Complications of HIV Infection

Most complications of HIV/AIDS are as a result of suppression of T cell-mediated immunity. Antiretroviral therapy (ART) is available to inhibit the replication of the human immunodeficiency virus. ART is increasingly replacing the term ‘highly active antiretroviral therapy’ (HAART) in common usage. ART helps to prolong life, restore the patient's immune system to something approaching normal activity and reduce the chances of opportunistic infection. Indeed, early use of ART has increased survival to near-normal duration and dramatically reduced the risk of developing AIDS (or late-stage HIV disease, as it is increasingly being called). Combinations of three or more drugs are given to lessen the possibility of resistance.

For more information see separate articles Acquired Immune Deficiency Syndrome (AIDS) and Human Immunodeficiency Virus (HIV).

Pulmonary complications

Pneumocystis jirovecii pneumonia

Pneumocystis jirovecii (formerly known as Pneumocystis carinii) has been one of the hallmarks of late-stage HIV disease but is now less common because of ART and primary prophylaxis. Nevertheless, it remains a significant cause of pathology and is increasing in non-AIDS immunosuppressed patients (mainly transplant recipients) in whom a reservoir of infection is maintained. Most late-stage HIV disease cases occur with a CD4 count of <200/mm$^3$ and mainly at <100/mm$^3$.

See separate article Pneumocystis Jirovecii Pneumonia for further details.

Bacterial pneumonia

The most common causes are Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis. In advanced cases, causative organisms may include Staphylococcus aureus, Klebsiella spp. and other Gram-negative rods. The presentation may be atypical, with diffuse infiltrates appearing on the X-ray.

Fungal infections

These may include Cryptococcus spp. In disseminated infection other fungi may be involved. The first-line treatment for most fungal lung infections is IV amphotericin.

Tuberculosis (TB)

This is very common in areas where TB is endemic. Many cases represent reactivation of previous infection. HIV-positive patients with TB are less likely to be sputum-positive with X-rays that show less cavitation and more involvement of lower lobes. They are more likely to relapse after completion of treatment and die prematurely. Treatment is the standard 3-4 drug regimen but multidrug-resistant TB strains are becoming more frequent. Studies of TB preventative therapy (eg, isoniazid, co-trimoxazole) are equivocal. Further research is needed to determine whether or not such therapy reduces the incidence of TB infection and overall mortality in children with HIV.

Mycobacterium avium complex

This is seen in late-stage HIV disease. Patients with a CD4 count of <50/mm$^3$ are at high risk. In industrialised countries, it is reported in 40% of patients with AIDS:

- **Presentation**: infection is disseminated and presents with fever, night sweats, weight loss, diarrhoea, abdominal pain, anaemia or hepatic dysfunction.
- **Diagnosis**: this is by culture from blood or bone marrow or may be recognised in tissue biopsy.
- **Treatment**: studies suggest the best regime for most strains is rifamycin, ethambutol and a macrolide. However, for Mycobacterium simiae a combination of macrolide, moxifloxacin and an additional drug such as IV amikacin is beneficial. Recently, trials have shown benefit from the use of aerolised rather than IV amikacin.

Central nervous system complications

Cerebral toxoplasmosis

Toxoplasmosis is less common than it was, since the advent of ART, although is still prevalent in resource-poor countries. Cerebral toxoplasmosis is the most frequent central nervous system (CNS) infection when CD4 count is <200/mm$^3$. It usually occurs due to reactivation of cysts in the brain, causing local lesions, typically multiple.

- **Presentation**: subacute symptoms include focal neurological disturbances, headache, confusion, fever and seizures.
- **Investigations**: CT scan: the appearance is of a mass with a ring of contrast enhancement and associated oedema.
  - **MRI**: this may show lesions not visible on CT.
  - **Polymerase chain reaction (PCR) test**: may be helpful.
Cryptococcal meningitis \[2\]
- **Presentation**: this is usually subacute with nonspecific symptoms such as headache, vomiting and a slight fever. Neurological signs are not a major feature. Less commonly, patients present with psychiatric symptoms, convulsions, cranial nerve palsies or truncal ataxia.
- **Investigations**: these reveal focal neurological lesions. Diagnosis is by identifying positive CSF cryptococcal antigen in the CSF.
- **Treatment**: amphotericin plus 5-flucytosine are first-line therapy. Fluconazole plus flucytosine are recommended as second-line or where intolerance develops. Voriconazole or posaconazole are other second-line options.
- **Prognosis**: the condition is responsive to treatment in 70-75% of patients capable of a good immune response but relapses are more frequent in the immunosuppressed.

Progressive multifocal leukoencephalopathy (PML) \[2\]
PML is a progressive demyelinating condition of advanced disease caused by the John Cunningham virus (JCV) and presents with focal neurological signs, changes in personality and ataxia. The diagnosis is by MRI and JCV detection by PCR in a CSF sample. There is no specific treatment and the patient usually dies within six months unless effective ART is used. Some patients develop PML during combined ART in the setting of immune reconstitution. Steroids may be useful in such cases.

HIV encephalopathy \[12, 13\]
- **Presentation**: HIV directly infects the nervous system and most patients dying of late-stage HIV disease have histological evidence of brain damage. Before the introduction of ART, the HIV-associated neurocognitive impairment was categorised as AIDS-dementia complex, HIV encephalitis or encephalopathy, with an estimated prevalence of 16% in patients with a diagnosis of AIDS. This has been given the umbrella term HIV-associated neurocognitive disorder (HAND). In the early stages, the concentration or memory is affected, with apparent depression and a gradual diminution of intellect. There may be increasing motor problems affecting activities of daily living. Movements may be slow. Examination may reveal incoordination, motor weakness, hyperreflexia and extensor plantar responses. Post-ART, the picture has changed. The prevalence of mild cognitive disorders has increased whilst that of dementia has decreased. The prevalence of dementia is now estimated to be less than 5%.
- **Investigations**: MRI shows reduced grey matter volume in the cortex and basal ganglia. In the late stages, there is a need to differentiate from cytomegalovirus (CMV) encephalitis, which usually presents with rapidly progressive convulsion and dementia. Investigations to exclude other causes of neurocognitive impairment may need to be carried out - eg, vitamin B12, folate level, TSH, syphilis, hepatitis C, glucose and vitamin B1 as well as screening for dyslipidaemia. CSF examination may be required, especially when there are other signs of CNS infection - eg, fever, CD4 cell counts below 200 cells/mm3 or positive serology for syphilis. Depression, anxiety and the effects of alcohol and drugs may all need to be eliminated. It is hoped that the search for reliable biomarkers will eventually lead to more specific methods of diagnosis.
- **Treatment**: ART has considerably improved the prognosis if given early enough. However, the virus may continue to remain, at low levels, in the body and continue to replicate, so prognosis must be guarded. At present no adjuvant therapy has been found helpful.

Peripheral neuropathy and myelopathy
This can occur at any stage of HIV infection but is more common in advanced disease. At this point, 10-15% of cases show distal symmetrical neuropathy affecting both sensory and motor systems. The condition may be exacerbated by antiretrovirals. It can cause postural hypotension, diarrhoea, impotence, impaired sweating and bladder dysfunction. HIV may directly involve the spinal cord, usually presenting with bilateral leg weakness and sensory symptoms. CMV infection presents with lumbosacral polyradiculopathy resulting in sacral paraesthesias and numbness, weakness of lower limbs and urinary retention. Treatment is mainly symptomatic with analgesics and anticonvulsants. Recombinant human nerve growth factor and capsaicin have both shown some efficacy in trials but the former is not commercially available and the latter is often not tolerated.

Ocular disease

CMV retinitis \[2, 16\]
In the absence of antiretroviral therapy, up to 30% cases of AIDS with CD4 count <50/mm³ show reactivation of CMV with destructive blinding retinitis. It usually presents with blurred vision, partial loss of vision in one eye, floaters or flashing lights. Typical retinal changes include irregular retinal pallor with haemorrhages in a perivascular distribution. These usually start peripherally and rapidly progress to involve the macula and whole retina, causing blindness. The main treatment is IV ganciclovir which is dose-limited in approximately 10% of patients by severe neutropenia and thrombocytopenia. Foscarnet is used in ganciclovir-resistant cases. Valganciclovir and cidofovir have also been found to be effective but only valganciclovir is available in the UK.

Tumours \[17, 18\]
The incidence of both Kaposi's sarcoma and non-Hodgkin's lymphoma have been markedly reduced since the introduction of ART, although the incidence of other cancers in HIV patients has not changed.

Kaposi's sarcoma \[19\]
**Presentation:** this characteristically presents as multiple ecchymotic skin nodules, macules or papules. It occurs in about 15% of patients. Despite the advent of ART, it often affects the face early in HIV. It is also found on mucosal surfaces, usually on the hard palate. Visceral disease commonly affects the lungs and gastrointestinal tract, causing dyspnea, cough, haemoptysis, abdominal pain or bleeding.

**Treatment:** the treatment of localised disease has been with radiotherapy, cryotherapy or intralesional vinblastine but is being superseded by pegylated liposomal doxorubicin or liposomal daunorubicin.[20, 21] The drugs are given intravenously and have been found to produce shrinkage of the tumour in the majority of patients. Paclitaxel, a taxane, is recommended for second-line treatment.

**Non-Hodgkin’s lymphoma**[19, 22] This develops in 3-10% of people living with HIV, with most tumours being extranodal. Around half of these are associated with Epstein-Barr virus (EBV) infection and these are more aggressive with lower survival rates. CNS sites are common, presenting with symptoms and signs of space-occupying cerebral tumours and this carries very poor prognosis with three months’ survival without ART. Tumours outside the CNS can respond to standard chemotherapy regimens. Rituximab should be given concomitantly. Opportunistic infections may cause death during chemotherapy.

**Oesophageal candidiasis**[2] This presents with retrosternal pain on swallowing and is usually caused by *Candida albicans*. This is a common complication of late-stage HIV disease. The first line of treatment is fluconazole. Other antifungal drugs tried in refractory cases include micafungin and posaconazole.

**Further reading & references**


9. aidsmap.com; Pattern of HIV-related central nervous system disorders varies by region, evolving alongside access to antiretroviral therapy, 2015.
17. HIV in Primary Care: Medical Foundation for AIDS & Sexual Health (2011)

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