HIV AND OPPURTUNISTIC INFECTIONS

HIV (human immunodeficiency virus) is a RNA virus with reverse transcriptase enzyme that attacks the body's immune system. If **HIV** is not treated, it can lead to AIDS (acquired immunodeficiency syndrome). There is currently no effective cure. Once people get **HIV**, they have it for life. But with proper medical care, **HIV** can be controlled.The virus has been isolated from a number of body fluids, including blood, semen, vaginal secretions, saliva, breast milk, tears, urine, peritoneal fluid and cerebrospinal fluid (CSF). However, not all of these are important in the spread of infection and the predominant routes of transmission remain: sexual intercourse (anal or vaginal); sharing of unsterilised needles or syringes; blood or blood products in areas where supplies are not screened or treated; and vertical transmission in utero, during labour or through breast feeding.

Pathogenesis

HIV, in common with other retroviruses, possesses the enzyme reverse transcriptase and consists of a lipid bilayer membrane surrounding the capsid (Fig. 41.1). Its surface glycoprotein molecule(gp120) has a strong affinity for the CD4 receptor protein found predominantly on the T-helper/inducer lymphocytes. Monocytes and macrophages may also possess CD4 receptors in low densities and can therefore also be infected. The process of HIV entry is more complex than originally thought, and in addition to CD4 attachment, subsequent binding to co-receptors such as CCR-5 or CXCR-4 and membrane fusion also occur (Fig. 41.2). After penetrating the host cell, the virus sheds its outer coat and releases its genetic material. Using the reverse transcriptase enzyme, the viral RNA is converted to DNA using nucleosides. The viral DNA is then integrated into the host genome in the cell nucleus, where it undergoes transcription and translation, enabling the production of new viral proteins. New virus particles are then assembled and bud out of the host cell, finally maturing into infectious virions under the influence of the protease enzyme. Immediately after primary HIV Infection (PHI, also known as ‘seroconversion’), there is a very high rate of viral turnover. Equilibrium is then reached, at which stage the infection may appear to be clinically latent, but in fact, as many as 10,000 million new virions are produced each day. Over time, as chronic infection ensues, cells possessing CD4 receptors, particularly the T-helper lymphocytes, are depleted from the body. The T-helper cell is often considered to be the conductor of the ‘immune orchestra’ and thus, as this cell is depleted, the individual becomes susceptible to a myriad of infections and tumours. The rate at which this immunosuppression progresses is variable and the precise interaction of factors affecting it is still not fully understood. It is well recognised that some individuals rapidly develop severe immunosuppression, whilst others may have been infected with HIV for many years whilst maintaining a relatively intact immune system. It is likely that a combination of viral, host (genetic) and environmental factors contributes to this variation.

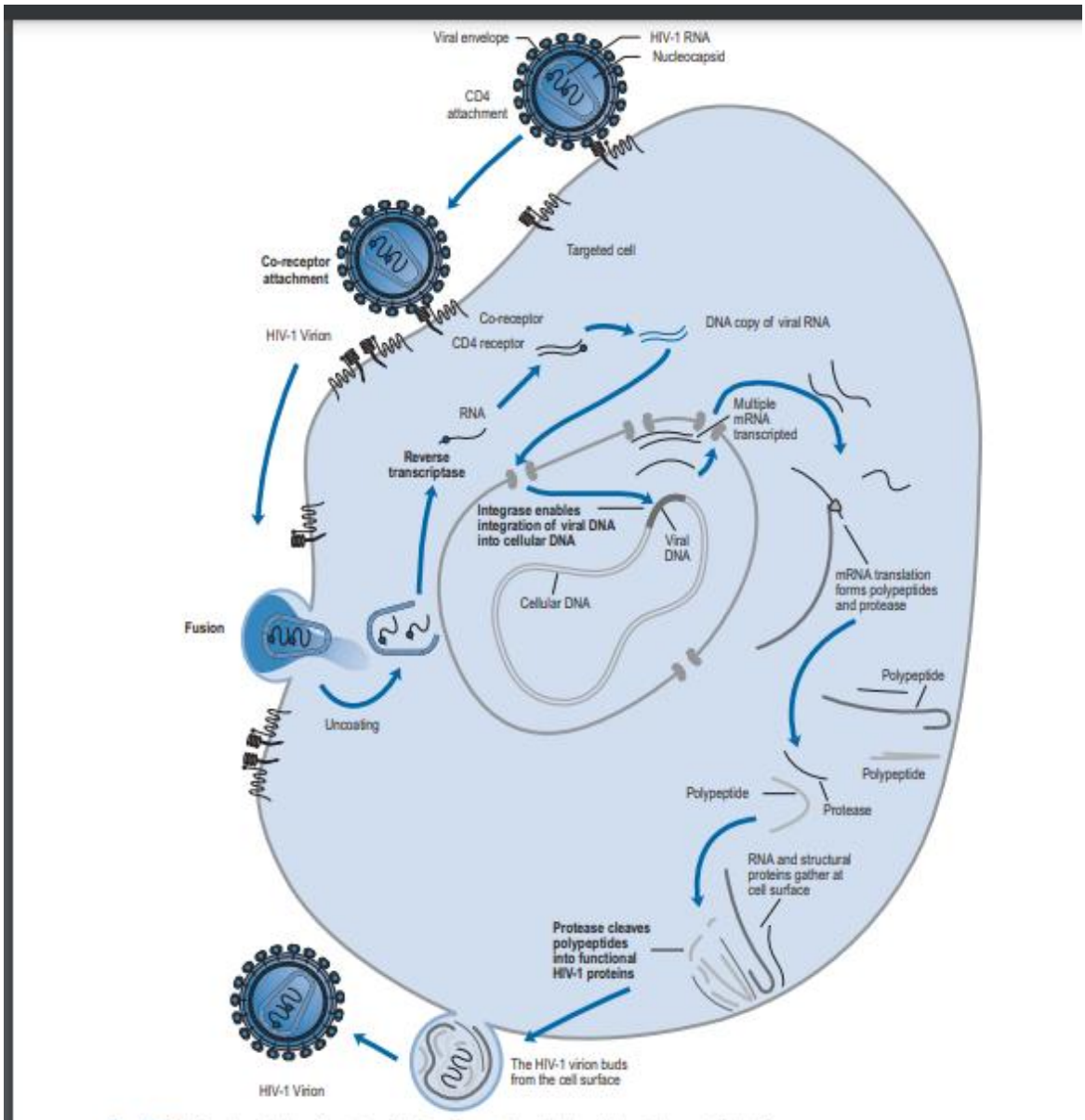

Fig. 41.2 Lifecycle of HIV and the sites of action of currently available antiretroviral agents (in bold).

Clinical manifestations

The sequelae of untreated HIV infection can be broadly considered in five categories:

• Opportunistic infections, that is, infections that would not normally cause disease in an immunocompetent host, for example, P. jiroveci pneumonia and cytomegalovirus (CMV) • Infections that can occur in immunocompetent patients but tend to occur more frequently, more severely and often atypically in the context of underlying HIV infection, for example, Salmonella, herpes simplex and Mycobacterium tuberculosis

• Malignancies, particularly those that occur rarely in the immunocompetent population, for example, Kaposi's sarcoma and non-Hodgkin's lymphoma

• Direct manifestations of HIV infection per se, for example, HIV encephalopathy, HIV myelopathy and HIV enteropathy

• Consequences of chronic immune activation including premature cardiovascular disease, neurocognitive dysfunction, bone mineral density loss.

In addition, approximately 70% of individuals develop a flu-like illness at seroconversion. This primary HIV infection (PHI) is characterised by fever, arthralgia, pharyngitis, rash and lymphadenopathy. Rarely, the degree of associated CD4 count depletion may be sufficient to result in development of an opportunistic illness such as oropharyngeal/oesophageal candidiasis or P. jiroveci pneumonia. Opportunistic infections generally fall into two categories: • DNA viruses, for example, CMV and JC virus • Intracellular pathogens, for example, P. jiroveci, Toxoplasma gondii and Mycobacterium avium. Although the clinical course of HIV disease varies with each individual, there is a fairly consistent and predictable pattern that enables appropriate interventions and preventive measures to be adopted. Patients can be classified into one of three groups according to their clinical status: asymptomatic, symptomatic or AIDS. Symptomatic disease is characterised by non-specific symptomatology such as fevers, night sweats, lethargy and weight loss, or by complications including oral candidiasis, oral hairy leucoplakia, and recurrent herpes simplex or herpes zoster infections. AIDS is defined by the diagnosis of one or more specific conditions including P. jiroveci pneumonia, M. tuberculosis infection and CMV disease.

Investigations and monitoring

Current and previous infections

The initial diagnosis of HIV infection is made by the detection of antibodies against HIV. With improved technology, it is usually possible to detect antibodies within 3–4 weeks of infection, although individuals are advised that a ‘window period’ of up to 3 months after exposure is required before infection can be excluded. After confirmation of HIV infection, the patient is usually tested for prior exposure to a number of potential pathogens, including syphilis, hepatitis A, B and C, CMV, varicella zoster (VZV), and T. gondii. This can enable subsequent treatment (in the case of undiagnosed syphilis), vaccination (if no prior exposure to hepatitis A, B, or VZV), prevention (if no prior exposure to Toxoplasma and CMV), prophylaxis (if previous exposure to Toxoplasma) and can aid subsequent diagnosis (according to CMV or Toxoplasma status).

CD4 count

The level of immunosuppression is most easily estimated by monitoring a patient's CD4 count. This measures the number of CD4-positive T-lymphocytes in a sample of peripheral blood. The normal range can vary between 500 and 1500 cells/ mm3 . As HIV disease progresses, the number of cells falls. Particular complications of HIV infection usually begin to occur at similar CD4 counts which can assist in differential diagnoses and enable the use of prophylactic therapies. For example, patients with a CD4 count of less than 200 cells/mm3 should always be offered prophylaxis against P. jiroveci pneumonia. Similarly, both patient and clinician are likely to use the CD4 count as the major indicator of when to consider starting antiretroviral therapy.

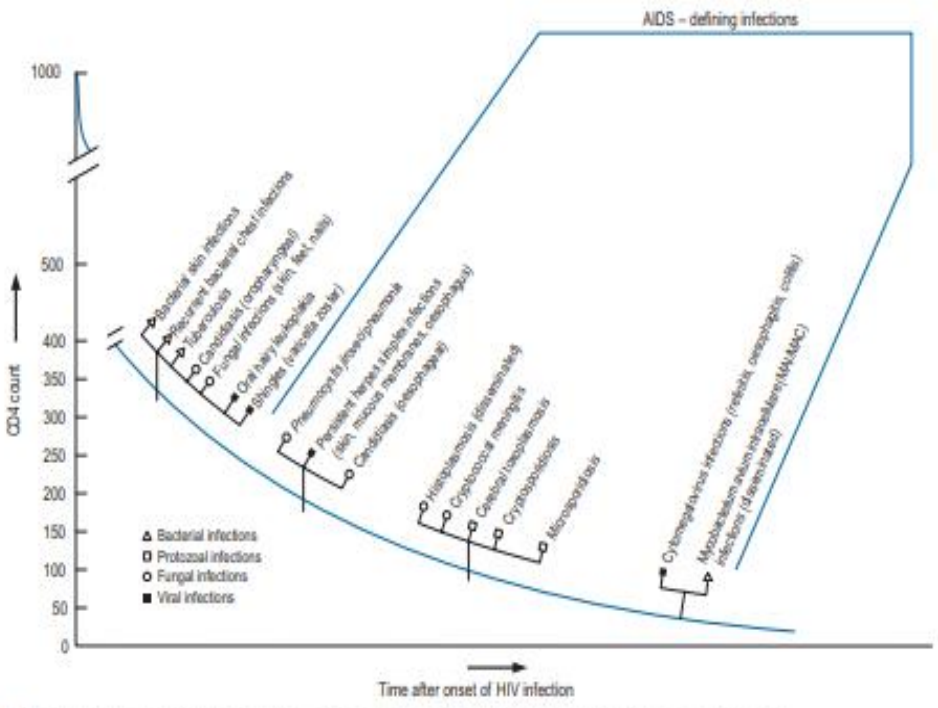

Fig. 41.3 Opportunistic complications of HIV infection and the CD4 count ranges at which they commonly occur.

Viral load

The measurement of plasma HIV RNA (viral load) estimates the amount of circulating virus in the blood. This has been proven to correlate with prognosis, with a high viral load predicting faster disease progression (Mellors et al., 1997). Conversely, a reduction in viral load after commencement of antiviral therapy is associated with clinical benefit. This measure, in combination with the CD4 count, allows patients and clinicians to make informed decisions regarding when to start and when to change antiviral therapies, enabling the more effective use of such agents. There are on-line calculators utilising viral load and CD4 count to model risk of disease progression or death based on large cohort studies.

Resistance testing

Due to the implications of transmitted (primary) resistance, it is recommended that all patients have a genotypic HIV resistance test performed soon after diagnosis; this will ensure that appropriate initial therapy is selected. Further resistance tests should be performed at any subsequent virological failure to direct therapy choice.

Tropism testing

Viruses may enter the cell using the CCR5 co-receptor, the CXCR4 co-receptor or both co-receptors. Those which just use one co-receptor are known as CCR5-tropic or CXCR4- tropic viruses; those which can use both receptor types are called dual-tropic. Where a mixture of virus populations is present, the term mixed-tropic is used. Different methods of determining tropism are currently under evaluation. The tests must be performed in real time as viral tropism changes as the disease progresses. If CCR5 inhibitors are to be used, it is essential to determine that the virus is CCR5-tropic, that is, that there is no significant use of the CXCR4 receptor.

Drug treatment

The drug treatment of HIV disease can be classified as

1. antiretroviral therapy,
2. the management of opportunistic infections or malignancies,
3. the management of 'non-HIV-related' co-morbidities, and symptom control.

For the first decade of the epidemic, most of the available drugs and therapeutic strategies were aimed at treating or preventing opportunistic complications and alleviating HIV-related symptoms. Whilst these are still important, there has been a shift in emphasis towards treatment aimed at reducing the HIV viral load, restoring immune function and reducing the potential consequences of co-morbidities. Due to the speed at which new antiretroviral agents are being developed, comprehensive data on drug interactions, side effects, etc., are often lacking. Thus, the ability to apply general pharmacological and pharmacokinetic principles, together with common sense, is required. The treatment of many of the opportunistic complications of HIV comprises an induction phase of high-dose therapy, followed by maintenance and/or secondary prophylaxis using lower doses. This is due to the high rate of relapse or progression after a first episode of diseases such as P. jiroveci pneumonia, cerebral toxoplasmosis (toxoplasmic encephalitis), systemic cryptococcosis and CMV retinitis. Where a cost-effective agent with an acceptable risk/benefit ratio exists, primary prophylaxis may be offered to individuals who are deemed to be at high risk of developing a particular opportunistic infection, for example, P. jiroveci pneumonia prophylaxis. Discontinuation of prophylaxis, both primary and secondary, is now usually possible in individuals who demonstrate immunological restoration on Highly Active Antiretroviral Therapy (HAART). Paradoxically, this immunological restoration may result in apparent clinical deterioration

with opportunistic infections during the first few weeks after initiation of HAART. This is known as immune reconstitution inflammatory syndrome (IRIS). The goals of therapy in HIV-positive individuals are to:

• improve the quality and duration of life;

• prevent deterioration of immune function and/or restore immune status;

• treat and/or prevent opportunistic infections;

• relieve symptoms.

Antiretroviral therapy

Antiretroviral therapy is currently one of the fastest evolving areas of medicine. The specific details of treatment will therefore continue to change as new drugs emerge, although it is likely that the following general principles will remain:

• A combination of three antiretroviral agents, selected on the basis of treatment history and resistance tests, should usually be prescribed to increase efficacy and reduce the development of drug-resistant virus

• Wherever possible, a regimen should contain at least one drug that penetrates the central nervous system and confers protection against HIV-related encephalopathy/ dementia

• Treatment strategies should be adopted that sequence drug combinations, being mindful of potential crossresistance and future therapy options

• Given the crucial importance of a high level of adherence to these therapies, the regimen adopted for a particular individual should, wherever possible, be tailored to suit the daily lifestyle

1. Nucleoside and nucleotide analogue reverse transcriptase inhibitors :NRTIs are phosphorylated intracellularly and then inhibit the viral reverse transcriptase enzyme by acting as a false substrate. Nucleotide analogues only require two intracellular phosphorylations, whereas activation of nucleoside analogues is a three-stage process. Eg: Abacavir , Didanosine , Emtricitabine , Lamivudine , Stavudine, Tenofovir , Zidovudine
2. Non-nucleoside reverse transcriptase inhibitors: NNRTIs inhibit the reverse transcriptase enzyme by binding to its active site. They do not require prior phosphorylation and can act on cell-free virions as well as infected cells. The NNRTIs available include: Efavirenz ,Nevirapine ,) Etravirine . Resistance to NNRTIs occurs rapidly in incompletely suppressive regimens and it is therefore essential that they are prescribed with at least two NRTIs or a combination of NRTIs and PIs. Cross-resistance between nevirapine and efavirenz, which are currently used as first-line NNRTIs, is high. The first of the second-generation NNRTIs, etravirine, is active against some viruses resistant to these agents.

3. Protease inhibitors :PIs bind to the active site of the HIV-1 protease enzyme, preventing the maturation of the newly produced virions so that they remain non-infectious. The following PIs are currently available: Atazanavir , Darunavir , Fosamprenavir , Indinavir,Lopinavir co-formulated with ritonavir , Nelfinavir, Ritonavir ,Saquinavir, Tipranavir .The use of ritonavir-boosted PIs has superseded use of single PIs, due to better pharmacokinetic profiles, superior efficacy data and reduced likelihood of resistance development. Newer second-generation PIs such as tipranavir and darunavir are effective against many viruses resistant to the earlier PIs.
4. Entry inhibitors :There are currently two types of entry inhibitors (fusion inhibitors and CCR5 inhibitors) with one agent available in each class. Fusion inhibitors block the structural rearrangement of HIV-1 gp41 and thus stop the fusion of the viral cell membrane with the target cell membrane, preventing viral RNA from entering the cell. CCR5 inhibitors selectively bind to the human chemokine receptor CCR5, preventing CCR5-tropic HIV-1 from entering cells. Enfuvirtide (T-20, Fuzeon®), a fusion inhibitor, is administered subcutaneously and is largely used in heavily treatment experienced patients. The main side effect is injection site reactions. However, following the licensing of new agents from different antiretroviral classes, enfuvirtide is now rarely used. Maraviroc (Celsentri®), a CCR5 inhibitor, is indicated for use in patients with only CCR5-tropic virus, which is determined by a tropism test just prior to commencing treatment. It is usually used in patients with resistance to one or more other antiretroviral classes.
5. Integrase inhibitors: Integrase inhibitors bind to the integrase enzyme, thus blocking the integration of viral DNA into host DNA. There is currently one licensed agent, raltegravir .

Toxicity of antiretroviral therapies

As more antiretroviral agents have become available and the number of patient-years of exposure to them has increased, our understanding of their various toxicities has grown significantly. there are also a number of class-specific or therapyrelated toxicities

Mitochondrial toxicity:.

Mitochondrial toxicity is increasingly recognised in patients with prolonged exposure to nucleoside analogue antiretrovirals, particularly stavudine, didanosine and, to a lesser extent, zidovudine, and is thought to explain such side effects as peripheral neuropathy, myopathy, pancreatitis and lactic acidosis. Rash and hepatitis. These are both recognised side effects of the NNRTI class, although the incidence and severity appear greatest with nevirapine, particularly in patients with a higher CD4 count (>250 cells/mm3 for women and >400 cells/mm3 for men). Management is either close observation (in mild-tomoderate cases) or withdrawal of the causative agent (in severe cases

.

Lipodystrophy.
Lipodystrophy has been well reported in individuals on HAART. This is characterised by one or both of lipoatrophy (fat loss, particularly from the face, upper limbs and buttocks) and lipohypertrophy (abnormal fat deposition, particularly affecting the abdomen and neck). Whilst these body shape changes are associated with drug therapy, predominantly stavudine and zidovudine for lipoatrophy and possibly PIs for lipohypertrophy,

Metabolic disturbances.
Hypercholesterolaemia and hypertriglyceridaemia, in particular, are frequently seen in patients receiving HAART. Again, the aetiology of these toxicities is likely to represent a combination of drug and host factors. However, they are particularly associated with PIs, although the incidence appears lower with atazanavir. Whilst it is likely that this hyperlipidaemia contributes to an increased cardiovascular disease risk, this needs to be considered in the context of traditional risk factors, for example, smoking, which may be present in this patient group. Management is to reduce all modifiable risk factors and either switch away from the likely causative agent to one more metabolically favourable or consider adjunctive lipid-lowering therapy, taking into consideration potential drug–drug interactions (Schambelan et al., 2002). Renal impairment and, rarely, Fanconi's syndrome have been reported with tenofovir. Creatinine clearance should be calculated and proteinuria quantified prior to starting therapy with this agent and should be monitored regularly.
Cardiovascular disease.
studies have suggested an increased risk of cardiovascular disease with some PIs (Kaletra® and indinavir) and with the NRTI, abacavir (Sabin et al., 2008; Worm et al., 2010). This risk is independent of the effect on lipids and the mechanism has yet to be determined. As with lipid disturbances, the decision to start or continue these agents needs to be considered as part of a holistic approach to cardiovascular risk.

HIV REGIMENS
REFFER NACO GUIDELINES NOTES

Opportunistic infections and malignancies

1. Oropharyngeal candidiasis. Candidiasis is a frequent manifestation of HIV infection and may occur early in the disease. Clinically, it is usually characterised by white plaques on the oral mucosa, but may present as erythematous patches or as angular cheilitis. If swallowing is difficult (dysphagia) or painful (odynophagia), oesophageal involvement may be suspected. First-line therapy for oral candidiasis is a systemic agent, usually fluconazole (50 mg daily for 7 days). An alternative is itraconazole (200 mg once daily) In cases of oesophageal candida, which is an AIDS-defining

illness, systemic therapy is necessary using higher doses of the above agents for a longer duration, for example, fluconazole 100mg once daily for 2 weeks

2. Cryptococcus neoformans. This causes a disseminated infection, usually with meningeal involvement, in individuals with HIV infection. Patients present with fever and headaches, often without the characteristic symptoms of meningism such as photophobia and neck stiffness. Diagnosis is normally made on the basis of CSF analysis, though serum cryptococcal antigen and blood cultures may also be indicative. For patients who are moderately or severely unwell, intravenous amphotericin B deoxycholate (0.7–1 mg/kg/day) or a lipid complex/liposomal formulation, with or without flucytosine (100 mg/kg/day in divided doses, oral or intravenous) is the first-line therapy.

3. Toxoplasmosis. T. gondii is a frequent cause of central nervous system disease in patients with AIDS. Individuals may present with headaches, fever, confusion, seizures or focal neurological symptoms and signs. Diagnosis is usually based on the appearance of ring-enhancing lesion(s) on computed tomography (CT scan). Definitive diagnosis is based on brain biopsy, which is rarely performed, but is generally made presumptively after response to therapy. First-line treatment is sulphadiazine and pyrimethamine, with folinic acid to prevent myelosuppression, for 6 weeks, followed by maintenance therapy with lower doses of the same agents until CD4 count is consistently maintained above 200cells/mm3 . The preferred alternative is clindamycin and pyrimethamine with folinic acid, with limited data for atovaquone, co-trimoxazole, clarithromycin and doxycycline. Adjunctive therapy with corticosteroids or anticonvulsants may be used in cases of severe oedema or seizures, respectively.

4. Cryptosporidiosis. Cryptosporidium parvum is a ubiquitous organism and a common cause of diarrhoea in immunocompetent individuals. In patients who are immunocompromised, persistent infection may occur characterised by abdominal pain, weight loss and severe diarrhoea. Diagnosis is generally based on stool analysis. Although many agents have been investigated for the treatment of cryptosporidiosis, the majority of results have been disappointing. Nitazoxanide is possibly the most promising agent, but failed to demonstrate superiority over placebo in severely immunocompromised patients. The optimal treatment for cryptosporidiosis (and indeed the majority of chronic opportunistic infections) is to increase immunological function with HAART. The mainstay of management in patients who are not able or willing to take HAART remains symptomatic control with nutritional supplementation, adequate hydration and antidiarrhoeal agents.

5. . Bacterial infections Bacterial infections are common in the context of HIV infection. Recurrent bacterial pneumonia, particularly Streptococcus pneumoniae, and diarrhoeal illnesses associated with Salmonella, Shigella or Campylobacter are particularly common. In general, these are treated the same as in immunocompetent individuals, although recurrent infections and/or septicaemia occur more frequently.

6. Cytomegalovirus. CMV is a herpes virus that is acquired by approximately 50% of the general population and over 90% of homosexual men. Like other herpes viruses, once infection has occurred, the virus remains dormant thereafter, but in individuals with advanced immunosuppression, reactivation may occur and cause disease. In the context of HIV infection, the most common sites of disease are the retina and gastrointestinal tract, though neurological involvement and pneumonitis are well reported

Diagnosis of CMV retinitis is based on clinical appearance; it may be detected in asymptomatic individuals but usually presents with symptoms of blurred vision, visual field defects or 'floaters'. Untreated CMV retinitis progresses rapidly to blindness and treatment substantially reduces the morbidity associated with this condition. The most commonly used agent for induction therapy is ganciclovir, which can be given intravenously or orally, as the pro-drug valganciclovir.Valganciclovir is well absorbed and a dose of 900mg twice daily has been shown to be as effective as intravenous ganciclovir for induction therapy. Significant side effects encountered with these agents include neutropenia, which may require colony-stimulating factor support, and thrombocytopenia. Maintenance treatment may also be given either intravenously (6mg/kg on 5 days a week) or orally (valganciclovir 900 mg once daily). An alternative agent to ganciclovir is foscarnet. It has a less favourable toxicity profile and is thus usually reserved for cases of therapeutic failure with ganciclovir. Its main adverse effects are electrolyte abnormalities, nephrotoxicity that requires dose adjustment or cessation of therapy,

CMV disease of the gastro-intestinal tract usually affects the oesophagus or colon, causing dysphagia and abdominal pain with diarrhoea, respectively. Diagnosis is based upon histological analysis of biopsy specimens. Treatment is as for CMV retinitis induction therapy; maintenance therapy is not usually given unless relapses occur.

7. Kaposi's sarcoma. This is the most common malignancy in people with HIV infection and may be triggered by infection with human herpes virus 8 (HHV-8). The majority of lesions affect the skin and appear as raised purple papules. These may be single or multiple and in severe cases may result in oedema, ulceration and infection. Visceral involvement is not uncommon but rarely causes clinically significant disease. In some cases, no therapeutic intervention is necessary and cosmetic camouflage may be

sufficient. Indeed, treatment of HIV with antiretroviral therapy usually results in improvement, and in most cases, complete resolution, of Kaposi's sarcoma. When individual lesions are troublesome, local radiotherapy or intralesional vinblastine can be beneficial.

8. Lymphomas. The most common lymphomas in patients with HIV infection are high-grade B-cell (non-Hodgkin's) types. Primary central nervous system lymphomas, which are extremely rare in the general population, are more common in individuals with HIV infection but tend to occur only in those with severe immunosuppression. Diagnosis of lymphoma is usually based upon histological confirmation from biopsy specimens. This may not be possible for primary central nervous system disease. The advent of HAART has dramatically reduced the incidence of all lymphomas.

Neurological manifestations

Neurological symptoms may be due to opportunistic infections, tumours or the primary neurological effects of HIV. HIV encephalopathy or AIDS dementia complex (ADC) is believed to result from direct infection of the central nervous system with HIV itself. Individuals who may otherwise be physically well can be debilitated by profound cognitive dysfunction and amnesia. Although psychometric test results are 41 therapeutics 646 usually suggestive of the underlying aetiology, it is wise to rule out any other cause with brain scanning and CSF analysis. The incidence of ADC has reduced dramatically with the use of HAART, and similarly, the use of HAART has been anecdotally associated with an improvement in outcome in many cases. Whilst it is known that the central nervous system penetration of some antiretroviral agents is better than others, the beneficial effects on ADC do not appear to be limited to those agents which penetrate well. Nonetheless, many clinicians would choose to include at least one agent with good penetration of the central nervous system in most HAART regimens, particularly in individuals with cognitive impairment. More recently, there have been increasing reports of more subtle cognitive impairment in patients with HIV receiving effective HAART therapy. The role of varying neuropenetrative agents in either the aetiology or the management of such patients is currently under investigation.