agents have demonstrated similar efficacy in the management of oesophageal candidiasis. Fluconazole however remains the preferred first-line agent where resistance is not suspected.⁶ Fluconazole therapy is associated with a rapid response, is well tolerated and is associated with few drug interactions. The dose of 100-200 mg daily is continued after a loading dose of 200 mg and is continued for 14-21 days. Intravenous fluconazole may be administered in patients who cannot swallow capsules. Maintenance therapy is required until cART-induced immune reconstitution occurs. Suppressing therapy is recommended for patients with recurrent disabling episodes. Long-term suppressive therapy with fluconazole 100 mg daily is effective at reducing relapses but may be associated with the development of resistance.⁷

Itraconazole solution (200 mg daily) is regarded by some to be an alternative first-line agent⁸, however this agent has variable absorption especially in those on gastric acid blockers and is associated with significantly more drug-drug interactions than fluconazole (Table 13.3). Voriconazole has been shown to be non-inferior to fluconazole (400 mg loading dose and 200 mg daily) in the treatment of oesophageal candidiasis but remains second-line treatment as it is associated with greater toxicity.³ A new class of antifungal agents, the echinocandins, has shown similar efficacy to fluconazole in the treatment of OC. Caspofungin (50 mg per day after a loading dose), has been demonstrated to be as effective as fluconazole.⁹ However the role of this agent as first-line treatment is limited because of the need for intravenous administration.

Most patients will experience substantial clinical improvement within 72 hours of commencing fluconazole. Those patients who do not will require endoscopy to confirm the diagnosis, exclude other diagnoses and to permit fungal speciation and antifungal susceptibility testing. Up to 30% of patients may have *Candida* isolates with fluconazole minimum inhibitory concentration (MIC) $\geq 16\mu$ g/mL. These isolates are likely to

Figure 13.1 Management of oesophageal candidiasis that fails to respond to 72 hours of fluconazole 200 mg daily



Note: (a) Liposomal formulations of amphotericin may be considered as initial therapy for persons who are likely to require prolonged therapy; and for those with pre-existing renal dysfunction and continued use of concomitant nephrotoxins⁸

respond to increased doses of fluconazole¹⁰ Overall clinical response rates are expected in up to 90% of cases even if the MIC is $\geq 64\mu\text{g/mL}$. Patients with a pure growth of a non-albicans *Candida* isolate with known intrinsic fluconazole resistance (e.g. *C. krusei*) should receive alternative therapy and discontinue fluconazole (Figure 13.1).

Up to 5% of cases of HIV-associated OC do not respond to fluconazole.^{3,11} Risk factors for fluconazole resistance include a low CD4 cell count and prior use of fluconazole.¹² Failure to respond to fluconazole may be secondary to several factors apart from drug resistance. These other factors include poor absorption, drug interactions and non-adherence. Conversely these factors may lead to the development of drug resistance. Fungal factors such as increased adherence to oesophageal mucosa of non-albicans species may also play a role.¹³ Two orally administered agents have been demonstrated to be efficacious in the treatment of fluconazole refractory oesophageal candidiasis (FROC). These include itraconazole solution (200 mg daily)¹⁴ and posaconazole.¹⁵ A number of intravenously administered agents have also been demonstrated to be effective in the treatment of FROC. These include voriconazole (200 mg twice a day)¹⁶ and caspofungin (50 mg daily after a loading dose).^{17,18} Approximately 75% of patients with FROC will respond to second-line agents. Antifungal susceptibility testing may be useful in fluconazole refractory disease.

Refractory cases may be treated with intravenous amphotericin (0.3-0.5 mg/kg daily), or liposomal amphotericin (0.9-1.5 mg/kg/day).^{8,16} Some isolates demonstrate cross-resistance between voriconazole and

fluconazole, so efficacy of voriconazole as a single agent may be limited.¹⁹ Combination oral antifungal agents with documented *in vitro* synergy may also be used in this context. These include the combination of terbinafine and either itraconazole²⁰ or voriconazole.²¹ (Table 13.3.) Immune reconstitution with cART has been demonstrated to improve refractory oesophagitis.²²

13.3.6 Prophylaxis

Although fluconazole has been demonstrated to prevent OC, primary prophylaxis is not recommended.²³ Reasons for this approach include the cost of prophylaxis, the possibility of drug interactions, the potential for antifungal resistance, the low mortality associated with the disease, and the relative ease with which OC responds to treatment.²⁴

13.3.7 Discontinuing maintenance therapy

In patients who achieve CD4 cells counts >100 cells/ μL following the initiation of cART, maintenance therapy for OC can be stopped.²⁵ Cases of primary and relapsed OC have been reported in patients on cART who have achieved undetectable viral load. These patients all had CD4 cell counts below 100 cells/ μL . These infections generally occurred during the first two months of cART, but some occurred later. Therefore, patients on maintenance azole therapy for OC should continue until they have experienced CD4 cell count rises above 100 cells/ μL for at least two months.²⁶

Table 13.3 Drugs used to treat candidiasis

Drug	Daily Dose	Side-effect	Drug interactions	Comment		
Fluconazole	Induction	200mg ^(a)	Gastrointestinal (GI) intolerance Hepatitis Alopecia Dizziness Hypokalemia Headache	Fluconazole increases levels of: Atovaquone, benzodiazepines, clarithromycin, opiates, warfarin, saquinavir, phenytoin, oral hypoglycemics, rifabutin (increases risk of uveitis), cyclosporine, cisapride	Co-administration of fluconazole and cisapride may cause life-threatening arrhythmias Fluconazole can be used with protease inhibitors and non-nucleoside reverse transcriptase inhibitors without dose modification	
	Non-responders	400mg				Fluconazole levels are decreased by: Rifabutin and rifampicin
	Maintenance (prior to immune recovery)	50-100 mg ^(b)				
Itraconazole solution	200mg (loading dose of 200mg twice a day followed by 200mg/day)	Same as fluconazole but more frequent rash and GI intolerance Hypokalemia Hypertension Oedema Ventricular fibrillation Hepatitis	Itraconazole increases levels of: Terfenadine, cisapride, astemizole, triazolam, lovastatin, simvastatin, rifabutin, rifampicin, phenytoin, phenobarbital	Owing to variable absorption, potential drug interactions and potential cardiac toxicity, therapeutic drug monitoring of Itraconazole may guide management		
			Itraconazole levels are decreased by: Indinavir, saquinavir ²			
			Decreased itraconazole absorption - Antacids, sucralfate, H2 blockers, omeprazole Increased Itraconazole metabolism: Rifabutin, rifampicin, phenobarbital, carbamazepine, didanosine isoniazid and phenytoin			
Voriconazole	200mg twice a day	Hepatitis Visual disturbance	Voriconazole increases levels of: Terfenadine, astemizole, cisapride, pimozide, quinidine, ergot alkaloids ¹			
			Cyclosporine, warfarin, statins, benzodiazepines, calcium channel antagonists, sulfonylureas, vinca alkaloids ³			
			Voriconazole levels are decreased by: Rifampicin, rifabutin, carbamazepine, phenobarbital ¹			
			Phenytoin ⁴			
			Omeprazole	Increase voriconazole dose from 200mg to 400mg twice a day Omeprazole dose should be halved		

(a) May load with 200mg for one day then reduce induction dose to 100mg daily

(b) In the presence of immune recovery, maintenance therapy may be omitted to avoid the development of azole resistance

1 Co-administration is contraindicated

2 Reduced dose of second drug

3 Monitor second drug

4 Careful monitoring

Note: For therapeutic drug monitoring, a specimen should be taken two hours post-dosing and at least five days after initiation of therapy. Target level for Itraconazole is ≥ 1 ug/mL

Source: Adapted from <http://www.mosbysdrugconsult.com/DrugConsult/003556.html>.

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13.4 *Mycobacterium avium* complex

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Mycobacterium avium and *Mycobacterium intracellulare* are two non-tuberculous mycobacteria that collectively form a group of organisms known as the *Mycobacterium avium* complex (MAC). MAC is ubiquitous in the environment. Infections with other non-tuberculous mycobacteria are well recognised but occur rarely. There is a strong relationship between CD4 cell count and the presence of disseminated MAC infection, with nearly all cases occurring at a CD4 cell count of <50 cells/μL.¹ Immune reconstitution manifestations of MAC infection generally occur at higher CD4 cell counts in the setting of cART, with an incidence rate of 3.5% in individuals commencing combination antiretroviral therapy (cART) with a CD4 cell count less than 100 cells/μL.² Disseminated MAC infection has become rare since the introduction of cART.³

13.4.1 Clinical presentation

Immunodeficient persons

The most common manifestation of MAC infection in people with HIV infection is that of disseminated disease. The typical clinical scenario is a markedly immunodeficient person (CD4 cell count <50 cells/μL) with fevers, drenching night sweats, weight loss, anaemia (or pancytopenia), diarrhoea, lymphadenopathy and hepatosplenomegaly with abnormal liver function tests (particularly an elevation of alkaline phosphatase). Intra-abdominal lymphadenopathy may occur and cause significant abdominal pain. Although uncommon, pulmonary involvement can present with a persistent dry cough, fever and loss of weight.

Immune reconstitution features

Restoration of cell-mediated immunity against MAC was recognised after zidovudine monotherapy for HIV,⁴ although clinical reports of immune reconstitution have been more frequent following the introduction of cART.⁵⁻⁹ There are three main clinical presentations of immune restoration disease (IRD) with MAC: peripheral lymphadenitis and fever; intra-abdominal disease (abdominal lymphadenopathy, chylous ascites, peritonitis, abscess and lesions or masses in the bowel); and lung disease (mediastinal lymphadenopathy, infiltrates, cavitory lesions and pulmonary nodules).² The lymphadenopathy may be peripherally located, with sinus formation and chronic percutaneous drainage of purulent material, or intra-abdominal (para-aortic and mesenteric), which is often associated with abdominal pain. A peripheral blood leukocytosis may be present. Biopsy specimens of lymph nodes typically reveal granulomata and acid-fast bacilli may be detected. Osteomyelitis, bursitis and skin nodules have also been reported. To avoid this syndrome it is important to exclude and treat MAC infection in a person with severe immunodeficiency and symptoms that are potentially related to disseminated MAC infection before the commencement of cART.

In the event of immune reconstitution MAC lymphadenitis, treatment should consist of standard therapy for MAC infection. Up to 20% of patients with MAC IRD fail to respond to up to two years of MAC therapy and experience persistent

or relapsing disease. These patients are more likely to have abdominal lymphadenopathy and less likely to have significant rises in CD4 cell counts in response to cART.¹⁰ In severe cases, a short course of prednisone may be used², but some people relapse on tapering the dose. In rare cases, surgical drainage, lymphadenectomy or the temporary interruption of cART may be required.¹¹

13.4.2 Diagnosis

The diagnosis of MAC infection can be made by culture of blood or histological examination and culture of bone marrow, enlarged lymph nodes or liver. Although the presence of MAC in stool culture has a 60% predictive value for the subsequent development of disseminated disease,¹² it is not diagnostic of disseminated disease. A presumptive diagnosis, pending the results of appropriate investigations, may be made in the typical clinical context (a person with a CD4 cell count <50 cells/μL, not taking MAC prophylaxis, with fevers, night sweats, weight loss and anaemia). Such a presumptive diagnosis may only be confirmed by the presence of MAC bacteriaemia or bone marrow culture in approximately 20% of cases.¹³ It is important to consider other causes of the symptom complex as multiple pathological processes can co-exist and mimic one another.

13.4.3 Management

The usual regimen for the treatment of MAC is clarithromycin 500 mg twice a day and ethambutol 15 mg/kg/day with or without rifabutin 300 mg daily. Treatment with a three drug regimen was associated with reduced mortality compared with two drugs in one study.^{14,15} If clarithromycin is not tolerated, then azithromycin 500 mg daily may be substituted. If clarithromycin is not used, then the dose of rifabutin should be increased to 450 mg daily. The dose of clarithromycin should not exceed 500 mg twice daily, as excess mortality has been observed at doses of 1000 mg twice daily.¹⁶ Alternative agents, including amikacin, ciprofloxacin or clofazimine, should only be used if there is no clinical response to initial therapy after six weeks. Antimicrobial-sensitivity testing is not routinely undertaken, but should be performed if a macrolide antibiotic (azithromycin or clarithromycin) has been used for prophylaxis, and breakthrough MAC infection has occurred. Some authors have recommended that macrolide resistance be routinely assessed as two of nine (22%) isolates in one small US study were found to be macrolide resistant despite little or no previous macrolide exposure.¹⁷

If cART is used in combination with MAC treatment, consideration of drug interactions between antiretroviral and antimycobacterial agents is required (Table 13.4). Where possible, the institution of cART should be delayed until clinical resolution to avoid the immune reconstitution syndrome, although there are no data to support this recommendation.

MAC therapy needs to be lifelong unless cART-associated immune reconstitution occurs. Maintenance therapy may be ceased when the viral load has been suppressed and the CD4 cell count is >100 cells/μL after treatment for 12 months.¹⁸

Table 13.4 Doses of antimycobacterial agents when combined with antiretroviral therapy

Antiretroviral	Antiretroviral dose with rifabutin	Rifabutin dose (standard 300 mg daily)	Antiretroviral dose with rifampicin	Rifampicin dose (standard 600mg daily)	Antiretroviral dose with clarithromycin	Clarithromycin dose (standard 500mg bd)
atazanavir/ritonavir (ATV/RTV)	Standard dose	150 mg on alternate days or 300 mg 3 times/week	Contraindicated – significant decrease in ATV levels	Not used	Standard dose	Use with caution
darunavir/ritonavir (DRV/RTV)	Standard dose	150 mg on alternate days or 300 mg 3 times/week	No data	No data	Standard dose	Reduce dose with renal failure
fosamprenavir/ritonavir (FPV/RTV)	Standard dose	150 mg on alternate days or 300 mg 3 times/week	Contraindicated – significant decrease in FPV levels	Not used	Standard dose	Consider dose reduction with renal failure
indinavir/ritonavir (IDV/RTV)	Standard dose	150 mg on alternate days or 300 mg 3 times/week	Contraindicated – significant decrease in IDV levels	Not used	Standard dose	Standard dose
lopinavir/ritonavir (LPV/RTV)	400 mg/100 mg bd	150 mg on alternate days or 300 mg 3 times/week	4 tablets bd	Standard dose	Standard dose	Reduce dose with renal failure
saquinavir/ritonavir (SQV/RTV)	Standard dose	150 mg on alternate days or 300 mg 3 times/week	400 mg/400 mg bd (1000mg/100 mg bd causes excess hepatitis)	Standard dose	400 mg/400 mg bd	Reduce dose with renal failure
tipranavir/ritonavir (TPV/RTV)	Standard dose	150 mg on alternate days or 300 mg 3 times/week	No data	No data	Standard dose	Reduce dose with renal failure
raltegravir (RAL)	Standard dose	Standard dose	Clinically meaningful reduction in concentration of 40-61%	Standard dose	No data	No data
maraviroc	Standard dose	Standard dose	600 mg bd (C_{min} reduced by 78%)	Standard dose	No data	No data
delavirdine (DLV)	Contraindicated – significant decrease in DLV levels	Increase rifabutin AUC 200% - toxicity Not used	Contraindicated – significant decrease in DLV levels	Not used	Standard dose	Adjust dose in renal failure
efavirenz (EFV)	Standard dose	450-600 mg/day	Increase EFV to 600-800mg/day	Standard	Not recommended (39% decrease in clarithromycin AUC)	Standard dose, monitor closely, including for rash
etravirine	Standard dose (C_{min} reduced 45%)	Standard dose	Contraindicated	Not used	Standard dose	40% reduction in AUC clarithromycin and 21% increase in inactive metabolite Consider alternative
nevirapine (NVP)	Standard dose	Standard dose	use alternative NNRTI ¹ (20-55% decrease in NVP levels) or increase to 300 mg bd	Standard dose	Standard dose (30% decrease AUC clarithromycin – monitor closely)	Standard dose

¹ With therapeutic drug monitoring and increased antiretroviral dosage, it may be possible to use these combinations if other antiretroviral options are not feasible
AUC = area under the curve; bd = twice daily; C_{min} = trough serum concentration

Note: All dosage alterations are modifications of daily treatment regimens.

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In all cases where HIV and mycobacterial infections are treated simultaneously, a careful review of potential drug interactions should be undertaken, with reference to a pharmacist or reliable drug-interaction website (such as www.hiv-druginteractions.org).

The degree of interaction varies, with some combinations being contraindicated and others requiring a dose modification of one or both agents. Ethambutol, pyrazinamide and isoniazid do not have significant pharmacokinetic interactions with current antiretroviral agents, although similar, synergistic or additive toxicities (e.g. peripheral neuropathy, hepatic toxicity or drug reactions) may occur. Generally, rifampicin and ritonavir should be avoided, if possible, when treating mycobacterial disease and HIV simultaneously, as both agents have significant cytochrome p450 mediated drug interactions.

If a histological diagnosis of mycobacterial infection is made and the results of cultures are unavailable, empirical therapy should cover both MAC and *M. tuberculosis* infections. In the circumstance of probable MAC infection, isoniazid 300 mg daily and pyridoxine 50 mg daily (to prevent peripheral neuropathy) should be added to the standard MAC regimen of rifabutin, ethambutol and clarithromycin until the identification of mycobacterial species is available. Isoniazid and pyridoxine should be ceased as soon as MAC has been identified. If *M. tuberculosis* is the most likely diagnosis then therapy should be targeted at this infection, although clarithromycin should be added to increase the spectrum of activity to include MAC until identification of the organism is available. If *M. tuberculosis* may be the aetiological agent and samples of sputum are positive on acid-fast bacilli smear¹⁹ or there is respiratory involvement, then respiratory isolation of the patient is required until organism identification is complete, or the sputa are negative on the acid-fast bacilli smear, or two weeks of effective therapy has been completed.

The side-effects of commonly used antimycobacterial agents are listed in Table 13.5. Regular clinical review should be undertaken while on therapy with at least monthly clinical visits initially. Liver function tests and haematological parameters should be monitored. Ophthalmological complications are extremely rare with a lower dose of ethambutol (15 mg/kg/day) so regular ophthalmological review is not warranted. However, patients should be warned of potential ophthalmological side-effects from ethambutol and to report these as soon as they occur.

13.4.4 Prognosis

The prognosis of untreated MAC infection therapy is poor. Combination antimicrobial therapy against MAC improves survival and cART provides an additional survival benefit.^{20,21}

13.4.5 Prophylaxis

Primary prophylaxis

Primary prophylaxis against MAC has been shown to reduce the incidence of MAC in patients with advanced immunodeficiency (CD4 cell count <50 cells/ μ L) and probably improves survival.²²⁻²⁴ Three agents have been studied. Azithromycin (1200 mg orally once weekly) is the best tolerated agent with the fewest drug interactions. Clarithromycin (500 mg orally twice daily) or rifabutin (300 mg orally daily) are alternatives. Both of these medications interact with antiretroviral drugs and other agents and dose adjustment or alteration of the cART regimen may be required (Table 13.4). Combination therapy with these agents is more efficacious, but is associated with greater toxicity.²³

Before instituting prophylaxis for MAC, it is important to exclude active MAC or *M. tuberculosis* infection. Prophylaxis with a single agent during active MAC or *M. tuberculosis* infection will lead to antimicrobial resistance.

Table 13.5 Side-effects of commonly used antimycobacterial agents

Drug	Side-effects
Amikacin	Nephrotoxicity, ototoxicity, neuromuscular blockade
Azithromycin	Diarrhoea, nausea, abdominal pain, vomiting, ototoxicity, abnormal liver function tests, central nervous system toxicity, leukopenia, erythema multiforme
Ciprofloxacin	Anorexia, nausea, diarrhoea, vomiting, abdominal pain, headache, restlessness, insomnia, psychosis, seizures, rash, arthralgia, intestinal nephritis, tendon rupture.
Clarithromycin	Diarrhoea, nausea, taste change, abdominal pain, headache, taste perversion, abnormal liver function tests, rash
Clofazimine	Skin pigmentation, anorexia, nausea, skin dryness, pruritus, abdominal pain, conjunctival irritation, retinal crystal deposition
Ethambutol	Optic neuritis (usually at higher dose i.e. 25 mg/kg/day), reduced visual acuity, restricted visual fields, scotomata, loss of colour discrimination, peripheral neuropathy, headache, rash, arthralgia, hyperuricaemia, gastrointestinal side-effects
Isoniazid	Peripheral neuropathy (prevent with co-administration of pyridoxine), allergy, lymphadenopathy and vasculitis, hepatitis (greater risk with increasing age, alcohol consumption and chronic liver disease), antinuclear antibody, blood dyscrasia, liver failure, other neurological manifestations (optic neuritis, encephalopathy, convulsions, psychosis) fever
Pyrazinamide	Arthralgia, hyperuricaemia, hepatitis, gastric irritation, photosensitivity, rash, fever, pruritus, thrombocytopenia, skin discolouration, side roblastic anaemia
Rifabutin	Leukopenia, nausea, vomiting, diarrhoea, polyarthralgia, uveitis, rash, discolouration of urine, tears, sweat, saliva, stool and skin, neutropenia, febrile illness, hepatitis, haemolysis, myositis
Rifampicin	Anorexia, nausea, vomiting, diarrhoea, rash, febrile reaction, hepatitis, abnormal liver function tests, discolouration of urine, tears, sweat, saliva, stool and skin, haemolysis, febrile illness

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Blood specifically cultured for MAC, chest radiograph and full investigation of fevers, weight loss, night sweats, anaemia, abnormal liver function tests, hepatosplenomegaly, respiratory symptoms or unexplained lymphadenopathy is required. A stool culture for MAC should be undertaken in persons with diarrhoea to exclude MAC enteritis before commencing prophylaxis.

Some authors have suggested that primary prophylaxis for disseminated MAC is not required for those who commence cART with CD4 cell counts below 50 cells/ μ L, because the risk of disseminated MAC is low, and patients can be followed closely for the signs of disseminated MAC infection.²⁵

In the event that MAC infection develops despite macrolide prophylaxis, antimicrobial sensitivity testing of MAC to macrolides is warranted, as macrolide resistance is detected in up to 30% of breakthrough isolates after clarithromycin prophylaxis²⁶ and 11% after azithromycin prophylaxis.²³

Secondary prophylaxis

Secondary prophylaxis involves the life-long continuation of therapy for MAC infection unless cART-induced immune reconstitution occurs. As with other mycobacterial infections, a maintenance phase of treatment with two drugs is recommended. Rifabutin is most commonly eliminated, as it is associated with significant drug interactions and uveitis. A strategy of twelve months of MAC treatment followed by cessation of treatment if the CD4 cell count is greater than 100/ μ L while on cART appears to be safe for people that achieve this degree of immune restoration.¹⁸

13.4.6 Discontinuing prophylaxis

Primary prophylaxis against MAC may be ceased with cART-associated immune reconstitution when the CD4 cell count is >100 cells/ μ L for three months in the setting of adequate viral suppression²⁷⁻²⁹ and after twelve months of MAC treatment in those receiving maintenance treatment (secondary prophylaxis).¹⁸

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13.5 *Mycobacterium tuberculosis*

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Mycobacterium tuberculosis is a transmissible agent that may present as a reactivation of latent disease in an immunocompromised person, or as primary infection after person-to-person transmission at any stage of HIV infection. World-wide, tuberculosis (TB) is the cause of death in 11% of all people with HIV infection. In Australia, *M. tuberculosis* infection has been an uncommon AIDS-defining condition, yet the proportion of cases of TB as an AIDS-defining infection increased from 0.4% to 2.3% to 4.6% between the periods 1993-1995, 1996-2000 and 2003-2005.^{1,2} In Australia, the most common risk factor for TB is originating from a high prevalence country. The risk of reactivation of TB in people with HIV is approximately 14% during the two years following exposure to *M. tuberculosis*, in contrast to the risk in HIV-negative persons of 10% in a lifetime.³ The development of TB in a person with HIV may accelerate HIV disease progression.⁴ Combination antiretroviral therapy (cART) and isoniazid preventive therapy have been shown to decrease the incidence of TB in HIV populations.⁵⁻⁷

13.5.1 Clinical presentation

M. tuberculosis infection may present with pulmonary disease or extrapulmonary disease at any CD4 cell count. The typical presentation includes fever, weight loss and constitutional symptoms with associated cough and chest pain. Pulmonary disease is present in most patients infected with both HIV and *M. tuberculosis*. Extrapulmonary disease (including involvement of lymph nodes, central nervous system and with bacteraemia) is common in the setting of HIV infection, especially with advanced immunodeficiency.⁸ With immune reconstitution associated with cART, disease localised to the lymph nodes with or without fistula formation has been recognised.^{9,10}

13.5.2 Diagnosis

The radiological features of TB in people with HIV with CD4 cell counts >200 cells/μL are similar to the general population, with a predominance of upper lobe abnormalities, cavitary disease and the presence of pleural effusions.⁸ In immunodeficient persons (CD4 cell count <200 cells/μL), mediastinal lymphadenopathy, non-cavitary disease and extra-pulmonary disease are more common.¹¹ Up to 10% of patients will have a normal chest x-ray.¹¹

The diagnosis of *M. tuberculosis* infection is made by the usual means: sputum microscopy and culture; chest radiograph; histological examination and culture of bone marrow, enlarged lymph nodes or liver. Patients with a relatively intact immune system will have a more granulomatous typical histological picture; in advanced immunodeficiency, granulomas are poorly formed, a picture associated with a lack of CD4 cell help. Tests involving nucleic acid amplification (NAA) have enabled more rapid diagnosis of *M. tuberculosis* infection in sputum specimens. However, the positive predictive value of these tests is reduced in smear-negative sputum samples. The specificity of NAA tests is high for other body fluids, for example for TB meningitis and pleural TB, but sensitivity is poor.

The tuberculin skin test (TST) is more likely to be positive in people with HIV with high CD4 cell counts than in those with significant immunodeficiency.⁸ However, in those with advanced immunodeficiency the yield of mycobacterial culture from extrapulmonary sites (such as lymph nodes and pleural fluid) is high, making the TST much less important in diagnostic terms. The cut-off for a positive TST in the HIV population is 5 mm of induration rather than the 10 mm cut-off used in the general population,

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as cutaneous measures of delayed-type hypersensitivity are reduced in people with HIV infection. People without HIV with a positive TST have a 5-10% life-time risk of developing clinical disease; in contrast patients with HIV with a positive TST have a 7-10% annual risk.¹² Alternatives to TST include the Interferon-gamma release assays (e.g. QuantiFERON-TB Gold assay). These tests are approved for the diagnosis of latent TB infection however data on their utility in the setting of HIV are only just emerging. In one of the largest studies in people with HIV, overall concordance between QuantiFERON-TB and TST was high, but agreement among subjects with positive tests by either modality was low.¹³ In another study, indeterminate results occurred in subjects with CD4 cell counts <200 cells/ μ L and the concordance between TST and QuantiFERON-TB Gold was poor (kappa 0.38). However the QuantiFERON-TB Gold results were more likely to be associated with risk factors for latent tuberculosis than TST, and may be more useful than TST in those with HIV infection.¹⁴ The place of QuantiFERON-TB as part of the routine assessment of patients with HIV infection needs to be further defined. Another assay, the enzyme-linked immunospot (ELISPOT) assay, which detects interferon (IFN)-gamma secreted by T cells exposed to TB antigens, has been evaluated for ability to detect TB antigen-specific immune responses in HIV-1 patients and has been found to be independent of CD4 cell counts. A combination of TB antigen-specific IFN-gamma responses and CD4 cell counts has the potential to distinguish active tuberculosis from latent infection.¹⁵ The recently released guidelines of the US Department of Health and Human Services (DHHS) recommended retesting for latent TB in those with a CD4 cell count less than 200 cells/ μ L once their CD4 cell count reaches 200 cells/ μ L following the commencement of cART.¹⁶

13.5.3 Management

The management of *M. tuberculosis* infection in the setting of HIV infection follows the general principles of TB-treatment in the general population. It requires systemic combination antimicrobial therapy and directly observed therapy (DOT) is preferred. The aims of DOT include reducing the risk of treatment failure, emergence of drug resistance and risk of disease transmission. There are additional layers of complexity with regard to the treatment of TB-HIV co-infection including:

- controversy over the optimal duration of therapy for TB especially in patients with advanced immunodeficiency
- significant rates of hepatotoxicity associated with TB therapy, potentially compounded by high rates of viral hepatitis co-infection
- significant drug-drug interactions between TB treatments and cART
- TB immune restoration disease
- the high pill burden and need for adherence to TB drugs and cART.

The usual regimen for fully sensitive isolates is a standard four-drug regimen of a rifamycin with isoniazid, pyrazinamide and ethambutol (with pyridoxine) (See Table 13.5 for side-effects of antimycobacterial agents). Dosing should occur at least three times a week, as less frequent rifamycin therapy was associated with acquired rifamycin resistance.¹⁶ After daily therapy with four drugs for two months, ethambutol and pyrazinamide may be ceased, and isoniazid and the rifamycin (rifabutin or rifampicin) continued daily or three times per week for a further four months. The replacement of rifampicin by rifabutin for first-line treatment of TB is not supported by current evidence due to a paucity of randomised, controlled studies in people

with HIV.¹⁷ However it is an attractive option because of drug-drug interactions with rifampicin and toxicity.¹⁸ If cART is used in combination with the above regimen, then consideration of drug interactions between antiretroviral agents and the rifamycin (a potent enzyme inducer) is paramount (refer to <http://www.hiv-druginteractions.org>). Rifampicin is the most potent inducer of cytochrome P450 3A4 enzymes, and when used with protease inhibitor (PI) therapy, subtherapeutic exposures to many of the PIs will occur e.g. atazanavir¹⁹ or ritonavir boosted atazanavir²⁰ and ritonavir-boosted saquinavir at currently used doses²¹ but may be adequate with higher doses of ritonavir.²² Treatment with an efavirenz-based regimen with rifampicin is effective.^{23,24} A recent overview on the management of cART and TB drug interaction has been published.²⁵ Although, nucleoside reverse transcriptase inhibitor combinations have less potential for drug-drug interactions when co-administered with TB therapy²⁶, the lower HIV response rates make such therapy a less preferred option. The integrase inhibitor, raltegravir, may also be useful in this setting as it is not metabolised through the P450 enzyme system, although clinical outcome data in TB are lacking.

13.5.4 Monitoring response to treatment and duration of treatment

Patients should be monitored closely, in order to ensure they are making the appropriate response to treatment with minimal drug-related toxicity. Patients should have clinical, microbiological (at least monthly sputum samples until two consecutive specimens are negative in those with pulmonary TB), and safety blood (especially liver function) assessment on a regular basis. Further radiological assessments during the course of treatment are often undertaken. Severe liver toxicity occurs in the first two months of therapy in 10% of patients.²⁷ Alternative regimens in patients who already have deranged liver function or who develop significantly abnormal liver function during treatment (transaminases more than three times the upper limit of normal) are described in the DHHS guidelines.¹⁶

The optimal duration of therapy depends on the site of disease and response to treatment. In patients with pulmonary disease, short-course therapy for six months is adequate, unless there is cavitation or persistent culture-positive sputum after two months of therapy, when therapy should be extended to nine months. Patients with miliary, meningeal or skeletal disease should be treated for at least 12 months. Other patients with extrapulmonary disease may receive short-course therapy. Concerns about relapse rates after short-course therapy have come from trials in countries with a high prevalence of TB^{28,29} and re-infection may be the explanation for this phenomenon.³⁰ As the prevalence of TB in Australia is low, short-course regimens are likely to be suitable.

Drug-resistant isolates of *M. tuberculosis* are common in many parts of the world, and multidrug-resistant TB should be considered in persons who are likely to have acquired the infection outside Australia and New Zealand, and in persons who have been previously treated for *M. tuberculosis* and have experienced a relapse. In India, 50% isolates are resistant to first-line drugs and 33% are resistant to second-line drugs in patients with HIV.³¹ In Thailand, the prevalence of drug-resistant TB has declined from 48% to 8% with the use of cART.³² Survival is significantly reduced in those with multidrug-resistant TB.³² If

antimicrobial-susceptibility testing reveals resistance to any of the drugs in the standard initial regimen, expert consultation is essential, but usually involves long courses of over 18 months of quadruple therapy which includes an aminoglycoside, a respiratory quinolone and one of a number of other compounds e.g. para-aminosalicylic acid (PAS), cycloserine, ethionamide.^{16,26} The duration of therapy and the number of drugs may need to be extended. Concerns about extensively drug-resistant TB (TB resistant to isoniazid, rifampicin and three of six second-line agents) have recently emerged, particularly in people with HIV infection.^{33,34}

In cases of marked immunodeficiency (CD4 cell count <50 cells/ μ L) where MAC is in the differential diagnosis, a histological diagnosis of mycobacterial infection is made and, in the absence of results of cultures, empirical therapy should cover both MAC and *M. tuberculosis* infections. In the circumstance of probable *M. tuberculosis* infection, clarithromycin should be added to the standard four-drug regimen until the identification of the mycobacterial species is available (either by NAA or culture) (See Section 13.4).

Adherence to TB control guidelines is important, as nosocomial transmission of TB has been identified in a low prevalence country in an outpatient setting.³⁵ Those with TB and HIV co-infection are not more infectious than people with TB alone.³⁶

There may be paradoxical reactions with worsening of pulmonary and extrapulmonary disease in people with HIV and *M. tuberculosis* co-infection following treatment of TB alone. However, these reactions may be more frequent and severe in persons commencing cART simultaneously with antimycobacterial therapy. In one study, these reactions occurred in 2% of historical controls without HIV infection, 7-12% of people with HIV treated with anti-TB therapy alone, and 36% of people with HIV treated with both cART and anti-TB therapy.^{9,37} Persons with both pulmonary and extrapulmonary disease at diagnosis are more likely to experience paradoxical reactions.^{16,26,38} Such reactions are probably related to immune restoration and are considered to be immune restoration disease (IRD). The most common clinical manifestations of TB-IRD from one series were fever (64%), new or worsening adenopathy (52%) and worsening pulmonary infiltrates (40%). Half the patients were hospitalised for a median of seven days, and the median duration of events was 60 days (range 11-442).³⁹ Hepatic involvement in TB-IRD has also been described.⁹ While the patient is on therapy, new lesions may become clinically apparent. These reactions may respond to non-steroidal, anti-inflammatory drugs or a brief course of prednisolone in severe cases. However, the best management for TB-IRD is not yet known, especially as the pathogenesis is still poorly understood. Failure of antimycobacterial therapy, non-adherence and drug-resistance need to be considered before adding corticosteroid therapy. Other diagnostic possibilities need to be excluded in cases with new disease manifestations.

cART is usually deferred until at least two months after commencement of *M. tuberculosis* treatment, as inflammatory reactions (TB-IRD), significant drug-drug interactions, and overlapping toxicities may occur during simultaneous therapy against HIV and *M. tuberculosis* infections. However, the risk of HIV-related disease progression needs to be considered on a case-by-case basis. One approach is to commence cART and anti-TB therapy simultaneously in persons with CD4 cell

counts <100 cells/ μ L and to delay cART during the initial two months of antimycobacterial therapy when CD4 cell counts are >100cells/ μ L.⁴⁰ Deferral of cART until completion of TB therapy may be suitable in the absence of other co-morbidities and less significant immunodeficiency. Overall, the optimum time to initiate cART is yet to be defined, with more recent studies suggesting superior outcomes with earlier initiation of antiretroviral therapy.⁹

13.5.5 Prognosis

The degree of immunodeficiency is the most important predictor of survival in people with HIV with *M. tuberculosis*. Anergy on delayed-type hypersensitivity skin testing, prior HIV-related conditions and a low CD4 cell count are independently associated with poorer survival.⁴¹⁻⁴³ Response rates to therapy for TB infection in people with HIV are similar to those in persons without HIV infection. The one-year survival for persons with HIV-TB co-infection improved from 58% in 1991 to 83% in 1997 in the USA.⁴⁴ In the resource-limited setting, a large reduction in the odds of death for patients receiving cART before or during TB treatment (odds ratio, 0.2; 95% confidence interval, 0.1-0.5) was noted.⁴⁵ Antiretroviral therapy is also associated with a substantial reduction in mortality during TB treatment for patients with HIV and TB co-infection in the developed world.^{46,47}

13.5.6 Prophylaxis

Secondary prophylaxis following successful treatment of disease is unnecessary, however, reinfection can occur. Treatment of latent *M. tuberculosis* infection without any overt manifestation of disease has become a more controversial area, and immune restoration with cART is an important strategy in maintaining latency. Currently, guidelines suggest primary prophylaxis should be offered to prevent the development of active disease, which occurs at a rate of 7% per year in people with HIV with latent TB.⁴⁸ Persons at risk are those with a positive Mantoux test with a reaction at least 5 mm in diameter or known exposure to a person with infectious *M. tuberculosis* disease. There is no benefit in providing prophylaxis to anergic persons unless they have had contact with a person with active TB.⁴⁹

Before instituting prophylaxis for *M. tuberculosis*, it is important to exclude active *M. tuberculosis* disease. Prophylaxis with a single agent during active *M. tuberculosis* replication will lead to drug resistance. Isoniazid with pyridoxine given daily for nine to 12 months is effective. Although daily rifabutin and pyrazinamide administered for two months is effective, the risk of severe hepatotoxicity is significantly higher and is not currently recommended.⁵⁰⁻⁵³

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13.6 Toxoplasmosis

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Latent infection with *Toxoplasma gondii* is relatively common in the Australian population with 25-45% of obstetric populations being seropositive.¹⁻³ This is similar to the prevalence reported in the USA but significantly lower than that seen in Europe. Infection with *T. gondii* is usually acquired from the ingestion of under-cooked meat (rather than contact with cats), which results in latent infection in immunocompetent individuals. If cellular immune response mechanisms become impaired then dissemination of infection may occur. There is a strong relationship between CD4 cell count and clinical syndromes of toxoplasmosis, with most infections in patients with HIV infection occurring when the CD4 cell count is less than 100 cells/ μ L.⁴ Since the introduction of combination antiretroviral therapy (cART), diagnoses of toxoplasmosis, like other opportunistic infections, have significantly declined.^{5,6}

13.6.1 Clinical presentation

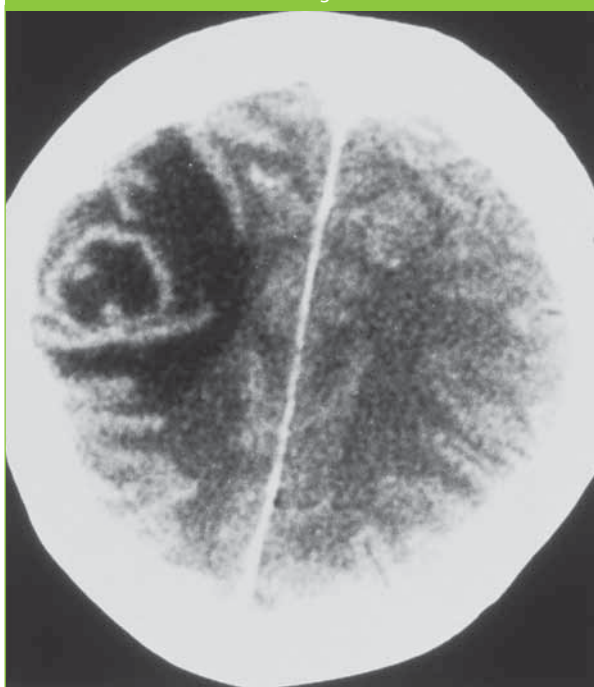
The most common manifestation of toxoplasmosis is encephalitis, which usually manifests as single or multiple intracerebral abscesses in association with fevers, headaches and a variety of focal neurological abnormalities that often progress over several weeks. Other clinical manifestations include retinitis, pneumonitis and disseminated infection.^{7,8}

Clinical reports of cerebral toxoplasmosis occurring after the initiation of cART are uncommon, with no clear differences in the clinical presentation prior to or following cART. At least some cases of toxoplasmosis have occurred in patients with a CD4 cell count of less than 200 cells/ μ L.^{9,10}

13.6.2 Diagnosis

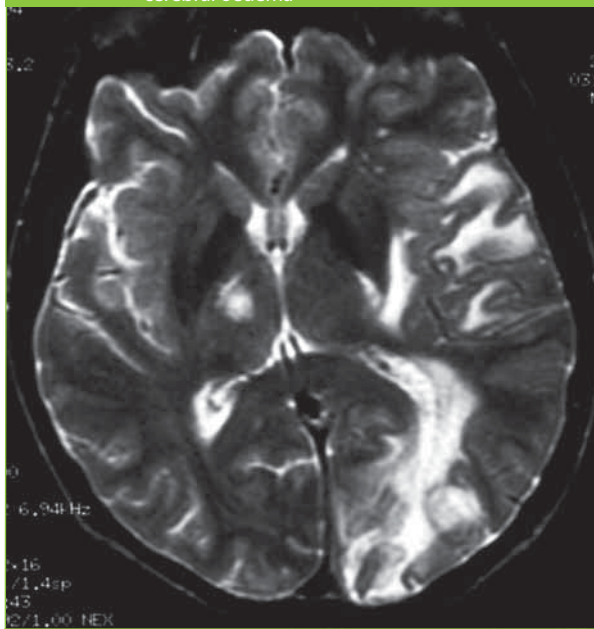
A definitive diagnosis of cerebral toxoplasmosis can only be made by the histological examination of brain tissue. However, a presumptive diagnosis of cerebral toxoplasmosis can be made by neuroimaging with either a computed tomography (CT) or magnetic resonance imaging (MRI) scan.¹¹ The lesions are usually multiple with ring enhancement and are associated with cerebral oedema. More lesions are detected by MRI scanning compared with CT scanning. (Images 13.3 and 13.4) Although a MRI or CT scan may have typical lesions, these imaging modalities, even if using diffusion-weighted imaging, are unable to reliably differentiate between toxoplasmosis and cerebral lymphoma, the principal differential diagnosis.¹² Typically, patients presenting with such MRI abnormalities and a consistent clinical syndrome are treated presumptively with therapy for toxoplasmosis for two to three weeks, at which time re-imaging is performed. If there is no improvement, brain biopsy should be considered. However, if the following features are present, early biopsy should be considered: the presence of a non-enhancing lesion, atypical features on MRI or in the clinical presentation, neurological deterioration while on treatment for toxoplasmosis, good adherence to sulphur-based *Pneumocystis jirovecii* prophylaxis or the serum toxoplasmosis IgG is negative.¹³

Image 13.3 Computerised axial tomograph scan of toxoplasmosis showing contrast-enhancing mass with surrounding cerebral oedema



Source: Jones PD, Beaman MH, Brew BJ. HIV and opportunistic neurological infections. In: Stewart G, editor. Managing HIV. Sydney: Australasian Medical Publishing Company, 1997:81. Used with permission.

Image 13.4 T2-weighted image of a patient with central nervous system toxoplasmosis, showing three space occupying lesions surrounded by cerebral oedema



Source: Bruce J Brew, St Vincent's Hospital, Sydney, NSW. Used with permission.

The main differential diagnosis for cerebral toxoplasmosis is primary central nervous system lymphoma (see Chapters 17 and 18). The diagnosis of toxoplasma retinitis needs to be distinguished from that of cytomegalovirus retinitis, and is based on its typical appearance as well as the appearances of fluorescein angiography.⁸

The diagnosis of toxoplasmosis occurring in other organ systems is dependent on the demonstration of *T. gondii* trophozoites in blood or appropriate tissue specimens. Most patients with toxoplasmosis will have *Toxoplasma* antibodies; however, relatively few patients will demonstrate a rise in specific immunoglobulin G (IgG) antibody titres. Less than 5% of patients with toxoplasmosis will be *Toxoplasma* IgG negative.¹⁴ Serological testing for *Toxoplasma* early in the course of HIV infection is recommended.

13.6.3 Management

The treatment of cerebral toxoplasmosis requires combination therapy with either sulphadiazine 4-6 g/day or clindamycin 24 g/day in four divided doses, and pyrimethamine 100-200 mg loading dose followed by 50-75 mg daily.^{15,16} If sulphadiazine is used then folinic acid 20-25 mg daily should be given to prevent haematological toxicity. If there is significant cerebral oedema then glucocorticoids may be used although there are few data to support their use. If seizures occur secondary to toxoplasmosis, an anticonvulsant is recommended during initial therapy. If patients are unable to tolerate sulphadiazine or clindamycin alternative therapies (for which there are only limited and non-comparative data) include azithromycin 1-1.5 g/day, atovoquone 3 g/day, dapsone 50-100 mg/day or clarithromycin 2 g/day, all in combination with pyrimethamine. Induction therapy should be for six to eight weeks with repeat imaging recommended by the end of the second to third week of therapy, and then again two to four weeks later.

The side-effects of commonly used antimicrobials are listed in Table 13.6. Regular clinical review during therapy is recommended with monitoring of haematological and biochemical parameters.

Table 13.6 Side-effects of commonly used agents for toxoplasmosis

Sulphadiazine	Fever, rash (including Stevens-Johnson syndrome), anaemia, haemolysis, leukopenia and thrombocytopenia, crystalluria and renal impairment, anorexia, abdominal pain, nausea, vomiting and diarrhoea, headaches
Clindamycin	Anorexia, nausea, vomiting and diarrhoea
Atovoquone	Rash
Pyrimethamine	Rash, anorexia, nausea, and diarrhoea.
Macrolides	Anorexia, abdominal pain, nausea, vomiting, and diarrhoea Rash, abnormal liver function tests
Dapsone	Rash (including Stevens-Johnson syndrome), haemolytic anaemia (need to exclude glucose-6-phosphate-dehydrogenase deficiency)

13.6.4 Prognosis

The prognosis from untreated cerebral toxoplasmosis is very poor. In the pre-cART era, trials of combination therapy demonstrated clinical response rates of about 67%. Toxoplasmosis in the cART era is uncommon but has a significantly better survival than in the pre-cART era. The five-year survival for patients with toxoplasmosis during the cART era is 78% compared with 7% in the pre-cART period.¹⁷

13.6.5 Prophylaxis

Primary prophylaxis

Primary prophylaxis against *T. gondii* infection is recommended in patients with a CD4 cell count of less than 200 cells/ μ L. Several agents have been studied. Trimethoprim-sulphamethoxazole (cotrimoxazole) for combined *Toxoplasma* and *Pneumocystis jirovecii* pneumonia prophylaxis is the treatment of choice. The recommended dose is trimethoprim 160 mg and sulphamethoxazole 800 mg given daily or a double dose (two tablets) twice weekly. An alternative regimen is dapsone 50 mg/day plus pyrimethamine 50-100 mg/day.

Secondary prophylaxis

Secondary prophylaxis or maintenance therapy is essential after initial therapy. A combination of sulphadiazine 2g/day plus pyrimethamine 25 mg/day is more effective at preventing relapse than clindamycin 1.2 g/day plus pyrimethamine 25 mg/day.

Discontinuing prophylaxis

Discontinuing primary prophylaxis appears to be safe if there is a sustained response to cART with a CD4 cell count above 200 cells/mL for at least three months, and an HIV viral load of <500 copies/mL. There is less evidence for discontinuing secondary prophylaxis, however the risk of relapse appears to be small (2% at one year) if there has been a similar response to cART as above. In patients on secondary prophylaxis, neuroimaging prior to stopping is recommended.^{18,19}

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13.7 Cryptococcosis

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Cryptococcus neoformans is an important fungal pathogen in patients with HIV. Two species of *C. neoformans* cause human disease: *C. neoformans* var *neoformans* and *C. neoformans* var *gattii*. It is a soil organism that is found worldwide. Inhalation of these organisms is thought to be the source of primary infection with subsequent dissemination to the central nervous system and other bodily organs. In patients with HIV infection, cryptococcosis is a feature of advanced disease, with most patients having CD4 cell counts <50 cells/ μ L.¹ Since the introduction of combination antiretroviral therapy (cART), the incidence of cryptococcosis, like that of many other opportunistic infections, has significantly decreased.²

13.7.1 Clinical presentation

Immunodeficient persons

Meningitis is the usual presentation of cryptococcosis. This may be subacute, with symptoms presenting over weeks to months, or acute, with symptoms emerging over several days. Fever and headache are the most common symptoms, reported in more than 80% of patients. Less commonly, patients have neck stiffness, photophobia, nausea, vomiting, malaise, or changes in mental state. Papilloedema is rarely found (unless the intracranial pressure is more than 35 cm H₂O, in which the rate of papilloedema is almost 30%).³ Patients may also present with dementia or seizures, and cryptococcal meningitis must be excluded in patients with HIV infection presenting with non-specific central nervous system symptoms. Lung involvement may accompany meningitis, and symptoms of fever, chest pain, dyspnoea and cough may be reported. Cryptococcal skin

lesions may be a clue to the diagnosis. These are small cutaneous lesions that may be mistaken for molluscum contagiosum.

Immune reconstitution features

Clinical reports of cerebral cryptococcosis occurring or relapsing after the initiation of cART are uncommon and generally do not appear to have any unusual clinical features.^{4,5} However, intracerebral cryptococcoma has been reported.⁶ Meningitis appears to occur in patients treated with antiretroviral agents with CD4 cell counts of less than 200 cells/ μ L. The reported cases of relapsed meningitis appear to occur when cART is commenced within several weeks of the cryptococcal meningitis being treated.⁴⁻⁷

13.7.2 Diagnosis

Any patient presenting with these symptoms should have a lumbar puncture, unless there is a contraindication such as a space-occupying lesion. A definitive diagnosis of cerebral cryptococcosis is made by the isolation of *Cryptococcus* on culture from the cerebrospinal fluid (CSF). However, CSF culture may sometimes be negative, especially early in the course of disease. The CSF should be examined by India ink stain (80% HIV-associated cryptococcal meningitis positive on India ink), and detection of cryptococcal polysaccharide antigen by latex agglutination is 90% sensitive and specific. The intracranial pressure is often raised, but the CSF protein or glucose may be normal and there may be few white cells. Computed tomography (CT) scanning of the brain may be normal or occasionally reveal cryptococcomas. Cryptococcal antigen may

be also be detected in blood or urine and blood cultures may be positive for *Cryptococcus*.⁸

13.7.3 Management

The treatment of cryptococcal meningitis should initially be with intravenous amphotericin B (0.5-0.8 mg/kg/day) with or without flucytosine (100 mg/day) for 14 days. There are several studies showing that this regimen is associated with higher rates of CSF sterilisation and less acute mortality. In patients with a clinical response at 14 days, treatment can be switched to oral fluconazole at a minimum dose of 400 mg daily for 8-10 weeks.^{9,10} There are currently no data to support the use of fluconazole as initial therapy. Repeat lumbar punctures should be performed to monitor a response to therapy, and if culture is negative at 8-10 weeks, the secondary prophylaxis phase of fluconazole at doses of 200 mg daily is instituted and generally continues for approximately 12 months.

Liposomal amphotericin may also be used for the treatment of cryptococcal meningitis. However, it has only been studied at doses of 4 mg/kg/day and is not recommended as first-line therapy.¹¹

Amphotericin B requires intravenous administration and is associated with a number of side-effects including acute infusion-related events. The side-effects of commonly used antifungal agents are listed in Table 13.7. Regular clinical review during therapy is recommended with monitoring of haematological and biochemical parameters.

Fluconazole	Mild to moderate nausea, vomiting, abdominal pain, diarrhoea Rash – may be associated with eosinophilia and pruritus Stevens-Johnson syndrome – rare, but may be fatal Increased liver function tests in 5-7% of patients Hepatic reactions including fulminant hepatic failure – rare Dizziness, headaches, alopecia
Amphotericin B	Acute infusion-related reactions – fevers, chills, rigors, nausea and headache – common Anaphylaxis – rare Renal tubular abnormalities including renal tubular acidosis, hypokalaemia and renal impairment in up to 80% of patients Anaemia and cardiac arrhythmias
Liposomal amphotericin B	As for amphotericin B except less frequent
Flucytosine	Gastrointestinal intolerance, dose-related leukopenia and thrombocytopenia, rash, hepatitis, and peripheral neuropathy Serum flucytosine levels should be monitored two hours post-dose Aim for peak level between 50-100 µg/mL

The optimal management of raised intracranial pressures (ICP) in cryptococcal meningitis is uncertain, however persistently raised ICP is associated with permanent neurological deficit and death. The approach of the Infectious Diseases Society of America (IDSA) is recommended.¹² The IDSA guidelines for

cryptococcal meningitis suggest an aggressive approach to the management of increased ICP. For patients with an initial CSF opening pressure of >25 cm H₂O in the lateral recumbent position, a lumbar puncture should be performed daily to remove a volume of CSF (up to 30 mL) sufficient to reduce the pressure to <20 cm H₂O or 50% of the initial opening pressure. In the absence of a lumbar drain, lumbar puncture should be repeated daily until the opening pressure is consistently less than 25 cm H₂O. The guidelines also suggest that a lumbar puncture be performed two weeks after treatment is initiated, both to exclude the possibility of an unrecognised case of elevated intracranial pressure and to obtain a CSF specimen for culture.

13.7.4 Prognosis

Untreated cerebral cryptococcal infection is usually fatal. Trials of combination therapy (in the pre-cART era) demonstrated clinical response rates of about 67%.⁹ Various factors at baseline are associated with poor prognosis: poor mental state, raised ICP (>35 cm H₂O), high CSF cryptococcal antigen, low CSF white-cell count, and the presence of fungaemia.³ Cryptococcal meningitis presenting in the cART era may be more severe and more likely to be disseminated than in the pre-cART era. The initial outcomes appear to be unchanged with approximately 20% of patients irrespective of receipt of cART dying in the first three months after diagnosis. If patients survive the first three months in the cART era, more than 50% will be alive five years after diagnosis compared with less than 10% in the pre-cART era.¹³

13.7.5 Prophylaxis

Primary prophylaxis

The United States Public Health Service 2002 guidelines for the prevention of opportunistic infections among people with HIV infection state that although controlled trials indicate that fluconazole and itraconazole can reduce the frequency of cryptococcal disease among patients who have advanced HIV disease, most specialist HIV physicians recommend that antifungal prophylaxis not be used routinely to prevent cryptococcosis. The reasons for this are the relative infrequency of cryptococcal disease, the lack of survival benefits associated with prophylaxis, the possibility of drug interactions, potential antifungal drug resistance and cost.¹² The need for prophylaxis or suppressive therapy for other fungal infections (e.g. candidiasis, histoplasmosis) should be considered when making decisions concerning prophylaxis for cryptococcosis. If used, fluconazole at doses of 100-200 mg daily is reasonable for patients whose CD4 cell counts are <50 cells/µL.¹²

Secondary prophylaxis

Secondary prophylaxis or maintenance therapy is essential after initial therapy as relapse is inevitable if the CD4 cell count remains low.^{14,15} Fluconazole at 200-400 mg daily is associated with a 2-3% relapse rate compared with a 18-25% relapse rate with either itraconazole or weekly amphotericin B.¹⁶

Discontinuing prophylaxis

Several cohort studies have shown that discontinuing maintenance therapy against prior cryptococcal infection is safe in individuals who have sustained increases in CD4 cell counts to >200 cells/µL for at least six months after initiating potent antiretroviral therapy.^{12,17,18}

13 Key opportunistic infections

Cryptococcus is an important but rare pathogen. Meningitis often presents subacutely and needs to be differentiated from other causes of impairment of the central nervous system. Poorer outcome is associated with raised intracranial pressure, poor mentation at presentation and high CSF cryptococcal antigen.

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13.8 Cryptosporidiosis

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Cryptosporidium, a coccidial parasite, predominantly causes gastrointestinal disease in immunocompromised patients with HIV infection. *Cryptosporidium hominis* and *Cryptosporidium parvum* are the most important *Cryptosporidium* species causing human disease. *Cryptosporidia* are spread by ingestion of oocysts excreted by people or animals with the infection. Predominant routes of transmission are via consumption of faecally contaminated water or food, person-to-person contact, animal-to-person contact, or contact with contaminated environmental sources (including swimming pool water). *C. hominis* is predominantly spread via person-to-person contact and is the most common genotype causing disease in Australia.¹

13.8.1 Clinical manifestations

Cryptosporidia cause a spectrum of gastrointestinal disease in patients with HIV infection, including an acute diarrhoeal syndrome, a chronic diarrhoeal syndrome and a syndrome of sclerosing cholangitis. The acute self-limiting diarrhoeal illness is characterised by a latent period of one week, followed by watery diarrhoea, abdominal cramping, anorexia, fever and vomiting. The diarrhoeal illness lasts for seven to 10 days. The chronic diarrhoeal syndrome is characterised by watery, voluminous stools associated with weight loss. Some patients may also experience abdominal cramping, vomiting and fever. *C. parvum* is more commonly associated with chronic diarrhoea and vomiting whereas *C. hominis* is generally associated with chronic diarrhoea without vomiting.² Patients with CD4 cell counts >180 cells/ μ L tend to have the self-limited diarrhoeal illness whereas patients with CD4 cell counts <180 cells/ μ L have more protracted illnesses.³ Cryptosporidiosis is now uncommon since the widespread availability of combination antiretroviral therapy (cART).

Patients with sclerosing cholangitis usually have CD4 cell counts <50 cells/ μ L⁴ and report right upper quadrant pain and fever. Examination may reveal hepatomegaly and investigations may reveal cholestatic liver function test abnormalities. Up to 80% of patients with sclerosing cholangitis also have pancreatic duct dilatation and features of chronic pancreatitis.⁵

C. hominis has been isolated from sputum from symptomatic immunodeficient patients with HIV, suggesting a possible role in respiratory disease in immunodeficient patients.⁶

Cryptosporidial immune reconstitution disease has been reported; a patient with chronic cryptosporidiosis presented with terminal ileitis one month following the successful initiation of antiretroviral therapy.⁷

13.8.2 Diagnosis

Routine stool examination for ova, cysts and parasites are not sufficient to detect *Cryptosporidium*. Because of its small size, it may be confused with a yeast.⁸ A specific request for the laboratory to assess the stool for *Cryptosporidium* is required.

Although modified acid-fast stains are the traditional method used to diagnose cryptosporidiosis, direct fluorescent antibody and enzyme immunoassays are both more sensitive and less operator-dependent than acid-fast staining. The direct fluorescent antibody and enzyme immunoassays are 98% to 99% sensitive and 100% specific for the diagnosis of *Cryptosporidium*.⁹ Cryptosporidial enteritis rarely requires biopsy for diagnosis. Histological features include villous atrophy, although villous blunting and fusion may occur. Haematoxylin and eosin stains demonstrate characteristic intracellular (but extra-cytoplasmic) vacuoles aligning the microvillus apical border.¹⁰

The diagnosis of pancreatobiliary cryptosporidiosis requires endoscopic retrograde cholangiopancreatography and ampullary biopsy. There are four distinct patterns of biliary disease observed: papillary stenosis alone, intrahepatic sclerosing cholangitis alone, sclerosing cholangitis in association with papillary stenosis (the most common), and long extrahepatic bile duct strictures with or without sclerosing cholangitis.¹¹

13.8.3 Management

The acute diarrhoeal illness does not require specific treatment. The most effective way to treat chronic cryptosporidiosis is to improve immune function using cART. Immune recovery induced by cART results in excellent clinical responses, as assessed by stool frequency, weight gain and oocyst clearance from stool.¹² However, rapid relapse of the disease has been described in patients who cease antiretroviral therapy, or in whom therapy fails, suggesting that cART controls rather than cures the disease.¹³ Treatment of chronic cryptosporidial enteritis in patients who do not achieve immune recovery with cART is problematic. There is no therapeutic agent that consistently eradicates intestinal cryptosporidiosis. A recent meta-analysis demonstrated that neither nitazoxanide nor paromomycin were effective in reducing mortality, relieving symptoms or oocyst clearance in persons with HIV.¹⁴ Recent case reports of eradication of *Cryptosporidia* with rifampicin in two patients with HIV-associated chronic cryptosporidiosis suggest that this drug may be considered in some cases.¹⁵ A therapeutic approach is outlined in Table 13.8. Hyperimmune bovine colostrum has no consistent effect on cryptosporidiosis.¹⁶

Symptomatic treatment of diarrhoea in refractory cases includes loperamide, codeine and somatostatin analogues. Pancreatobiliary cryptosporidiosis requires endoscopic retrograde cholangiopancreatography for both diagnosis and management. This procedure allows biliary sphincterotomy and stenting to be performed in patients with ampullary stenosis. Coincident pancreatic disease is a likely cause of ongoing pain despite biliary sphincterotomy.

13.8.4 Prophylaxis

There is no good evidence that boiling water or the use of water filters prevents disease. Following recent contamination of a city water supply with *Cryptosporidia*, no increase in chronic

	Agent	Dose	Comment
First line	Paromomycin	500 mg four times daily or 1 gm bd	Studies of the efficacy of paromomycin have yielded variable results. In several trials, paromomycin has been shown to decrease stool frequency and oocyte excretion. ²⁰ However, some trials have demonstrated no clinical benefit even at high doses ²¹
Relapse	Azithromycin plus paromomycin	600mg azithromycin bd plus paromomycin (1000 mg bd) for 4 weeks, followed by paromomycin (1000 mg bd) for 8 weeks.	An uncontrolled trial demonstrated that this regimen resulted in diminished cyst passage and improved clinical symptoms ²²
Alternative	Nitazoxanide	1-2 g daily for 2 weeks (500-1000 mg bd) available under the SAS ¹	A double-blind randomised controlled trial of nitazoxanide demonstrated parasitological cure in 65% patients ²³
	Roxithromycin	300 mg bd for 2 weeks	Case reports and supportive <i>in vitro</i> data
	Rifaximin	600 mg three times daily for 2 weeks	Case reports
<p>¹ The Therapeutic Goods Administration's Special Access Scheme for access to unapproved therapeutic goods. Information on this scheme is online at http://www.health.gov.au/tga/docs/html/sasinfo.htm.</p>			
bd= twice daily			

cryptosporidiosis was reported. Nonetheless, some authors recommend increased water hygiene in patients at risk of chronic cryptosporidiosis.¹⁷ Observational data demonstrate that clarithromycin and rifabutin used as *Mycobacterium avium* complex prophylaxis are associated with reduced rates of cryptosporidial disease.¹⁸ In this same study, patients on azithromycin were not shown to have such a benefit. However, only a small number of patients were taking azithromycin, limiting the conclusions about its efficacy in this study. Despite its zoonotic potential, pet ownership does not represent a major risk factor for the acquisition of *Cryptosporidium* for patients with HIV.¹⁹

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13.9 Cytomegalovirus

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Disease resulting from reactivated cytomegalovirus (CMV) infection is a significant cause of mortality and morbidity in patients with profound immunodeficiency (CD4 cell count <50 cells/ μ L) secondary to HIV disease. Although almost any organ system can be affected, the most commonly affected sites in individuals with HIV infection are the retina, colon, oesophagus and central nervous system. CMV retinitis is diagnosed clinically, but most other forms of CMV disease are diagnosed histologically in association with viral polymerase chain reaction (PCR) assay and/or culture. The availability of effective oral agents has simplified the management of CMV disease in patients with advanced HIV disease.

13.9.1 Clinical presentations

Cytomegalovirus retinitis

CMV retinitis was the most common manifestation of reactivated CMV disease and the most common cause of blindness in patients with AIDS, prior to the introduction of combination antiretroviral therapy (cART). Up to 25% of patients with AIDS developed CMV retinitis and those with CD4 T-cell counts <50 cells/ μ L are at greatest risk.^{1,2} The typical clinical scenario is for a patient with a previous AIDS diagnosis to present with unilateral visual disturbance: decreased visual acuity, floaters or unilateral visual field loss. Initially the lesions are located peripherally. Untreated lesions spread centrally within the affected eye towards the macula and optic disc, and haematogenously to the other eye. CMV retinitis may be asymptomatic. Patients with CD4 cell counts <50 cells/ μ L and patients with non-retinitis CMV disease are advised to have regular ophthalmological checks to permit early detection and treatment of CMV retinitis. Pupillary dilatation and examination by indirect ophthalmoscopy is essential to visualise peripheral lesions. It is recommended that immunodeficient patients be educated about symptoms of CMV retinitis and advised to present promptly should they experience these symptoms.

Cytomegalovirus gastrointestinal disease

CMV may cause disease in all parts of the gastrointestinal tract; ulcerative disease of the colon and oesophagus are the most common sites and occur in 5-10% of patients with AIDS and CMV end-organ disease. Less common sites include the biliary tree, mouth and rectum. Patients with CMV colitis present with chronic diarrhoea, weight loss, abdominal pain, nausea, vomiting, and fever. Colonoscopy reveals widespread submucosal haemorrhages and diffuse mucosal ulcerations.

CMV is the aetiological agent in 10% to 20% of cases of oesophageal disease in patients with HIV. The clinical presentation of CMV oesophagitis is indistinguishable from *Candida* oesophagitis. Patients who fail to respond to empirical antifungal therapy within 72 hours after presenting with dysphagia and fever should be investigated for the possibility of CMV oesophagitis with endoscopy and biopsy.

Cytomegalovirus neurological disease

CMV typically causes two broad types of neurological dysfunction in immunodeficient individuals: ascending polyradiculopathy and ventriculoencephalitis. CMV polyradiculopathy presents with urinary retention and bilateral leg weakness (a Guillain-Barre-like syndrome) with progressive deterioration over weeks leading to a flaccid paraplegia. CMV ventriculoencephalitis usually presents in the setting of symptomatic CMV disease at another site. Typically, patients present with lethargy, mental slowing, confusion and fever. Cranial nerve defects can occur. Spastic myelopathy and sacral paraesthesia have been reported.

Other manifestations of CMV end-organ disease include pneumonitis, but this is much rarer in HIV infection than it is in the transplant setting.

Immune reconstitution features

An immune recovery vitritis is a well recognised complication following the initiation of cART. Clinically, this condition presents in a similar way to CMV retinitis, with which it was initially confused.³ The prime distinguishing feature is inflammation of the anterior chamber and vitreous humour, which is unusual in CMV retinitis. Other distinguishing characteristics are recent onset of cART (four to seven weeks) and a CD4 cell count >200 cells/ μ L at the time of diagnosis. Attempts to isolate CMV from the vitreous humour are unsuccessful. Immune recovery vitritis can occur in patients with previously treated CMV retinitis or in patients with no history of CMV retinitis. The inflammatory reaction in most cases is self-limited and does not require specific anti-CMV therapy. However, sight-threatening immune recovery uveitis can occur and may require intervention with corticosteroids.⁴ The recognition of this syndrome mandates thorough ophthalmological review of patients who present with profound immunodeficiency prior to initiation of cART as treatment of asymptomatic CMV retinitis is warranted. Delaying the initiation of cART until maintenance CMV therapy is established is recommended. The exact timing of cART initiation has not been defined (See Section 22.2).

13.9.2 Diagnosis

Retinitis

The diagnosis of CMV retinitis is made on clinical grounds. Typical lesions are yellow-white and granular in appearance and follow a vascular distribution. The lesions are associated with perivascular exudates and haemorrhages. The differential diagnosis includes HIV retinopathy, progressive outer retinal necrosis and other ocular opportunistic infections, such as toxoplasmosis, herpes simplex, herpes zoster, tuberculosis and syphilis. CMV retinitis lesions are referred to as 'cottage cheese and ketchup' to distinguish them from the typical 'cotton wool' appearance of HIV retinopathy.

Other Cytomegalovirus end-organ disease

The diagnosis of CMV disease in other organs cannot be made on clinical grounds alone. Isolation of the virus or detection of CMV antigens or DNA from appropriate clinical specimens is required. Viral culture of appropriate specimens on human fibroblast monolayers is the gold standard, and characteristic cytopathic effects may be detected within a few days (however, this is unavailable in many laboratories today, which prefer to use molecular techniques in its place). A rapid technique involving the detection of an immediate-early antigen following overnight culture is also available. Molecular techniques involve CMV PCR assay or techniques to detect CMV antigens. The detection of CMV antigens or CMV DNA in blood, cerebrospinal fluid (CSF) or tissues may yield positive results prior to a positive culture for CMV. CMV inclusions (Owl's eye), neutrophilic infiltration and non-specific inflammatory changes are seen on histological examination of CMV-infected tissue. However, CMV viraemia in blood may be present in the absence of end-organ disease and vice versa. Hence, at the present time, the best way to use quantitative CMV PCR to monitor response to therapy in those with proven end-organ disease, or to initiate therapy in the absence of clinically apparent end-organ disease, is unclear.⁵⁻⁷

The diagnosis of CMV neurological disease is often one of exclusion. Magnetic resonance imaging (MRI) generally demonstrates periventricular enhancement. The CSF findings are non-specific and generally reveal a normal-to-elevated protein level and a normal-to-low CSF glucose. There may be a lymphocytic or neutrophilic pleocytosis. CSF CMV culture is usually negative. A positive CSF PCR coupled with typical changes on the MRI adds greatly to the likelihood of CMV neurological disease. Biopsy demonstrates periventriculitis with ependymal necrosis and CMV intranuclear inclusion bodies.⁸

13.9.3 Management

Principles

The choice of initial therapy depends on the location and severity of the end-organ disease. The approach to the management of CMV end-organ disease is frequently one of induction-maintenance with specific antiviral agents coupled with the use of cART to effect immune restoration. Choices for induction therapy (usually of two to three weeks duration) include valganciclovir, intravenous ganciclovir, intravenous foscarnet or cidofovir, with the latter therapies usually used for recurrent or relapsed disease. Combination therapy is sometimes used, in particular for CNS disease although there is a paucity of data to support this approach. The appropriate timing of cART initiation in patients with

CMV end-organ disease is not known, however, a brief delay would seem prudent to avoid or reduce the risk of immune restoration disease.

The following agents are available:

Ganciclovir

Ganciclovir is a guanosine derivative with anti-CMV activity. After intracellular conversion by a viral phosphotransferase, encoded by CMV gene region UL97, ganciclovir triphosphate is a selective inhibitor of CMV DNA polymerase.

The following formulations are available: oral, intravenous and intravitreal implant. The latter offers no protection or treatment for CMV outside the eye. Oral ganciclovir has poor bioavailability and is not appropriate for induction therapy of acute CMV disease. The main side-effects of ganciclovir, particularly the parenteral form, are haematological toxicity (neutropenia and thrombocytopenia), renal dysfunction, nausea and diarrhoea. In some cases, adjunctive use of G-CSF maybe needed in order to avoid or treat neutropenia.

Valganciclovir

Valganciclovir is a pro-drug (a valine ester) of ganciclovir and has significantly enhanced oral absorption compared with oral ganciclovir with 60% bioavailability. Blood levels obtained are equivalent to those achieved with intravenous ganciclovir (i.e. 900 mg valganciclovir = 5 mg/kg intravenous ganciclovir) although the peak level is higher with the intravenous formulation of the drug. Valganciclovir has similar efficacy and tolerability as intravenous ganciclovir in the induction and maintenance of CMV retinitis.⁹ However, there is a paucity of data on the use of valganciclovir in the treatment of CMV neurological or gut disease in patients with HIV infection. There are considerably more data on its use both prophylactically and for treatment of CMV disease in the organ transplant setting.¹⁰⁻¹³

Foscarnet

Foscarnet, a pyrophosphate analogue, inhibits viral DNA polymerase. Because this agent does not require phosphorylation to be active, it is also effective against most ganciclovir-resistant CMV isolates. Foscarnet has similar efficacy to intravenous ganciclovir in treating acute CMV retinitis and preventing relapses.¹⁴ Foscarnet needs to be administered intravenously. The predominant dose-limiting toxicity is nephrotoxicity. Foscarnet is considerably less well tolerated than ganciclovir and therefore is not recommended as first-line therapy. Foscarnet-resistant mutants emerge with continued treatment. Adverse effects include: anaemia, nephrotoxicity, electrolyte disturbance and neurological dysfunction including seizures.

Cidofovir

Cidofovir is a cytosine nucleotide analogue that has widespread antiviral activity against the herpes group of viruses. Cidofovir has the theoretical advantage of not requiring viral activation. It is active against some ganciclovir-resistant strains. The drug's prolonged intracellular half-life permits it to be administered once every two weeks as maintenance therapy. Cidofovir has similar efficacy to intravenous ganciclovir in previously untreated patients with CMV retinitis.¹⁵ Furthermore, cidofovir is associated with improved outcomes in patients with relapsed CMV retinitis who had previously been treated with

either ganciclovir, foscarnet or both.¹⁶ Renal toxicity, secondary to a dose-dependent proximal tubular effect, is significant with cidofovir but can be alleviated, to some extent by co-administration with probenecid.

Cytomegalovirus retinitis

Oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, intravenous cidofovir and the ganciclovir intraocular implant coupled with valganciclovir are all effective treatments for CMV retinitis. Slow-release ganciclovir intravitreal implants are more effective in controlling CMV retinitis within the affected eye than intravenous ganciclovir.¹⁷ However, the co-administration of systemic therapy, usually oral valganciclovir¹⁸ rather than oral ganciclovir,¹⁹ is required to prevent CMV disease outside the treated eye. Implants remain active for up to six months. With the availability of effective oral agents with good bioavailability and the expectation that many patients with CMV retinitis are not likely to require long-term maintenance because of cART-induced immune recovery, the role of implants in the management of CMV retinitis is likely to decrease. The use of an implant plus oral valganciclovir has not been compared with oral valganciclovir alone. Some ophthalmologists would use oral valganciclovir alone.

Cytomegalovirus gastrointestinal disease and Cytomegalovirus neurological disease

Most specialists would use parenteral therapy with ganciclovir for two to four weeks until symptoms and signs have resolved. In severe disease, combination intravenous ganciclovir and foscarnet may be preferred to stabilise disease but is associated with high rates of toxicity. There is a paucity of data using oral valganciclovir in this setting although it may be used in the maintenance phase.

Treatment failure

In those patients with cART-induced immune recovery, relapse is much less likely. Overall, ganciclovir resistance is less common in the cART era. The two-year incidence of ganciclovir resistance decreased from 28% to 9% before and after 1996.²⁰ Ganciclovir resistance is associated with progression of retinal disease in the cART era.²¹ Risk factors for resistance include long-term therapy. Low level resistance to ganciclovir occurs with mutations of the CMV UL97 gene, high-level resistance with mutations of the UL97 plus UL54 genes. Resistance to foscarnet and cidofovir occur with mutations of the UL54 gene. Cross resistance exists between ganciclovir and cidofovir and sometimes foscarnet, especially when high-level resistance to ganciclovir exists.¹⁸ Resistance testing may be useful (if available) in patients with treatment failure. Patients with treatment failure may respond to re-induction with the agent used initially for treatment. Alternatively, the use of combination therapy may be tried, or if the relapse is in the eye, placement of a ganciclovir implant in order to achieve very high levels of the drug locally may be warranted.

In the absence of cART-induced immune recovery, maintenance therapy is required. Time to relapse is prolonged from 37 to 145 days in patients who receive maintenance therapy.²² Relapses of non-retinitis CMV disease are less common and maintenance therapy is not recommended for these patients.

13.9.4 Prophylaxis

The most effective strategy in the prevention of CMV disease is to induce immune recovery in the patient on cART. However, patients who fail to achieve optimal immune recovery on cART may be at risk of CMV disease. Primary prophylaxis for CMV is not generally undertaken in Australia because of concerns of cost, pill burden and the potential to develop resistance. Trials of oral ganciclovir for primary prophylaxis against CMV disease in patients with advanced HIV disease have demonstrated variable efficacy.^{23,24} Valganciclovir has not been evaluated in this context.

Primary prophylaxis of patients based upon monitoring of CMV PCR levels in blood is not currently recommended. However, there are some data to support such an approach.^{25,26}

Discontinuing maintenance therapy

CMV maintenance therapy can be discontinued in patients who experience immune recovery following the introduction of cART and who have a CD4 cell count >100 cells/ μ L for three to six months. These recommendations are based on several studies that show that individuals with sustained immune recovery remain free of active CMV disease for up to 18 months after ceasing CMV prophylaxis.²⁷⁻²⁹

The safety of this approach for patients with sight-threatening lesions has not been formally evaluated. The decision to cease CMV prophylaxis should be undertaken only with ophthalmological consultation and followed by regular ophthalmological review. However, the risk of reactivation of CMV retinitis in persons who discontinue maintenance therapy is estimated to be low at 0.016 per person-years follow-up.³⁰

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13.10 Microsporidiosis

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Microsporidia are ubiquitous obligate intracellular parasites, and are distributed worldwide. Recent work has suggested that *Microsporidia* may have evolved from fungi.^{1,2} Although previously recognised as a cause of veterinary disease, the first human disease was described in 1985 in a patient with AIDS with unexplained diarrhoea.³ As with cryptosporidiosis, microsporidiosis is a rare manifestation of HIV disease in the era of effective combination antiretroviral therapy (cART).

The most common site of disease is the small intestine. Two microsporidial species, *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*, are the most common species identified in patients with HIV infection. *E. bieneusi* infection is usually confined to the small intestine (and occasionally involves the biliary tree). It causes 80% of microsporidial diarrhoea. *E. intestinalis* infects the small intestine, but can also cause more widespread disease.

Infection occurs following ingestion or inhalation of *Microsporidia* spores. Transmission of *microsporidial* species is thought to be primarily through faecal-oral or urinary-oral routes. Recent work suggests that microsporidiosis may be a zoonotic infection.⁴ Encephalitozoon keratoconjunctivitis may occur through contact with aerosols or surfaces contaminated with urine containing *Microsporidia*.⁵

13.10.1 Clinical presentation

The most common clinical manifestation of microsporidiosis in patients with AIDS is diarrhoea. Like *Cryptosporidia*, *Microsporidia* can cause self-limiting diarrhoea in immunocompetent patients.⁶ *Microsporidia* account for up to 20% of diarrhoeal illness in patients with AIDS.⁷ Typically patients have CD4 cell counts of less than 50 cells/ μ L.¹ Immunodeficient patients present with chronic (initially intermittent) non-bloody diarrhoea that may be accompanied by fever, anorexia and weight loss. *E. bieneusi* may cause cholangitis or cholecystitis. Uncommon non-gastrointestinal manifestations of *microsporidial* infections include sinusitis, keratoconjunctivitis, hepatitis, peritonitis, adrenalitis, nephritis, pituitary gland infection, osteomyelitis, encephalitis, myositis and pneumonia.⁸

13.10.2 Diagnosis

Stool microscopy is the investigation of choice in the diagnosis of microsporidiosis. As microsporidial shedding may be intermittent, at least three stool specimens are required. Special stains such as the modified Ziehl-Nielsen, Warthin-Starry, fluorescent, and trichrome stains have varying specificity and sensitivity for different *Microsporidia* species. These stains, however, do not provide species-specific identification, which requires either electron microscopic analysis of a small bowel biopsy or polymerase chain reaction analysis.⁹ Electron microscopy is considered the gold standard, but is not routinely available. The use of monoclonal antibodies and oligonucleotide microarray assays to detect pathogenic microsporidial species

in human clinical specimens have been reported recently and may increase the diagnostic yield.^{10,11}

13.10.3 Management

No specific therapy is required in patients with self-limited *Microsporidia* enteritis in whom CD4 cell counts are above 200 cells/ μ L. For patients with lower CD4 cell counts, the most important management strategy is achieving immune recovery following the initiation of cART.¹² Aspartyl protease inhibitors such as lopinavir, ritonavir and saquinavir have been shown to have antimicrosporidial effects *in vitro*, however there are no reports of greater beneficial responses using a protease inhibitor based antiretroviral regimen.¹³

Albendazole (400 mg twice a day) is successful in the treatment of *E. intestinalis*, but other microsporidial species have variable responses to this drug.^{14,15} Although clearance of *Microsporidia* has been reported with cART alone, treatment with albendazole is recommended to reduce the duration of symptoms. Fumagillin (20 mg taken three times a day) is active against *E. bieneusi* and has been demonstrated to eradicate the organism,¹⁶ but is not licensed in Australia.

Uncontrolled studies have suggested that thalidomide may reduce stool frequency and lead to weight gain in patients with microsporidial diarrhoea.¹⁷ The potential mechanisms are unclear. Thalidomide has no direct antimicrosporidial effect.¹⁸ The following drugs have been used with variable success to treat microsporidiosis: metronidazole, atovaquone, azithromycin, itraconazole, sulfa-based drugs and nitazoxanide. Specific dietary intervention is advantageous in patients with microsporidiosis and malabsorption. Medium-chain triglyceride-based diets, as opposed to long-chain triglyceride-based diets reduce stool frequency and lead to weight gain.¹⁹ Octreotide may provide symptomatic reduction in stool frequency and volume.

13.10.4 Prophylaxis

There are no primary prophylaxis strategies. Patients with disease secondary to non-*E. intestinalis* frequently relapse following cessation of albendazole therapy in the absence of cART-induced immune recovery. These patients may require long-term suppressive therapy with albendazole or an alternative agent. The role of fumagillin in this context has not been studied.

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13.11 Progressive multifocal leukoencephalopathy

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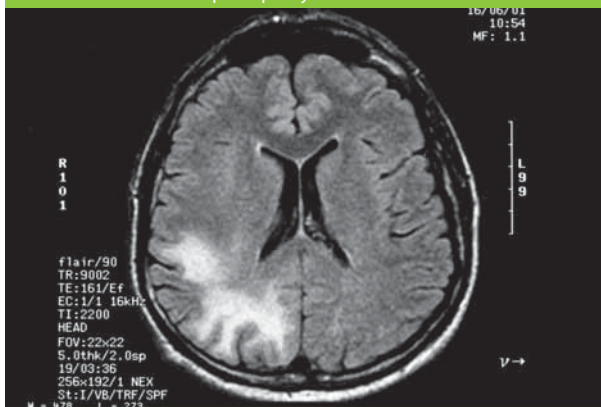
Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system (CNS) caused by a double-stranded DNA polyomavirus known as the John Cunningham virus (JCV). Serological evidence of infection with the JCV is present in at least 80% of adults. Infection occurs during childhood and adolescence, following which the JCV remains in the body, replicating within the kidneys¹, peripheral blood mononuclear cells, the reticuloendothelial system, and, possibly, the brain.

PML usually manifests at the time of immunocompromise induced by HIV infection, organ transplantation, haematological malignancy, connective tissue disease, long-term immunosuppressive therapy² and idiopathic CD4 cell lymphocytopenia.³ Administration of natalizumab therapy (a monoclonal antibody to alpha4 integrin) for Crohn's disease or multiple sclerosis has been well documented as a risk factor for development of PML, with an estimated risk of 1 in 1000 treated patients.⁴⁻⁶

However, a sizeable number of patients have no discernible disturbance of their immune function. The JCV infects oligodendrocytes and leads to demyelination of the white matter of the brain and, rarely, the spinal cord (Image 13.5).

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Image 13.5 Magnetic resonance imaging of the brain of a HIV-positive patient showing progressive multifocal leukoencephalopathy



Note: A confluent signal abnormality of the white matter is seen in the frontoparietal region of the brain. Source: Brew B, St Vincent's Hospital, Sydney, NSW. Used with permission.

PML occurred in 4% of AIDS patients in Australia before the availability of combination antiretroviral therapy (cART).⁷ Despite the benefits of cART, there has not been a significant fall in the incidence of PML in parts of Europe,^{8,9} nor has the USA seen a

decrease in the incidence of PML as an AIDS-defining event.¹⁰ In patients with HIV infection, PML is usually seen at the time of moderate or advanced immunosuppression. In studies from the pre-cART era, the median CD4 cell count was low at diagnosis of PML: 53 cells/ μ L (range 0-420 cells/ μ L)¹¹ in one study, and 30 cells/ μ L in an Australian study.⁷ However, CD4 cell counts were somewhat higher in a post-cART study in which 60% of patients were receiving cART at the time of PML diagnosis (median 104 cells/ μ L, range 4-1030 cells/ μ L).¹² It is important to emphasise that PML can occur in patients with HIV infection with normal CD4 cells counts.

As a corollary, PML can occur in patients who have very low or undetectable plasma HIV viral loads and who are receiving cART: in one study, one-third of the patients diagnosed with PML had a plasma HIV viral load less than 500 copies/mL.¹² In this same study, the overall median plasma HIV viral load was 3362 copies/mL (range <500 copies –1.5 million copies/mL).¹²

13.11.1 Clinical features

The signs and symptoms of PML typically develop and progress over several weeks or, occasionally, over several months. Patients may present with cognitive impairment, headache, sensory and motor deficit of the limbs, or both, disturbance of gait, vision, speech, and swallowing.^{7,13} Clinical examination

may reveal hemiparesis, hemineglect, visual field defects (including homonymous hemianopia), cerebellar signs and gait disturbance. Rarely there is evidence of brainstem and spinal cord involvement.

The presentation of PML is notable for the absence of fever in the patient and the infrequency of seizures.

13.11.2 Diagnosis

The key investigations that may be used in the diagnosis of PML include magnetic resonance imaging (MRI) of the brain, assessment of the cerebrospinal fluid (CSF) for JCV by polymerase chain reaction (PCR), and performance of a brain biopsy for histopathological review and JCV PCR. The typical findings of these and other investigations are discussed in Table 13.9.

In a patient with the typical clinical, radiological and histopathological features of PML, the diagnosis is established. However, a more common and practical approach is to accept the diagnosis of PML in a patient when the typical clinical and radiological findings of PML are present and there is a positive JCV PCR from the patient's CSF analysis.

Table 13.9 Investigational findings for patients with HIV infection with progressive multifocal leukoencephalopathy (PML)

Magnetic resonance imaging (MRI) of the brain (Image 13.5)
<p>Key findings typically show several areas of T2-weighted high signal intensity in the subcortical white matter that have a scalloped appearance. T1-weighted hypointensity is found in the corresponding areas.</p> <p>The frontal and parieto-occipital regions are most commonly involved.</p> <p>The presence of mass effect or contrast enhancement is very uncommon in PML, but can occur. In some reports from the post-cART era, mass effect and contrast enhancement have been associated with improved outcome for patients. These findings have been noted to occur after the commencement of cART.¹</p> <p>The MRI evidence of progression of PML includes increased hypointensity on T1-weighted images and increased high signal on fluid-attenuated inversion recovery/fast-spin echo (FLAIR-FSE) images.⁴¹</p> <p>In practice, MRI of the brain often plays a key role in the diagnosis of PML.</p>
Computed tomography (CT) scan
<p>Non-contrast CT brain scans typically reveal areas of hypointensity in the subcortical white matter that are not associated with mass effect and do not enhance with contrast.</p> <p>The lesions of PML on CT scans may mistakenly be interpreted as vasogenic oedema or infarction, especially if the diagnosis of underlying HIV infection is not known.</p>
Cerebrospinal fluid JC virus polymerase chain reaction (PCR) assay
<p>Qualitative JC virus PCR is readily available in Australia, but quantitative JC virus PCR assays are available in a few laboratories only.</p> <p>Sensitivity: approximately 65%</p> <p>Specificity: approximately 92-100%</p> <p>Positive predictive value: 88-100%</p> <p>Negative predictive value: 88.5-98.5%⁴²</p> <p>In practice, the JC virus PCR in CSF may be positive in less than 50% of patients with PML.</p>
Brain biopsy
<p>The brain biopsy findings of PML on light microscopy show areas of demyelination in the subcortical white matter. Accompanying findings include enlarged oligodendrocytes, foamy macrophages and pleomorphic astrocytes.⁴³</p> <p>Severe disease is characterised by intense demyelination that may lead to tissue destruction and cavitation.⁴³ If viral inclusions with a ground-glass appearance are found within the nuclei of oligodendrocytes, a diagnosis by light microscopy can be made.</p> <p>In practice, both the light microscopy findings and in situ hybridisation for JC virus are used for a tissue diagnosis of PML.</p> <p>Electron microscopy may also be used to secure a definitive diagnosis of PML.</p> <p>Overall, approximately 80% of PML patients who undertake a brain biopsy will be ascribed either a definite or probable diagnosis of PML.¹³</p>

13 Key opportunistic infections

Unfortunately, the clinician is often faced with the situation where the characteristic clinical and radiological features of PML are present, but there is a negative CSF JCV PCR, and the patient either declines a brain biopsy or a brain biopsy is technically unfeasible. Failure to detect JCV by PCR in CSF has increased in the cART era (10% in pre-cART era to 40% post cART era), and the test is also more likely to be negative in those with higher CD4 cell counts.⁴ Occasionally a repeat CSF analysis will be positive for JCV PCR in this setting. Otherwise the practitioner must consider other possible causes of the clinical and MRI findings (see differential diagnoses below): if the original CSF analysis was negative for cytomegalovirus (CMV), varicella-zoster virus and herpes simplex virus, and the CSF cytology was normal, then it is reasonable to have increased confidence in the diagnosis of PML.

Differential diagnoses

In the setting of advanced immunodeficiency, HIV infection may cause diffuse (rather than multifocal) changes in the deep (rather than subcortical) white matter and periventricular area. These diffuse changes may be misinterpreted as PML.¹³ Very occasionally, CNS infection with CMV or varicella-zoster virus can induce changes which resemble PML on MRI.¹³ Negative CSF PCR results for CMV and varicella-zoster virus, and a close review of the MRI findings, should help to exclude these entities in individual patients.

In a patient without HIV infection, CNS lymphoma has been reported to present with diffuse leukoencephalopathy without contrast enhancement.¹⁴

Cyclosporine, tacrolimus, levamisole, fludarabine and 5-fluorouracil¹⁵ have been reported to cause leukoencephalopathy. Although these case reports have not come from the HIV setting, 5-fluorouracil is used in HIV infection to treat gastrointestinal malignancy.

13.11.3 Prognosis

A patient characteristic associated with prognosis in patients with HIV with PML is the patient's age: one study found that patients younger than 45 years had improved survival.¹⁶

Baseline levels of CSF JCV viral load significantly predict survival in patients with HIV infection treated with cART¹⁷, and clearance of JCV from the CSF is associated with prolonged survival.^{5,17,18} A high CD4 cell count (>100 cells/ μ L) in patients treated with cART at the time of diagnosis of PML^{6,12,19} and a rise in CD4 cell count following commencement of cART²⁰ are associated with increased survival in PML. Recent research has suggested that patients who can mount a specific cellular immune response to the JCV have an increased chance of prolonged survival after diagnosis with PML.²¹ Up to 10% of patients may experience spontaneous remission and prolonged survival.

13.11.4 Management

An overview of the treatment of PML with cART

The use of cART to treat patients with HIV infection with PML has been associated with prolonged survival in several studies.^{12,16,22} In one study the median survival of patients who did not receive cART was 80 days compared with 246 days in those patients who did receive cART.²⁰

The use of cART in the treatment of PML may be associated with a prompt clinical response, including complete recovery

in some patients.²² The median time to clinical improvement in PML after commencement of cART is not well documented, but, in one small study, clinical improvement was often not evident until week four of therapy.²² In the authors' experience, patients who do improve generally do so within the first four to 12 weeks of cART, and they may go on to experience subtle symptomatic and objective improvements over the next 12 to 24 months.

Unfortunately, the benefits of cART may not extend to all patients with PML. A recent review of 118 patients with HIV infection with PML showed that up to one-third failed to respond to cART, dying within a median time of 12 weeks from diagnosis.²³ In this large study, the baseline CD4 cell count was significantly-associated with survival. Additionally, in the same review, residual neurological deficit occurred in approximately 50% of survivors, an observation made by other authors.²⁰

Immune reconstitution features

Immune reconstitution disease in PML involves an inflammatory reaction with reactive gliosis, multinucleated histiocytes and intraparenchymal infiltration by CD8 lymphocytes.^{24,25} PML has also been reported to develop soon after the commencement of cART,^{22,23,26,27} possibly reflecting a similar immune reconstitution process in patients who perhaps had incipient PML at the time of commencing cART.

Clinical and radiological deterioration during the first four weeks of cART may be followed by recovery and stabilisation, or progressive deterioration.^{22,24,28,29} It is thought that cART-induced immune reconstitution may be associated with enhancement of lesions on imaging and inflammatory changes on brain biopsy.^{24,28,30,31} Some authors have treated these patients with prednisone.^{24,32} Initially, it is probably reasonable to watch these patients cautiously, while maintaining the cART regimen.

Recommended combination antiretroviral therapy regimens

Patients who develop PML and who are antiretroviral-naïve or receiving suboptimal antiretroviral therapy should commence or change cART regimens, respectively. Although unproven in clinical studies,³³ it is reasonable to suggest that the cART regimen should include drugs that have good CSF penetration. Thus a three- or four-drug combination similar to those used for HIV-1-associated dementia (see Chapter 18.2.3) is recommended.

For patients who are on cART and who have a very low or undetectable plasma and CSF HIV viral load at the time that PML is diagnosed, the cART regimen can be switched in the hope that any low-level HIV viral replication will be controlled.

Cytosine arabinoside, interferon-alpha and cidofovir

Intravenous cytosine arabinoside was not beneficial in the treatment of HIV-related PML in a large, placebo-controlled, randomised study,¹¹ and is rarely used. Subcutaneous interferon-alpha was associated with improved survival in a retrospective study,³⁴ but has not yet been tested in clinical trials. It is not used routinely to treat PML, because of its potentially significant toxicity. Cidofovir has proved disappointing in two studies of cART alone versus cART plus cidofovir to treat PML: there was no survival benefit, nor any benefit in neurological outcome.^{20,35}

Recently the use of the antidepressant agent, mirtazapine, has been associated with improved outcome in HIV-negative patients with PML.^{36,37} Other agents that have been suggested as potential treatment for PML include the thiazolidenones,³⁸ and the antipsychotic agents, risperidone and olanzapine.^{39,40}

Monitoring

The monitoring of a patient with PML is summarised in Figure 13.2. Patients diagnosed with PML should be reviewed weekly during the first month of commencing cART therapy to monitor for deterioration in symptoms and signs during this period. Following this, the patient should be seen every two to four weeks for the first three months.

If the JCV is detected in the CSF at baseline, then a repeat lumbar puncture should be performed to look for JCV clearance at six to 12 weeks, although there are few data available to guide the clinician about the optimum time to repeat the JCV PCR.

Repeat MRI should be performed at six, 12 and 24 weeks after cART initiation or switch. It should also be noted that some patients improve significantly without any obvious change in MRI abnormalities.

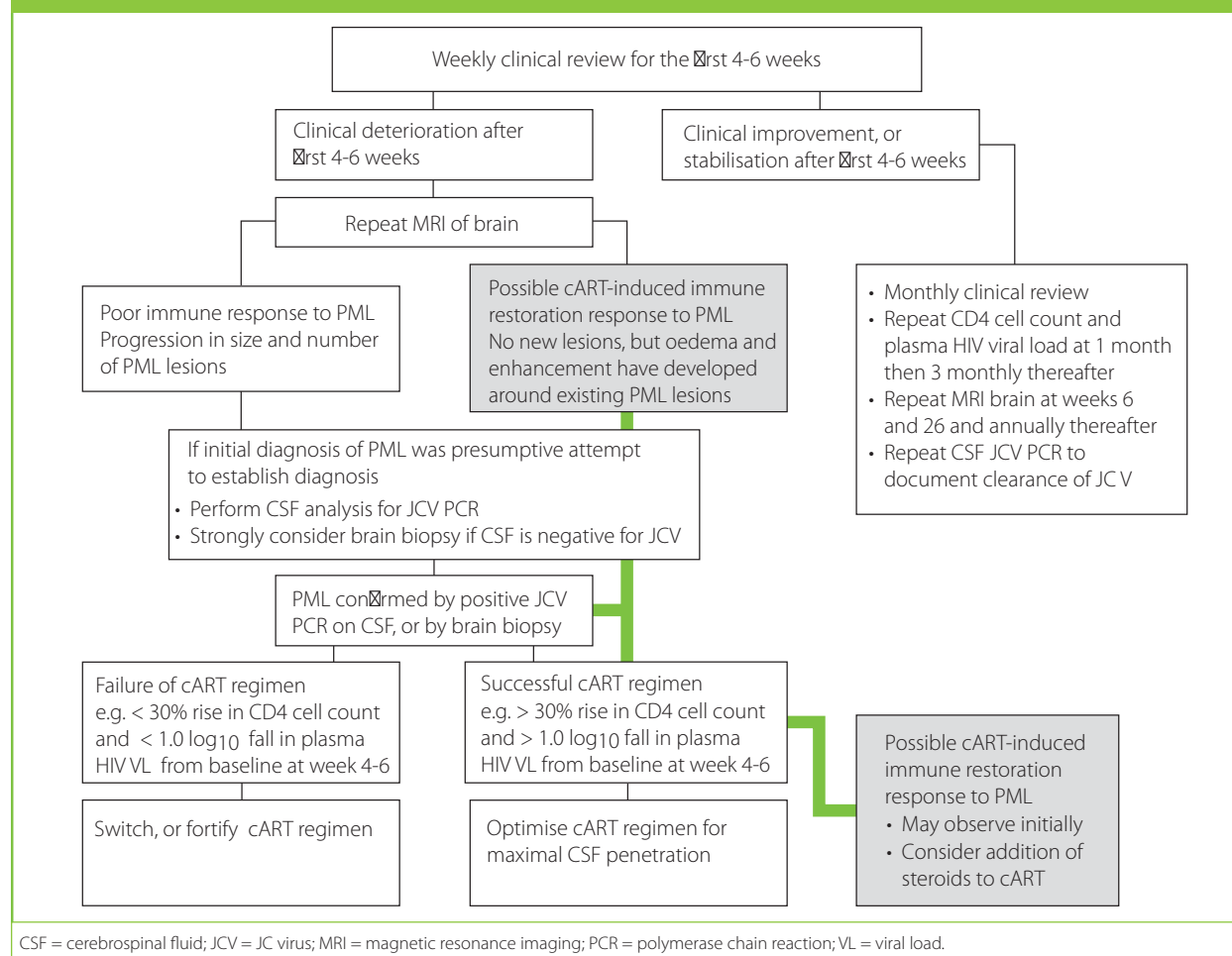
If a patient deteriorates despite a successful virological and immunological response to cART, then consideration should be

given to a brain biopsy if the diagnosis of PML was presumptive and not virologically proven.

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Figure 13.2 Monitoring patients with HIV infection with progressive multifocal leukoencephalopathy



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