

02-12 HIV infection and AIDS

12 HIV infection and AIDS

HIV infection and AIDS G Maartens Clinical examination in HIV disease 306 Epidemiology 308 Global and regional epidemics 308 Modes of transmission 308 Virology and immunology 309 Diagnosis and investigations 310 Diagnosing HIV infection 310 Viral load and CD4 counts 311 Clinical manifestations of HIV 311 Presenting problems in HIV infection 312 Lymphadenopathy 313 Weight loss 313 Fever 313 Mucocutaneous disease 314 Gastrointestinal disease 316 Hepatobiliary disease 317 Respiratory disease 318 Nervous system and eye disease 319 Rheumatological disease 321 Haematological abnormalities 322 Renal disease 322 Cardiac disease 322 HIV-related cancers 322 Prevention of opportunistic infections 323 Preventing exposure 323 Chemoprophylaxis 323 Immunisation 324 Antiretroviral therapy 324 ART complications 325 ART in special situations 326 Prevention of HIV 327

306 • HIV INFECTION AND AIDS Clinical examination in HIV disease Inset (oral hairy leucoplakia) Courtesy of Audiovisual Dept, St Mary's Hospital, London. Observation Oropharynx Mucous membranes Neck Lymph node enlargement Tuberculosis Lymphoma Kaposi's sarcoma Persistent generalised lymphadenopathy Parotidomegaly Eyes Retina Toxoplasmosis HIV retinopathy Progressive outer retinal necrosis • Weight loss • Tachypnoea • Fevers and sweats Skin Abdomen Hepatosplenomegaly Chest Lungs Pleural effusion Tuberculosis Kaposi's sarcoma Parapneumonic Central nervous system Higher mental function HIV dementia Progressive multifocal leucoencephalopathy Focal signs Toxoplasmosis Primary CNS lymphoma Neck stiffness Cryptococcal meningitis Tuberculous meningitis Pneumococcal meningitis Anogenital region Rashes Legs Peripheral nerve examination Spastic paraparesis Peripheral neuropathy Kaposi's sarcoma Molluscum contagiosum Gingivitis/periodontitis Cervical lymphadenopathy Oropharyngeal candidiasis Teeth Oral hairy leucoplakia Cytomegalovirus retinitis Anal cancer Papular pruritic eruption

Herpes zoster Seborrhoeic dermatitis Herpes simplex Aphthous ulcers Kaposi's sarcoma Condylomas Herpes simplex Ulcers

Clinical examination in HIV disease • 307

HIV clinical staging classifications World Health Organisation (WHO) clinical stage (used in low- and middle-income countries) Centers for Disease Control (CDC) clinical categories (used in high-income countries) Stage 1 Category A Asymptomatic Persistent generalised lymphadenopathy Primary HIV infection Asymptomatic Persistent generalised lymphadenopathy Stage 2 Category B Unexplained moderate weight loss (< 10% of body weight) Recurrent upper respiratory tract

infections Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections Bacillary angiomatosis Candidiasis, oropharyngeal (thrush) Candidiasis, vulvovaginal; persistent, frequent or poorly responsive to therapy Cervical dysplasia (moderate or severe)/cervical carcinoma in situ Constitutional symptoms, such as fever (38.5°C) or diarrhoea lasting > 1 month Oral hairy leucoplakia Herpes zoster, involving two distinct episodes or more than one dermatome Idiopathic thrombocytopenic purpura Listeriosis Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess Peripheral neuropathy Stage 3 Unexplained severe weight loss ($> 10\%$ of body weight) Unexplained chronic diarrhoea for > 1 month Unexplained persistent fever ($> 37.5^{\circ}\text{C}$ for > 1 month) Persistent oral candidiasis Oral hairy leucoplakia Pulmonary tuberculosis Severe bacterial infections Acute necrotising ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (< 80 g/L (8 g/dL)), neutropenia ($< 0.5 \times 10^9/\text{L}$) and/or chronic thrombocytopenia ($< 50 \times 10^9/\text{L}$) Stage 4 Category C Candidiasis of oesophagus, trachea, bronchi or lungs Cervical carcinoma – invasive Cryptococcosis – extrapulmonary Cryptosporidiosis, chronic (> 1 month) Cytomegalovirus disease (outside liver, spleen and nodes) Herpes simplex chronic (> 1 month) ulcers or visceral HIV encephalopathy HIV wasting syndrome Cystoisosporiasis (formerly known as isosporiasis), chronic (> 1 month) Kaposi's sarcoma Lymphoma (cerebral or B-cell non-Hodgkin) Mycobacterial infection, non-tuberculous, extrapulmonary or disseminated Mycosis – disseminated endemic (e.g. coccidioidomycosis, talaromycosis (formerly penicilliosis), histoplasmosis) Pneumocystis pneumonia Pneumonia, recurrent bacterial Progressive multifocal leucoencephalopathy Toxoplasmosis – cerebral Tuberculosis – extrapulmonary (CDC includes pulmonary) Sepsis, recurrent (including non-typhoidal Salmonella) (CDC only includes Salmonella) Symptomatic HIV-associated nephropathy* Symptomatic HIV-associated cardiomyopathy* Leishmaniasis, atypical disseminated* *These conditions are in WHO stage 4 but not in CDC category C.

308 • HIV INFECTION AND AIDS particularly in southern Africa, where average life expectancy of the general population fell to below 40 years before the introduction of ART. Modes of transmission HIV is transmitted by sexual contact, by exposure to blood (e.g. injection drug use, occupational exposure in health-care workers) and blood products, or to infants of HIV-infected mothers (who may be infected in utero, perinatally or via breastfeeding). Worldwide, the major route of transmission is heterosexual. The risk of contracting HIV after exposure to infected body fluid is dependent on the integrity of the exposed site, the type and volume of fluid, and the level of viraemia in the source person. The approximate transmission risk after exposure is given in Box 12.2. Factors that increase the risk of transmission are listed in Box 12.3. A high proportion of patients with haemophilia in high-income countries had been infected through contaminated blood products by the time HIV antibody screening was adopted in 1985. Routine screening of blood and blood products for HIV infection has virtually eliminated this as a mode of transmission. However, the World Health Organisation (WHO) estimates that, because of the lack of adequate screening facilities in resource-poor countries, 5–10% of blood transfusions globally are with HIV-infected blood. Epidemiology The acquired immunodeficiency syndrome (AIDS) was first recognised in 1981, although the earliest documented case of HIV infection has been traced to a blood sample from the Democratic Republic of Congo in 1959. AIDS is caused by the human immunodeficiency virus (HIV), which progressively impairs cellular immunity. The origin of HIV is a zoonotic infection with simian immunodeficiency viruses (SIV) from African primates, probably first infecting local hunters. SIVs do not cause disease in their natural primate hosts. HIV-1 was transmitted from chimpanzees and HIV-2 from sooty mangabey monkeys. HIV-1 is the cause of the global HIV pandemic, while HIV-2,

which causes a similar illness to HIV-1 but progresses more slowly and is less transmissible, is restricted mainly to western Africa. It has been estimated that both HIV-1 and HIV-2 first infected humans about 100 years ago. HIV-2 will not be discussed further in this chapter. There are three groups of HIV-1, representing three separate transmission events from chimpanzees: M ('major', worldwide distribution), O ('outlier') and N ('non-major and non-outlier'). Groups O and N are restricted to West Africa. Group M consists of nine subtypes: A-D, F-H, J and K (subtypes E and I were subsequently shown to be recombinants of other subtypes). Globally, subtype C (which predominates in sub-Saharan Africa and India) accounts for half of infections and appears to be more readily transmitted. Subtype B predominates in Western Europe, the Americas and Australia. In Europe, the prevalence of non-B subtypes is increasing because of migration. Subtypes A and D are associated with slower and faster disease progression, respectively. Global and regional epidemics

In 2015 it was estimated that there were 36.7 million people living with HIV/AIDS, 2.1 million new infections and 1.1 million AIDS-related deaths. The global epidemiology of HIV has been changed by expanding access to combination antiretroviral therapy (ART), which reached 17 million people in 2015: the annual number of AIDS-related deaths has almost halved since the peak in 2005, the number of new infections has decreased by 40% since the peak in 1997, and the number of people living with HIV has increased. Regions have marked differences in HIV prevalence, incidence and dominant modes of transmission (Box 12.1). HIV has had a devastating impact in sub-Saharan Africa,

12.2 Risk of HIV transmission after single exposure to an HIV-infected source

Exposure	Approximate risk
Sexual Vaginal intercourse: female to male	0.05%
Vaginal intercourse: male to female	0.1%
Anal intercourse: insertive	0.05%
Anal intercourse: receptive	0.5%
Oral intercourse: insertive	0.005%
Oral intercourse: receptive	0.01%
Blood exposure Blood transfusion	90%
Intravenous drug-users sharing needles	0.67%
Percutaneous needlestick injury	0.3%
Mucous membrane splash	0.09%
Mother to child Vaginal delivery	15%
Breastfeeding (per month)	0.5%

12.1 Regional HIV prevalence in 2015, incidence trend and dominant mode of transmission

Region	People living with HIV (millions)	HIV incidence trend (2011–2015)	Dominant transmission
Sub-Saharan Africa	25.5	Decreasing	Heterosexual
Asia and Pacific	5.1	Stable	IDU, heterosexual
Latin America and Caribbean			
Stable MSM, heterosexual			Western and Central Europe, and North America
2.4 Stable MSM			Eastern Europe and Central Asia
1.5 Increasing IDU			Middle East and North Africa
0.23 Stable IDU, MSM (IDU = injection drug-users; MSM = men who have sex with men)			

Virology and immunology • 309

Fig. 12.1 Life cycle of HIV. Red arrows indicate sites of action of antiretroviral drugs. Proviral DNA Cell nucleus Integration Double-stranded DNA Fusion Fusion inhibitors Binding to co-receptor CCR5 or CXCR4 Attachment to CD4 receptor Maturation Viral release Reverse transcriptase inhibitors Chemokine receptor antagonist Chemokine co-receptor (CCR5 or CXCR4) Genomic RNA Reverse transcription of viral RNA genome Reverse transcription Integrase inhibitors Transcription Translation Viral proteins Viral mRNA Protease inhibitors Cleavage of polypeptides and assembly

12.3 Factors increasing the risk of transmission of HIV

- Common to all transmission categories • High viral load
- Sexual transmission • STIs, especially genital ulcers • Cervical ectopy • Rectal or vaginal lacerations • Menstruation • Uncircumcised male partner • Receptive anal intercourse • Depot intramuscular progesterone contraceptive use
- Injection drug use transmission • Sharing equipment • Linked commercial sex • Intravenous use • Concomitant cocaine use • Incarceration

Occupational transmission • Deep injury • Visible blood on device • Needle was in a blood vessel
Vertical transmission • Prolonged rupture of membranes • Older gestational age (STIs = sexually transmitted infections)
Virology and immunology HIV is an enveloped ribonucleic acid (RNA) retrovirus from the lentivirus family. After mucosal exposure, HIV is transported via dendritic cells to the lymph nodes, where infection becomes established. This is followed by viraemia and dissemination to lymphoid organs, which are the main sites of viral replication. Each mature virion has a lipid membrane lined by a matrix protein that is studded with glycoprotein (gp) 120 and gp41 spikes. The inner cone-shaped protein core (p24) houses two copies of the single-stranded RNA genome and viral enzymes. The HIV genome consists of three characteristic retroviral genes - gag (encodes a polyprotein that is processed into structural proteins, including p24), pol (codes for the enzymes reverse transcriptase, integrase and protease) and env (codes for envelope proteins gp120 and gp41) - as well as six regulatory genes. HIV infects cells bearing the CD4 receptor; these are T-helper lymphocytes, monocyte-macrophages, dendritic cells, and microglial cells in the central nervous system (CNS). Entry into the cell commences with binding of gp120 to the CD4 receptor (Fig. 12.1), which results in a conformational change in gp120 that permits binding to one of two chemokine co-receptors (CXCR4 or CCR5). The chemokine co-receptor CCR5 is utilised during initial infection, but later on the virus may adapt to use CXCR4. Individuals who are homozygous for the CCR5 delta

310 • HIV INFECTION AND AIDS
Diagnosis and investigations
Diagnosing HIV infection Globally, the trend is towards universal HIV testing, rather than testing only those patients at high risk or those with manifestations of HIV infection. However, in the UK, testing is still targeted to high-risk groups (Box 12.4). HIV is diagnosed by detecting host antibodies either with rapid point-of-care tests or in the laboratory, where enzyme-linked immunosorbent assay (ELISA) tests are usually done. Most tests detect antibodies to both HIV-1 and HIV-2. A positive antibody test from two different immunoassays is sufficient to confirm infection. Western blot assays can also be used to confirm infection but they are expensive and sometimes yield indeterminate results. Screening tests often include an assay for p24 antigen in addition to antibodies, in order to detect patients with primary infection before the antibody response occurs. Nucleic acid amplification tests (usually polymerase chain reaction, PCR) to detect HIV RNA are used to diagnose infections in infants of HIV-infected mothers, who carry maternal antibodies to HIV for up to 15 months irrespective of whether they are infected, and to diagnose primary infection before 32 mutation do not express CCR5 on CD4 cells and are immune to HIV infection. Chemokine co-receptor binding is followed by membrane fusion and cellular entry involving gp41. After penetrating the cell and uncoating, a deoxyribonucleic acid (DNA) copy is transcribed from the RNA genome by the reverse transcriptase enzyme, which is carried by the infecting virion. Reverse transcription is an error-prone process and multiple mutations arise with ongoing replication, which results in considerable viral genetic heterogeneity. Viral DNA is transported into the nucleus and integrated within the host cell genome by the integrase enzyme. Integrated virus is known as proviral DNA and persists for the life of the cell. Cells infected with proviral HIV DNA produce new virions only if they undergo cellular activation, resulting in the transcription of viral messenger RNA (mRNA) copies, which are then translated into viral peptide chains. The precursor polyproteins are then cleaved by the viral protease enzyme to form new viral structural proteins and enzymes that migrate to the cell surface and are assembled using the host cellular apparatus to produce infectious viral particles; these bud from the cell surface, incorporating the host cell membrane into the viral envelope. The mature virion then infects other CD4 cells and the process is repeated. CD4 lymphocytes that are

replicating HIV have a very short survival time of about 1 day. It has been estimated that in asymptomatic HIV-infected people, more than 10¹⁰ virions are produced and 10⁹ CD4 lymphocytes destroyed each day. The CD4 lymphocytes are destroyed primarily by the host immune response rather than by cytopathic effects of HIV. A small percentage of T-helper lymphocytes enter a postintegration latent phase. Latently infected cells are important as sanctuary sites from antiretroviral drugs, which act only on replicating virus. Current ART is unable to eradicate HIV infection due to the persistence of proviral DNA in long-lived latent CD4 cells. The host immune response to HIV infection is both humoral, with the development of antibodies to a wide range of antigens, and cellular, with a dramatic expansion of HIV-specific CD8 cytotoxic T lymphocytes, resulting in a CD8 lymphocytosis and reversal of the usual CD4:CD8 ratio. CD8 cytotoxic T lymphocytes kill activated CD4 cells that are replicating HIV, but not latently infected CD4 cells. HIV evades destruction despite this vigorous immune response, in part because the highly conserved regions of gp120 and gp41 that are necessary for viral attachment and entry are covered by highly variable glycoprotein loops that change over time as a result of mutations selected for by the immune response. The initial peak of viraemia in primary infection settles to a plateau phase of persistent chronic viraemia. With time, there is gradual attrition of the T-helper lymphocyte population and, as these cells are pivotal in orchestrating the immune response, the patient becomes susceptible to opportunistic diseases. The predominant opportunist infections in HIV-infected people are the consequences of impaired cell-mediated rather than antibody-mediated immunity (e.g. mycobacteria, herpesviruses). However, there is also a B-lymphocyte defect with impaired antibody production to new antigens and dysregulated antibody production with a polyclonal increase in gamma globulins, resulting in an increased risk of infection with encapsulated bacteria, notably *Streptococcus pneumoniae*. The immune activation in response to HIV infection does not completely resolve on effective ART. This residual inflammatory state has been implicated in the pathogenesis of several non-AIDS morbidities that occur at a higher rate in HIV-infected people on ART than in the general population: cardiovascular, neurological and liver disease, chronic kidney disease and non-AIDS cancers.

12.4 Patients who should be offered and recommended HIV testing in the UK

1 Patients accessing specialist sexual health services (including genitourinary medicine)

- All patients who attend for testing or treatment
- Patients accessing primary care (including emergency care) and secondary care
- All patients attending their first appointment at:
 - Drug dependency programmes
 - Pregnancy termination services
 - Services treating hepatitis B or C, lymphoma or tuberculosis
- All patients who:
 - Have symptoms that may indicate HIV or for which HIV is part of the differential diagnosis
 - Are from a country or group with high rate of HIV infection
 - Are male, or trans women, who have sex with men
 - Report sexual contact with someone from a country with high rate of HIV infection
 - Disclose high-risk sexual practices, e.g. 'chemsex' (p. 332)
 - Are diagnosed with, or request testing for, a sexually transmitted infection
 - Report a history of injecting drug use
 - Are the sexual partners of people known to be HIV-positive or at high risk of HIV
- In areas of high² and extremely high³ prevalence:
 - All patients not previously diagnosed with HIV who register with a general practice or undergo blood testing for any reason
- In areas of extremely high prevalence³:
 - All emergency care and secondary care patients not previously diagnosed with HIV
- At each general practice consultation consider offering opportunistic HIV testing
- Prison inmates
 - All new inmates not previously diagnosed with HIV

¹Adapted from National Institute for Health and Care Excellence NG60 – HIV testing: increasing uptake among people who may have undiagnosed HIV NICE guideline (Dec. 2016).

²Prevalence of diagnosed HIV is 2–5 per 1000 people aged 15–59.

³Prevalence of diagnosed HIV is ≥ 5 per 1000 people aged 15–59.

The CD4 count varies by up to 20% from day to day and is also transiently reduced by intercurrent infections. Due to this variability, major therapeutic decisions should not be taken on the basis of a single count. The percentage of lymphocytes that are CD4+, rather than the absolute count, is routinely used in paediatrics, as the normal CD4 counts in infants and young children are much higher than in adults. In adults, the CD4 percentage is occasionally useful when evaluating significant reductions in an individual's CD4 count, which may be associated with transient lymphopenia due to intercurrent infection or pregnancy. In this case, the CD4 percentage will be unchanged. The normal CD4 count is over 500 cells/mm³. The rate of decline in CD4 count is highly variable. People with CD4 counts between 200 and 500 cells/mm³ have a low risk of developing major opportunistic infections. Morbidity due to inflammatory dermatoses, herpes zoster, oral candidiasis, tuberculosis, bacterial pneumonia and HIV-related immune disorders (e.g. immune thrombocytopenia) becomes increasingly common as CD4 counts decline. Once the count is below 200 cells/mm³, there is severe immune suppression and a high risk of AIDS-defining conditions. It is important to note that patients can be asymptomatic despite very low CD4 counts and that major opportunistic diseases occasionally present with high CD4 counts. The CD4 count should be performed every 3–6 months in patients on ART, together with measurement of the viral load.

The level of viraemia is measured by quantitative PCR of HIV RNA, known as the viral load. Determining the viral load is crucial for monitoring responses to ART (p. 324). People with high viral loads (e.g. > 100 000 copies/mL) experience more rapid declines in CD4 count, while those with low viral loads (< 1000 copies/mL) usually have slow or even no decline in CD4 counts. Transient increases in viral load occur with intercurrent infections and immunisations, so the test should be done at least 2 weeks afterwards. Viral loads are variable; only changes in viral load of more than 0.5 log₁₀ copies/mL are considered clinically significant.

Clinical manifestations of HIV

Clinical staging of patients should be done at the initial medical examination, as it provides prognostic information and is a key criterion for initiating prophylaxis against opportunistic infections. Two clinical staging systems are used internationally (p. 307). In both, patients are staged according to the most severe manifestation and do not improve their classification. For example, a patient who is asymptomatic following a major opportunistic disease (AIDS) remains at stage 4 or category C of the WHO and CDC systems, respectively, and never reverts to earlier stages. Finally, patients do not always progress steadily through all stages and may present with AIDS, having been asymptomatic.

Primary HIV infection

Primary infection is symptomatic in more than 50% of cases but the diagnosis is often missed. The incubation period is usually 2–4 weeks after exposure. The duration of symptoms is variable but is seldom longer than 2 weeks. The clinical manifestations (Box 12.8) resemble those of infectious mononucleosis/glandular fever (p. 241), but the presence of maculopapular rash or mucosal ulceration strongly suggests primary HIV infection antibodies have developed. PCR is more sensitive than p24 antigen detection for diagnosing primary infection. The purpose of HIV testing is not simply to identify infected individuals, but also to educate people about prevention and transmission of the virus. Counselling in the client's home language is essential both before testing and after the result is obtained (Boxes 12.5 and 12.6). There are major advantages to using rapid point-of-care HIV tests in that pre- and post-test counselling can be done at the same visit. A number of baseline investigations should be done at the initial medical evaluation (Box 12.7). The extent of these investigations will depend on the resources available.

Viral load and CD4 counts

CD4 lymphocyte counts are usually determined by flow cytometry but cheaper methods have been developed for low-income countries. The CD4 count is

the most clinically useful laboratory indicator of the degree of immune suppression; it is used, together with clinical staging, in decisions to start prophylaxis against opportunistic infections, and is of great value in the differential diagnosis of clinical problems.

12.6 How to carry out post-test counselling

- Test result negative • Discuss transmission and need for behaviour modification • Advise second test 3 months after last exposure
- Test result positive • Explain meaning of result • Organise medical follow-up • Assess coping strategy • Stress importance of disclosure • Explain value of antiretroviral therapy • Provide written information and useful Internet resources • Discuss confidentiality issues • Organise emotional and practical support (names/phone numbers) • Facilitate notification of sexual partners

12.5 How to carry out pre-test counselling

- Discuss meaning of positive and negative test results • Realise importance of maintaining confidentiality • Identify person to whom positive result could be disclosed • Explore knowledge and explain natural history of HIV • Discuss transmission and risk reduction • Assess coping strategy • Explain test procedure • Obtain informed consent

12.7 Baseline investigations

- CD4 count • Viral load • Hepatitis B surface antigen • Hepatitis C antibody • Liver function tests • Full blood count • Urinalysis, serum creatinine • Syphilis serology • Cervical smear in women • Serum cryptococcal antigen (if CD4 < 100) • Tuberculin skin test • Sexually transmitted infection screen

312 • HIV INFECTION AND AIDS response. The median time from infection to the development of AIDS in adults is about 9 years (see Fig. 12.2). A small proportion of untreated HIV-infected people are long-term non-progressors, with CD4 counts in the reference range for 10 years or more. Some long-term non-progressors have undetectable viral loads and are known as 'elite controllers'. Minor HIV-associated disorders

A wide range of disorders indicating some impairment of cellular immunity occur in most patients before they develop AIDS (CDC category B or WHO stages 2 and 3). Careful examination of the mouth is important when patients are being followed up, as oral candidiasis and oral hairy leucoplakia are common conditions that require initiation of prophylaxis against opportunistic infections, irrespective of the CD4 count. Acquired immunodeficiency syndrome

AIDS is defined by the development of specified opportunistic infections, cancers and severe manifestations of HIV itself (p. 307). CDC category C is the most widely used definition of AIDS. WHO updated its classification more recently and added a few conditions of similar prognosis to its stage 4 disease. Presenting problems in HIV infection

HIV itself is associated with a wide variety of clinical manifestations, and opportunistic diseases add many more. All body systems can be affected by HIV. The CD4 count is useful in differential diagnosis (Box 12.9): opportunistic diseases that may present at higher CD4 counts become increasingly common as CD4 counts decline, so the CD4 count helps to rule out certain disorders. For example, in a patient with a pulmonary infiltrate and a CD4 count of 350 cells/mm³, pulmonary tuberculosis is a likely diagnosis and PJP is very unlikely, but if the patient's CD4 count is 50 cells/mm³, both PJP and tuberculosis are likely. Globally, tuberculosis is the most common cause of morbidity and mortality in HIV-infected patients. Tuberculosis should be considered in the differential diagnosis of most presenting problems in patients from communities where tuberculosis is common. rather than the other viral causes of infectious mononucleosis. In infectious mononucleosis due to Epstein-Barr virus (EBV) or in cytomegalovirus (CMV), rashes generally occur only if aminopenicillins are given. Atypical lymphocytosis occurs less frequently than in EBV infection. Transient lymphopenia, including CD4 lymphocytes, is found in most cases (Fig. 12.2), which may result in opportunistic infections, notably oropharyngeal candidiasis. Major opportunistic infections like *Pneumocystis jirovecii* pneumonia (PJP) may rarely occur. Thrombocytopenia and moderate elevation of liver enzymes are commonly present. The differential diagnosis of primary HIV includes acute EBV,

primary CMV infection, rubella, primary toxoplasmosis and secondary syphilis. Early diagnosis is made by detecting HIV RNA by PCR or p24 antigenaemia. The appearance of specific anti-HIV antibodies in serum (seroconversion) occurs 2–12 weeks after the development of symptoms. The window period during which antibody tests may be false negative is prolonged when post-exposure prophylaxis has been used. Asymptomatic infection A prolonged period of clinical latency follows primary infection, during which infected individuals are asymptomatic. Persistent generalised lymphadenopathy with nodes typically < 2 cm diameter is a common finding. Eventually, the lymph nodes regress, with destruction of node architecture as disease advances. Viraemia peaks during primary infection and then drops as the immune response develops, to reach a plateau about 3 months later. The level of viraemia post seroconversion is a predictor of the rate of decline in CD4 counts, which is highly variable and explained in part by genetic factors affecting the immune Fig. 12.2 Virological and immunological progression of untreated HIV infection.

Clinical latency Constitutional symptoms Opportunistic diseases Death Primary infection Acute HIV syndrome Wide dissemination of virus Seeding of lymphoid organs

HIV RNA copies per mL plasma

CD4+ T-lymphocyte count (cells/mm³)

9 10

Weeks CD4 Viral load Years 9 12 12.8 Clinical features of primary infection • Fever • Maculopapular rash • Pharyngitis • Lymphadenopathy • Myalgia/arthritis • Diarrhoea • Headache • Oral and genital ulceration • Meningo-encephalitis • Bell's palsy

Presenting problems in HIV infection • 313

warrants further investigation. Lymph node needle aspiration (using a wide-bore needle such as 19G if tuberculosis is suspected) should be performed. One slide should be air-dried and sent for staining for acid-fast bacilli, which has about a 70% yield in tuberculosis. The other slide should be fixed and sent for cytology. If caseous liquid is aspirated, this should be sent for mycobacterial culture or PCR. If needle aspiration is unhelpful, or if lymphoma or Kaposi's sarcoma is suspected, excision biopsy should be performed. Weight loss Weight loss is a very common finding in advanced HIV infection. The HIV wasting syndrome is an AIDS-defining condition and is defined as weight loss of more than 10% of body weight, plus either unexplained chronic diarrhoea (lasting over 1 month) or chronic weakness and unexplained prolonged fever (lasting over 1 month). This is a diagnosis of exclusion. If the weight loss is rapid (more than 1 kg a month), then major opportunistic infections or cancers become more likely. Painful oral conditions and nausea from drugs contribute by limiting intake. Depression is very common and can cause significant weight loss. Measurement of C-reactive protein is helpful in the work-up of weight loss, as this is markedly raised with most opportunistic diseases but not with HIV itself. Erythrocyte sedimentation rate (ESR) is elevated by HIV infection and is therefore not useful. The presence of fever or diarrhoea is helpful in the differential diagnosis of weight loss (Fig. 12.3). Fever Fever is a very common presenting feature. Common causes of prolonged fever with weight loss are listed in Figure 12.3. Non-typhoid Salmonella bacteraemia, which commonly presents with fever in low-income

the most common cause of PUO in low- and middle-income countries, and in these settings a trial of empirical therapy is warranted after cultures have been sent. In high-income countries, disseminated *Mycobacterium avium* complex (MAC) infection is an important cause of PUO, often also presenting with diarrhoea and splenomegaly. Disseminated endemic mycoses (e.g. histoplasmosis, coccidioidomycosis, talaromycosis) present with PUO, often with papular skin eruptions or mucosal ulcerations (Fig. 12.4). Skin biopsy for histology and fungal culture is often diagnostic. Mucocutaneous disease The skin and mouth must be carefully examined, as mucocutaneous manifestations are extremely common in HIV and many prognostically important conditions can be diagnosed by simple inspection. The differential diagnosis of dermatological conditions is simplified by categorising disorders according to the lesion type (Box 12.10). Some common dermatological diseases, notably psoriasis, are exacerbated by HIV. The risk of many drug rashes is increased in HIV-infected patients. Skin biopsy should Fig. 12.4. Disseminated histoplasmosis presenting with diffuse papular rash and fever. Skin biopsy was diagnostic. Courtesy of Professor Graeme Meintjes. Fig. 12.5 Severe mucocutaneous herpes simplex. Chronic anogenital or perioral ulcers are very common in advanced HIV infection. 12.10 Differential diagnosis of skin conditions by lesion type

Scaly rashes • Seborrhoeic dermatitis • Psoriasis* (exacerbated by HIV) • Tinea corporis* • Dry skin/ichthyosis • Norwegian scabies* • Drug rashes* Pruritic papules • Pruritic papular eruption ('itchy red bump disease') • Eosinophilic folliculitis • Scabies* Papules and nodules (non-pruritic) • Molluscum contagiosum* • Secondary syphilis • Kaposi's sarcoma • Bacillary angiomatosis • Cryptococcosis • Warts* • Disseminated endemic mycoses (histoplasmosis, coccidioidomycosis and talaromycosis) Blisters • Herpes simplex • Herpes zoster • Fixed drug eruptions • Drug rashes (especially toxic epidermal necrolysis) Mucocutaneous ulcers • Ecthyma • Herpes simplex • Aphthous ulcers (minor and major) • Histoplasmosis • Drug rashes (Stevens-Johnson syndrome) Hyperpigmentation • Post-inflammatory (especially pruritic papular eruption) • Zidovudine • Emtricitabine (palms and soles) *See Chapter 29 for more information.

Presenting problems in HIV infection • 315

- classic KS: rare, indolent and restricted largely to elderly Mediterranean or Jewish men
- endemic KS: occurs in sub-Saharan Africa, is more aggressive, presents at earlier ages than classic KS, and affects men more than women
- KS in patients on immunosuppressant drugs: usually transplant recipients, who experience disseminated disease
- AIDS-associated KS. In Africa, the male-to-female ratio of AIDS-associated KS is much lower than is seen with endemic KS, but men are still more affected than women, despite the fact that the seroprevalence of human herpesvirus 8 is the same in both sexes. AIDS-associated KS is always a multicentric disease. Early mucocutaneous lesions are macular and may be difficult to diagnose. Subsequently, lesions become papular or nodular, and may ulcerate. KS lesions typically have a red-purple colour (Fig. 12.6 and p. 306) but may become hyperpigmented, especially in dark-skinned patients. As the disease progresses, the skin lesions become more numerous and larger. Lymphoedema is common, as lymphatic vessels are infiltrated. KS also commonly spreads to lymph nodes and viscera, especially to the lungs and gastrointestinal tract. Visceral disease occasionally occurs in the absence of mucocutaneous involvement. B symptoms of fever, night sweats and weight loss may occur. KS may respond to ART. Chemotherapy should be reserved for those patients who fail to remit on ART, or be given together with ART if there are poor prognostic features such as visceral involvement, oedema, ulcerated lesions and B symptoms.

Bacillary angiomatosis Bacillary angiomatosis is a bacterial infection caused by *Bartonella henselae* or *B. quintana*. Skin lesions range from solitary superficial

red-purple lesions resembling KS or pyogenic granuloma, to Herpes simplex infections Recurrences of herpes simplex infection are very common and primarily affect the nasolabial and anogenital areas (Fig. 12.5). As immune suppression worsens, the ulcers take longer to heal and become more extensive. Ulcers that persist for more than 4 weeks are AIDS-defining. The diagnosis is clinical, but PCR of vesicle fluid or from ulcer swabs may be diagnostic with unusual presentations. Response to a course of antiviral drug such as aciclovir is good but relapses are common. Frequent relapses that persist despite ART should be treated with aciclovir 400 mg twice daily for 6–12 months (Box 12.11). Herpes zoster This usually presents with a pathognomonic vesicular rash on an erythematous base in a dermatomal distribution (p. 239). The median CD4 count at the first episode of zoster is 350 cells/mm³. In patients with advanced HIV disease, the rash may be multidermatomal and recurrent episodes may occur. Disseminated zoster is rare. In HIV-infected patients, zoster is generally more extensive and has a longer duration, and there is a higher risk of developing post-herpetic neuralgia. High doses of aciclovir or its congeners should be given for all cases with active disease, irrespective of the time since the onset of the rash. Post-herpetic neuralgia is difficult to manage. Analgesic adjuvants, e.g. amitriptyline and pregabalin, should be commenced in all patients with prolonged pain. Topical capsaicin has modest efficacy. Kaposi's sarcoma Kaposi's sarcoma (KS) is a spindle-cell tumour of lymphoendothelial origin. All forms of KS are due to sexually transmitted human herpesvirus 8, also known as KS-associated herpesvirus. KS occurs in four patterns:

12.11 Treatment of common opportunistic infections in adults with AIDS

Opportunistic infection Treatment Alternative treatment Secondary prophylaxis*

Pneumocystis jirovecii pneumonia Co-trimoxazole 20/100 mg/kg/day (in 4 divided doses) for 21 days; maximum per dose 320/1600 mg Early adjunctive prednisone 40 mg twice daily, if hypoxic Clindamycin 900 mg 3 times daily IV (switch to 600 mg 3 times daily PO once improving) plus primaquine 30 mg daily for 21 days Co-trimoxazole 160/800 mg daily Cerebral toxoplasmosis Sulfadiazine 15 mg/kg 4 times daily plus pyrimethamine 200 mg stat, then 75 mg daily plus folinic acid 15–25 mg daily for 6 weeks Co-trimoxazole 320/1600 mg twice daily for 4 weeks, then 160/800 mg twice daily for 3 months Co-trimoxazole 160/800 mg daily Cryptococcosis Liposomal amphotericin B 4 mg/kg/day IV plus flucytosine 25 mg/kg 4 times daily for 14 days, followed by fluconazole 400 mg daily for 8 weeks Amphotericin B 1 mg/kg/day IV plus fluconazole 800 mg daily for 14 days, followed by fluconazole 400 mg daily for 8 weeks Fluconazole 200 mg daily (for minimum of 1 year)

Oesophageal candidiasis Fluconazole 200 mg daily for 14 days Itraconazole 200 mg daily for 14–21 days Not usually recommended Disseminated Mycobacterium avium complex Clarithromycin 500 mg twice daily plus ethambutol 15 mg/kg daily Azithromycin 500 mg daily plus ethambutol 15 mg/kg daily Continue treatment for minimum of 1 year Herpes simplex ulcers Aciclovir 400 mg 3 times daily for 5–10 days Valaciclovir 500 mg or famciclovir 125 mg twice daily for 5–10 days Aciclovir 400 mg twice daily only if recurrences are frequent/severe Cystoisospora belli diarrhoea Co-trimoxazole 160/800 mg 4 times daily for 10 days Ciprofloxacin 500 mg twice daily for 10 days Co-trimoxazole 160/800 mg daily *Secondary prophylaxis may be discontinued once CD4 counts have increased to > 200 cells/mm³ on antiretroviral therapy for at least 3 months.

316 • HIV INFECTION AND AIDS (p. 306) that can be scraped off to reveal a red raw surface. Erythematous candidiasis is more difficult to diagnose and presents with a reddened mucosa and a smooth shiny tongue. Angular cheilitis due to Candida is a common manifestation. Topical antifungals are usually effective. Antifungal lozenges are more effective than antifungal solutions. Systemic azole therapy, usually fluconazole, should be given if topical therapy fails or if there are oesophageal symptoms. Oral hairy leucoplakia (p. 306) appears as corrugated white plaques

running vertically on the side of the tongue and is virtually pathognomonic of HIV disease. It is usually asymptomatic and is due to EBV. Oral ulcers are common. Herpetiform oral ulcers occur in primary infection. Herpes simplex typically affects the nasolabial area but may cause oral ulcers. In early disease, minor aphthous ulcers are common. In advanced disease, giant aphthous ulcers occur. These destroy tissue, are painful and need to be differentiated from herpes simplex and CMV ulcers by biopsy. They respond to systemic glucocorticoids and ART. A number of disseminated endemic mycoses, notably histoplasmosis (p. 303), may cause oral ulcers, usually associated with constitutional symptoms. Finally, superficial oral ulcers may occur as part of the Stevens-Johnson syndrome, usually caused by sulphonamides or NNRTIs. KS often involves the mouth, especially the hard palate (see above and Fig. 12.6). Nodular oral lesions are associated with a worse prognosis. Gingivitis is very common. Good oral hygiene and regular dental check-ups are important. Acute necrotising ulcerative gingivitis and periostitis (p. 306) can result in loss of teeth; they should be treated with a course of metronidazole and a dental referral should be made. Nail disorders Fungal infections (onychomycosis, p. 1240) are very common and often involve multiple nails. Blue-black discoloration of nails is common and may be due to HIV or to the antiretroviral drug zidovudine.

Gastrointestinal disease Oesophageal diseases Oesophageal candidiasis (Fig. 12.7) is the most common cause of pain on swallowing (odynophagia), dysphagia and regurgitation. Concomitant oral candidiasis is present in about 70% of patients. Systemic azole therapy, e.g. fluconazole 200 mg daily for 14 days, is usually curative but relapses are common (Box 12.11). Patients whose oesophageal symptoms fail to respond to azoles should be investigated with oesophagoscopy. Major aphthous ulceration and CMV ulcers are the most likely causes and need to be differentiated by biopsy. Occasionally, herpes simplex oesophagitis or KS is responsible.

Diarrhoea Chronic diarrhoea is a very common presenting problem in patients with advanced HIV, especially in areas where there is no access to safe water. It is a major cause of wasting. The differential diagnosis of diarrhoea depends on whether the presentation is with large- or small-bowel symptoms (see Fig. 12.3). The presentation and aetiology of acute diarrhoea are similar to those in HIV-uninfected patients. multiple subcutaneous nodules or plaques. Lesions are painful and may bleed or ulcerate. The infection may become disseminated with fevers, lymphadenopathy and hepatosplenomegaly. Diagnosis is made by biopsy of a lesion and Warthin-Starry silver staining, which reveals aggregates of bacilli. Treatment with doxycycline or azithromycin is effective.

Papular pruritic eruption Papular pruritic eruption ('itchy red bump disease') is an intensely itchy, symmetrical rash affecting the trunk and extremities. It is thought to be due to an allergic reaction to insect bites. In sub-Saharan Africa, it is the most common skin manifestation of HIV. Post-inflammatory hyperpigmentation is common. Topical glucocorticoids, emollients and antihistamines are useful but response is variable. Measures to reduce insect bites are logical but difficult to implement in low-income settings.

Drug rashes Cutaneous hypersensitivity to drugs is said to occur 100 times more frequently in HIV infection. The most common type is an erythematous maculopapular rash, which may be scaly. The drugs most commonly associated with rashes are sulphonamides and non-nucleoside reverse transcriptase inhibitors (NNRTIs - see below). Severe, life-threatening features of drug rashes include blistering (when this affects more than 30% of surface area it is known as toxic epidermal necrolysis), involvement of mucous membranes (Stevens-Johnson syndrome, pp. 1224 and 1254), or systemic involvement with fever or organ dysfunction (especially hepatitis, which is often delayed for a week or two after the rash develops). Because sulphonamides are important in the treatment and prophylaxis of opportunistic infections, rechallenge or desensitisation is often attempted in patients who have previously experienced rashes, provided the reaction was not life-threatening. Details of rashes caused by ART are given

below. Oral conditions Oropharyngeal candidiasis is very common. It is nearly always caused by *C. albicans* (p. 300), but azole-resistant *Candida* species may be selected for if there have been repeated courses of azole drugs. Pseudomembranous candidiasis is the most common manifestation, with white patches on the buccal mucosa Fig. 12.6 Oral Kaposi's sarcoma. A full examination is important to detect disease that may affect the palate, gums, fauces or tongue.

Presenting problems in HIV infection • 317

fever, weight loss and diarrhoea, but the diarrhoea is seldom profuse. Hepatobiliary disease
Chronic viral hepatitis Hepatitis B and/or C (HBV and HCV) co-infection is common in HIV-infected people due to shared risk factors for transmission. The natural history of both HBV and HCV is altered by HIV co-infection. In the ART era, chronic liver disease from viral hepatitis has emerged as a major cause of morbidity and mortality. HBV and HCV are further described on pages 873 and 877. Hepatitis B HBV infection is common in several groups of people at risk of HIV infection: residents of low- and middle-income countries, injection drug-users, haemophiliacs and MSM. HIV co-infection increases HBV viraemia, is associated with less elevation of transaminase (presumably due to immune suppression), and increases the risk of liver fibrosis and hepatocellular carcinoma. Several nucleoside reverse transcriptase inhibitors (NRTIs; lamivudine, emtricitabine and tenofovir) are also effective against HBV. HBV status should be checked at baseline in all HIV-infected patients. Treatment with anti-HBV drugs should be considered for all patients who have active HBV replication (HBeAg-positive or HBV DNA > 2000 IU/ mL) and/or evidence of inflammation or fibrosis on liver biopsy (see also p. 876). A flare of hepatitis may be associated with improved immune function after starting ART or discontinuing
Large-bowel diarrhoea Acute diarrhoea caused by the bacterial enteric pathogens *Campylobacter*, *Shigella* and *Salmonella* occurs more frequently than in HIV-uninfected people and the illness is more severe. Bacteraemia is much more common, notably due to non-typhoid *Salmonella* (p. 262). Diarrhoea caused by *Clostridium difficile* should be considered if there has been prior exposure to antibiotics, as is often the case in patients with symptomatic HIV. CMV colitis presents with chronic large-bowel symptoms and fever in patients with CD4 counts below 100 cells/mm³. On colonoscopy, ulcers are seen, mostly involving the left side of the colon. Biopsy of ulcers shows typical 'owl's-eye' inclusion bodies. Small-bowel diarrhoea
Chronic small-bowel diarrhoea may be due to HIV enteropathy but this is a diagnosis of exclusion. It typically presents with chronic watery diarrhoea and wasting without fever. Infection with one of three unicellular organisms is responsible for most cases: cryptosporidiosis, microsporidiosis and cystoisosporiasis (formerly known as isosporiasis) (Box 12.12). All three organisms are intracellular parasites that invade enterocytes. If the diagnosis is not made by stool microscopy on at least two specimens, a duodenal biopsy should be performed (Fig. 12.8). Electron microscopy is essential for speciation of microsporidia. About 40% of patients with disseminated MAC infections have watery diarrhoea. Fever is a prominent feature of MAC infection, which helps differentiate it from cryptosporidiosis, microsporidiosis and cystoisosporiasis. Intestinal tuberculosis typically involves the ileocaecal area and may present with Fig. 12.7 Oesophageal candidiasis. Endoscopy showing typical pseudomembranous candidiasis. Fig. 12.8 Cryptosporidiosis. Duodenal biopsy may be necessary to confirm cryptosporidiosis or microsporidiosis. The arrow indicates an oöcyst. 12.12
Common causes of chronic watery diarrhoea
Cryptosporidiosis Microsporidiosis Cystoisosporiasis (formerly isosporiasis)
Organism Protozoan Fungus Protozoan
Species *Cryptosporidium parvum* *C. hominis* *Enterozoon bienersi* *Encephalitozoon intestinalis* etc. *Cystoisospora belli*
Animal host Multiple Multiple No
Distribution Global Global Tropics
Stool examination Acid-fast stain Trichrome

stain Polymerase chain reaction Acid-fast stain Specific treatment No established therapy
Albendazole (some species) Co-trimoxazole

318 • HIV INFECTION AND AIDS regions (Fig. 12.9) but may be normal initially. High-resolution CT scan is more sensitive than chest X-ray, usually showing typical 'ground-glass' interstitial infiltrates. Pneumatoceles may occur and may rupture, resulting in a pneumothorax. The diagnosis is made with silver stains, PCR or immunofluorescence of broncho-alveolar lavage or induced sputum (note that spontaneously produced sputum should not be sent, as the yield is low). Treatment is with high-dose co-trimoxazole, together with adjunctive systemic glucocorticoids if the patient is hypoxic (see Box 12.11).

Pulmonary tuberculosis Tuberculosis is the most common cause of admission in countries with a high tuberculosis incidence. Pulmonary tuberculosis in patients with mild immune suppression typically presents as in HIV-uninfected patients, with a chronic illness and apical pulmonary cavities (p. 588). However, in patients with CD4 counts below 200 cells/mm³, there are four important differences in the clinical presentation of pulmonary tuberculosis:

- Tuberculosis progresses more rapidly, with a subacute or even acute presentation. The diagnosis therefore needs to be made and therapy commenced promptly. A trial of empirical therapy is often started while awaiting the results of mycobacterial cultures.
- The chest X-ray appearance alters: cavities are rarely seen, pulmonary infiltrates are no longer predominantly in apical areas, and pleural effusions and hilar or mediastinal lymphadenopathy are common (Fig. 12.10). A normal chest X-ray is not unusual in symptomatic patients with tuberculosis confirmed on sputum culture. These atypical findings can result in a delayed or missed diagnosis.
- Sputum smears, which are positive in most HIV-uninfected adults with pulmonary tuberculosis, are negative in more than half of patients. The main reason for this is the absence of pulmonary cavities.
- Many patients have disseminated tuberculosis, sometimes with a classic miliary pattern on chest X-ray, but more antiretrovirals that have anti-HBV activity. HBV co-infection increases the risk of antiretroviral hepatotoxicity. Hepatitis C HCV infection is extremely common in injection drug-users and haemophiliacs. HIV co-infection increases HCV viraemia and increases the risk of liver fibrosis and hepatocellular carcinoma. Treatment for HCV should preferably be deferred in patients with CD4 counts < 200 cells/mm³ until they are stable on ART. As with HBV co-infection, a flare of hepatitis may be associated with improved immune function after starting ART, and there is an increased risk of antiretroviral hepatotoxicity. Response to anti-HCV therapy is similar to that seen in HIV-uninfected people, but there are important drug-drug interactions between several antiretrovirals and the newer HCV protease inhibitors.

HIV cholangiopathy HIV cholangiopathy, a form of secondary sclerosing cholangitis (p. 888), may occur in patients with severe immune suppression. In some patients, coexisting intestinal infection with CMV, cryptosporidiosis or microsporidiosis is present, but it is uncertain if these organisms play an aetiological role. Papillary stenosis is common and is amenable to cautery via endoscopic retrograde cholangiopancreatography (ERCP), which provides symptomatic relief. Acalculous cholecystitis is a common complication of cholangiopathy. ART may improve the condition.

Respiratory disease Pulmonary disease is very common and is the major reason for hospital admission. Most patients who are admitted for respiratory diseases will have either bacterial pneumonia, pulmonary tuberculosis or PJP. PJP is more common in high-income countries, while tuberculosis is more common in low- and middle-income countries. An approach to the differential diagnosis of all three conditions is given in Box 12.13.

Pneumocystis jirovecii pneumonia The key presenting feature of *Pneumocystis jirovecii* pneumonia (PJP) is progressive dyspnoea with a duration of less than 12 weeks. Dry cough and fever are common. The chest X-ray typically shows a bilateral interstitial

infiltrate spreading out from the hilar Fig. 12.9 Pneumocystis pneumonia: typical chest X-ray appearance. Note the interstitial bilateral infiltrate. 12.13 Comparative features of bacterial pneumonia, Pneumocystis jirovecii pneumonia and pulmonary tuberculosis

	Bacterial pneumonia	Pneumocystis jirovecii pneumonia	Pulmonary tuberculosis
Duration	Acute	Subacute	Variable
Dyspnoea	Common	Prominent	Occasional
White cell count	Increased	Normal	Variable
Chest X-ray Infiltrate	Consolidation	Interstitial	Variable
	Bilateral infiltrate	Occasional	Usual
Effusion	Common	Occasional	No
Nodes	Common	Rare	No
C-reactive protein	Markedly increased	Variable	Increased

Presenting problems in HIV infection • 319

Lymphoid interstitial pneumonitis is a slowly progressive disorder causing a diffuse reticulonodular infiltrate. It is caused by a benign polyclonal lymphocytic interstitial infiltrate and is part of the diffuse infiltrative lymphocytosis syndrome (DILS – see p. 321). Patients may have other features of DILS, notably parotidomegaly. KS often spreads to the lungs. Typical chest X-ray appearances are large, irregular nodules, linear reticular patterns and pleural effusions. Bronchoscopy is diagnostic. Nervous system and eye disease The central and peripheral nervous systems are commonly involved in HIV, either as a direct consequence of HIV infection or due to opportunistic diseases. An approach to common presentations is outlined in Figure 12.11. Cognitive impairment HIV-associated neurocognitive disorders HIV is a neurotropic virus and invades the CNS early during infection. Meningo-encephalitis may occur at seroconversion. About 50% of HIV-infected people have abnormal neuropsychiatric testing. The term HIV-associated neurocognitive disorder (HAND) describes a spectrum of disorders: asymptomatic neurocognitive impairment (which is the most common), minor neurocognitive disorder and HIV-associated dementia (also called HIV encephalopathy). The proportion of patients with symptomatic HAND increases with declining CD4 counts. HIV-associated dementia is a subcortical dementia characterised by impairment of executive function, psychomotor retardation and impaired memory. There is no diagnostic test for HIV-associated dementia. CT or magnetic resonance imaging (MRI) shows diffuse cerebral atrophy out of keeping with age. It is important to exclude depression, cryptococcal meningitis and neurosyphilis. ART usually improves HIV-associated dementia but milder forms of HAND often persist. Progressive multifocal leucoencephalopathy Progressive multifocal leucoencephalopathy (PML) is a progressive disease that presents with stroke-like episodes and cognitive commonly presenting with pulmonary infiltrates together with extrapulmonary tuberculosis. The most common sites of concomitant extrapulmonary tuberculosis are the pleura and lymph nodes. Acid-fast bacilli are more often found on wide-needle aspirate of nodes than on sputum (p. 313). Pleural aspirate showing a lymphocytic exudate suggests tuberculosis as a likely cause and pleural biopsy will usually confirm the diagnosis. Tuberculosis in HIV-infected patients responds well to standard short-course therapy (p. 592). Bacterial pneumonia The incidence of bacterial pneumonia is increased about 100-fold by HIV infection. The severity, likelihood of bacteraemia, risk of recurrent pneumonia, and mortality are all increased compared with HIV-uninfected patients. The aetiology is similar to that of community-acquired pneumonia in HIV-uninfected patients with co-morbidity: *S. pneumoniae* is the most common cause, followed by *Haemophilus influenzae*, *Enterobacteriaceae* (e.g. *Klebsiella pneumoniae*) and *Staphylococcus aureus*. The prevalence of atypical bacteria in HIV-infected patients with pneumonia is similar to that in the general population. Treatment is with a broad-spectrum β -lactam (e.g. ceftriaxone, amoxicillin-clavulanate), with the addition of a macrolide if the pneumonia is severe. Uncommon bacteria causing pneumonia include

Pseudomonas aeruginosa, *Nocardia* (which mimics tuberculosis) and *Rhodococcus equi* (which can cause pulmonary cavities). Miscellaneous causes of pulmonary infiltrates Pulmonary cryptococcosis may present as a component of disseminated disease or be limited to the lungs. The chest X-ray appearances are variable. Cryptococcomas occur less commonly than in HIV-uninfected people. The most common radiographic pattern seen in HIV infection is patchy consolidation, often with small areas of cavitation resembling tuberculosis. Pleural involvement is rare. The disseminated endemic mycoses (histoplasmosis, coccidioidomycosis and talaromycosis) often cause diffuse pulmonary infiltrates, mimicking miliary tuberculosis. Fig. 12.10 Chest X-ray of pulmonary tuberculosis in advanced HIV infection. Lower-zone infiltrates and hilar or mediastinal nodes in a patient with a CD4 count of < 200 cells/mm³. Fig. 12.11 Presentation and differential diagnosis of HIV-related neurological disorders. (CMV = cytomegalovirus; HAND = HIV-associated neurocognitive disorder; PCNSL = primary CNS lymphoma; PML = progressive multifocal leucoencephalopathy) Neurological presentation Space-occupying lesion Cognitive impairment Meningitis Toxoplasmosis PCNSL Tuberculoma Cryptococcoma Cryptococcal Tuberculous Pneumococcal HIV HAND Depression Neurosyphilis Cryptococcal meningitis PML CMV encephalitis

320 • HIV INFECTION AND AIDS Primary CNS lymphoma Primary CNS lymphomas (PCNSLs) are high-grade B-cell lymphomas associated with EBV infection. Characteristically, imaging demonstrates a single homogeneously enhancing, periventricular lesion with surrounding oedema (Fig. 12.14). If it is considered safe to perform a lumbar puncture, PCR for EBV DNA in the CSF has a high sensitivity and specificity for PCNSL. Brain biopsy is definitive but carries a risk of morbidity and may be non-diagnostic in up to one-third. The prognosis is poor. Tuberculoma Lesions resemble toxoplasmosis on imaging, except that oedema tends to be less marked and single lesions occur more commonly. impairment. Vision is often impaired due to involvement of the occipital cortex. PML is caused by the JC virus. A combination of characteristic appearances on MRI (Fig. 12.12) and detection of JC virus DNA in the cerebrospinal fluid (CSF) by PCR is diagnostic. No specific treatment exists and prognosis remains poor despite ART. CMV encephalitis This presents with behavioural disturbance, cognitive impairment and a reduced level of consciousness. Focal signs may also occur. Detection of CMV DNA in the CSF supports the diagnosis. Response to anti-CMV therapy is usually poor. Space-occupying lesions Space-occupying lesions in AIDS patients typically present over days to weeks. The most common cause is toxoplasmosis. As toxoplasmosis responds rapidly to therapy, a trial of antitoxoplasmosis therapy should be given to all patients presenting with space-occupying lesions while the results of diagnostic tests are being awaited. Cerebral toxoplasmosis Cerebral toxoplasmosis is caused by reactivation of residual *Toxoplasma gondii* cysts from past infection, which results in the development of space-occupying lesions. The characteristic findings on imaging are multiple space-occupying lesions with ring enhancement on contrast and surrounding oedema (Fig. 12.13). *Toxoplasma* serology shows evidence of previous exposure (positive immunoglobulin (Ig)G antibodies); a negative serological test effectively rules out toxoplasmosis but a positive test is not specific. The standard therapy for toxoplasmosis is sulfadiazine with pyrimethamine, together with folinic acid, to reduce the risk of bone marrow suppression (see Box 12.11). However, co-trimoxazole has been shown to be as effective and less toxic, and is also more widely available. Response to a trial of therapy is usually diagnostic, with clinical improvement in 1–2 weeks and shrinkage of lesions on imaging in 2–4 weeks. Definitive diagnosis is by brain biopsy but this is seldom necessary. Fig. 12.12 Progressive multifocal leucoencephalopathy. Nonenhancing white-matter lesions without surrounding oedema are seen. Fig. 12.13 Cerebral toxoplasmosis. Multiple ring-enhancing lesions with surrounding oedema are

characteristic. Fig. 12.14 Primary CNS lymphoma. A single enhancing periventricular lesion with moderate oedema is typical.

Presenting problems in HIV infection • 321

of the spine is normal but is an important investigation to exclude other causes. Most patients have concomitant HIV-associated dementia. CMV polyradiculitis presents with painful legs, progressive flaccid paraparesis, saddle anaesthesia, absent reflexes and sphincter dysfunction. CSF shows a neutrophil pleocytosis (which is unusual for a viral infection), and the detection of CMV DNA by PCR confirms the diagnosis. Functional recovery is poor despite treatment with ganciclovir or valganciclovir. Psychiatric disease Significant psychiatric morbidity is very common and is a major risk factor for poor adherence. Reactive depression is the most common disorder. Diagnosis is often difficult, as many patients have concomitant HAND. Substance misuse is common in many groups of people at risk of HIV. Some antiretroviral drugs can cause psychiatric adverse effects and these are detailed on page 326. Retinopathy CMV retinitis presents with painless, progressive visual loss in patients with severe immune suppression. On fundoscopy, the vitreous is clear. Haemorrhages and exudates are seen in the retina (p. 306), often with sheathing of vessels ('frosted branch angiitis'). The disease usually starts unilaterally but progressive bilateral involvement occurs in most untreated patients. Diagnosis is usually clinical, but if there is doubt, demonstrating CMV DNA by PCR of vitreous fluid is diagnostic. Treatment with ganciclovir or valganciclovir stops progression of the disease but lost vision does not recover. Some patients may develop immune recovery uveitis in response to ART, with intraocular inflammation, macular oedema and cataract formation that require prompt treatment with oral and intraocular glucocorticoids to prevent further visual loss. Three other conditions may mimic CMV retinitis: ocular toxoplasmosis, which typically presents with a vitritis and retinitis without retinal haemorrhages; HIV retinopathy, a microangiopathy that causes cotton wool spots, which are not sight-threatening; and varicella zoster virus, which can cause rapidly progressive outer retinal necrosis. Rheumatological disease The immune dysregulation associated with HIV infection may result in autoantibody formation, usually in low titres. Mild arthralgias and a fibromyalgia-like syndrome are common in HIV-infected people. Arthritis HIV can cause a seronegative arthritis, which resembles rheumatoid arthritis. A more benign oligoarthritis may also occur. Reactive arthritis is more severe in HIV infection (p. 1031). Diffuse infiltrative lymphocytosis syndrome Diffuse infiltrative lymphocytosis syndrome (DILS) is a benign disorder involving polyclonal CD8 lymphocytic infiltration of tissues, which has some features in common with Sjögren's syndrome (p. 1038). It is linked to human leucocyte antigen (HLA)-DRB1. Most patients have a marked CD8 lymphocytosis. DILS usually presents in patients with mild immune suppression. The most common manifestation is bilateral parotid gland enlargement; the glands are often massive, with lymphoepithelial cysts There may be evidence of tuberculosis elsewhere. The CSF may show features consistent with tuberculous meningitis. Response to antituberculosis therapy is slow and paradoxical expansion of lesions despite therapy is not uncommon. Stroke There is a higher incidence of stroke in patients with HIV disease. Atherosclerosis is accelerated by the presence of inflammation due to the immune response to HIV, which is not completely suppressed by ART, and by dyslipidaemia caused by some antiretroviral drugs. HIV vasculopathy, which is thought to be a vasculitis, can also cause a stroke. It is important to exclude tuberculous meningitis and meningovascular syphilis in all patients who present with a stroke. Meningitis Cryptococcal meningitis Cryptococcus neoformans is the most common cause of meningitis in AIDS patients.

Patients usually present subacutely with headache, vomiting and decreased level of consciousness. Neck stiffness is present in less than half. CSF pleocytosis is often mild or even absent, and protein and glucose concentrations are variable. It is important to request CSF cryptococcal antigen tests in all HIV-infected patients undergoing lumbar puncture, as this test has a high sensitivity and specificity. Treatment is with amphotericin B (plus flucytosine if available) for 2 weeks, followed by fluconazole (see Box 12.11). Raised intracranial pressure is common and should be treated with repeated therapeutic lumbar punctures, removing sufficient CSF to reduce pressure to less than 20 cmH₂O. (Most experts are reluctant to withdraw more than 30 mL at a time.)

Tuberculous meningitis The presentation and CSF findings of tuberculous meningitis are similar to those in HIV-uninfected patients (p. 1120), except that concomitant tuberculosis at other sites is more common in HIV infection.

Peripheral nerve disease HIV infection causes axonal degeneration, resulting in a sensorimotor peripheral neuropathy in about one-third of AIDS patients. The incidence increases with lower CD4 counts, older age and increased height. Sensory symptoms predominate. Treatment involves foot care, analgesia and analgesic adjuvants. ART has minimal effect on halting or reversing the process. The NRTIs stavudine and didanosine, now largely abandoned due to their toxicity, can cause drug-induced peripheral neuropathy, which is typically more painful and more rapidly progressive than HIV neuropathy. Acute inflammatory demyelinating polyneuropathy is an uncommon manifestation, usually occurring in primary infection. It resembles Guillain-Barré syndrome (p. 1140), except that CSF pleocytosis is more prominent. Mononeuritis may also occur, commonly involving the facial nerve.

Myelopathy and radiculopathy The most common cause of myelopathy in HIV infection is cord compression from tuberculous spondylitis. Vacuolar myelopathy is seen in advanced disease and is due to HIV. It typically presents with a slowly progressive paraparesis with no sensory level. MRI

322 • HIV INFECTION AND AIDS is immune-mediated platelet destruction resembling idiopathic thrombocytopenic purpura (p. 971). This responds to glucocorticoids or intravenous immunoglobulin, together with ART. Splenectomy should be avoided if possible because it further increases the risk of infection with encapsulated bacteria. Severe thrombocytopenia with a microangiopathic anaemia also occurs in a thrombotic thrombocytopenic purpura-like illness (p. 979), which has a better prognosis and fewer relapses than the classical disease.

Renal disease Acute kidney injury is common, usually due to acute infection or nephrotoxicity of drugs (e.g. tenofovir (p. 412), amphotericin B (p. 126)) HIV-associated nephropathy (HIVAN) is the most important cause of chronic kidney disease (CKD) and is seen most frequently in patients of African descent and those with low CD4 counts. Progression to end-stage disease is more rapid than with most other causes of CKD, and renal size is usually preserved. HIVAN presents with nephrotic syndrome, CKD or a combination of both. ART has some effect in slowing progression of HIVAN. Other important HIV-associated renal diseases include HIV immune complex kidney diseases and thrombotic microangiopathy. With the overall improvement in life expectancy from ART, conditions such as diabetes mellitus, hypertension and vascular disease add to the burden of CKD. Outcomes of renal transplantation are good in patients on ART.

Cardiac disease HIV-associated cardiomyopathy resembles idiopathic dilated cardiomyopathy (p. 539) but progresses more rapidly. ART may improve cardiac failure but does not reverse established cardiomyopathy. Pericardial disease due to opportunistic diseases is not uncommon. Globally, the most common cause is tuberculous pericardial effusions. Tuberculous constrictive pericarditis is less common than in HIV-uninfected people. KS and lymphoma may cause pericardial effusions. Septic pericarditis, usually due to *S. pneumoniae*, is uncommon. HIV is associated with an increased risk of myocardial

infarction due to accelerated atherogenesis caused by the inflammatory state, which is not completely suppressed by ART, and by dyslipidaemia caused by some antiretroviral drugs. HIV-related cancers The AIDS-defining cancers are KS (see above), cervical cancer and non-Hodgkin lymphoma (NHL, p. 964). NHL may occur at any CD4 count but is more commonly seen with counts below 200 cells/mm³. Almost all NHLs are B-cell tumours and most are stage 3 or 4. Long-term remission rates similar to those in patients without HIV can be achieved with NHL in AIDS patients using ART and chemotherapy (including the anti-B-cell monoclonal antibody rituximab if it is a B-cell tumour). The incidence of a number of other cancers induced by viruses is also increased in HIV-infected people (Box 12.14). Regular cytological examination of the cervix, and of the anus in people who practise anal sex, should be performed to detect pre-malignant lesions, which are easier to treat. In general, the incidence of cancers that are not induced by viruses is similar to that in the general population. on histology (Fig. 12.15). Sicca symptoms are common but usually mild. Lymphocytic interstitial pneumonitis is the most common manifestation outside the salivary glands. Generalised lymphadenopathy may occur, with nodes larger than those seen with persistent generalised lymphadenopathy of HIV. Hepatitis, mononeuritis, polyarthritis and polymyositis may also occur. The manifestations outside the salivary glands usually respond to systemic glucocorticoids. Parotid gland enlargement may be treated by aspiration of parotid cysts and instillation of a sclerosant for cosmetic reasons, and surgery is best avoided. DILS may regress on ART but response is variable. Haematological abnormalities Disorders of all three major cell lines may occur in HIV. In advanced disease, haematopoiesis is impaired due to the direct effect of HIV and by cytokines. Pancytopenia may occur as a consequence of HIV but it is important to exclude a disorder infiltrating the bone marrow, such as mycobacterial or fungal infections, or lymphoma. Anaemia Normochromic, normocytic anaemia is very common in advanced HIV disease. Opportunistic diseases may cause anaemia of chronic disease (e.g. tuberculosis) or marrow infiltration (e.g. MAC, tuberculosis, lymphoma, fungi). Anaemia is a common adverse effect of zidovudine, which also causes a macrocytosis. Red cell aplasia is rare and may be caused either by parvovirus B19 infection or by lamivudine. Neutropenia Isolated neutropenia is occasionally due to HIV but is nearly always caused by drug toxicity (e.g. zidovudine, co-trimoxazole, ganciclovir). Thrombocytopenia Mild thrombocytopenia is common in HIV-infected people. Transient thrombocytopenia is frequently found in primary infection. The most common disorder causing severe thrombocytopenia Fig. 12.15 CT scan of parotid glands showing multiple cysts (arrows) in a patient with the diffuse infiltrative lymphocytosis syndrome.

Prevention of opportunistic infections • 323

Safer sex HIV-infected individuals should practise safer sex in order to reduce the transmission of HIV. Even if their partners are HIVinfected, condoms should be used, as HIV mutants that have developed antiretroviral drug resistance can be transmitted. Safer sex will also lower the risk of acquiring herpes simplex virus and human herpesvirus 8. Pets *Toxoplasma gondii* can be acquired from kittens or cat litter, and people living with HIV infection should avoid handling either. Cryptosporidiosis can be transmitted from animals, and patients should be advised to wash their hands after handling animals. Chemoprophylaxis Chemoprophylaxis is the use of antimicrobial agents to prevent infections. Primary prophylaxis is used to prevent opportunistic infections that have not yet occurred. Secondary prophylaxis is used to prevent recurrence of opportunistic infections because many may recur after an initial response to therapy (see Box 12.11). Secondary prophylaxis can be discontinued when ART results in immune reconstitution, with CD4 counts

increasing to over 200 cells/mm³, but for CMV and MAC, prophylaxis can be stopped if CD4 counts increase to more than 100 cells/mm³. Co-trimoxazole primary prophylaxis Co-trimoxazole reduces the incidence of a number of opportunistic infections (Box 12.15), resulting in lower hospitalisation and mortality rates. The indications for initiating co-trimoxazole are either clinical evidence of immune suppression (WHO clinical stages 3 or 4) or laboratory evidence of immune suppression (CD4 count < 200 cells/mm³). In low-income countries where malaria and/or severe bacterial infections are highly prevalent, the WHO recommends initiating co-trimoxazole regardless of CD4 counts or clinical stage. The recommended dose of co-trimoxazole is 960 mg daily, but trials have shown that half this dose is as effective and may be associated with less toxicity. Co-trimoxazole prophylaxis can be discontinued when CD4 counts increase to more than 200 cells/mm³ on ART, except in low-income countries where it should be continued life-long. Co-trimoxazole prophylaxis is well tolerated. The most common side-effect is hypersensitivity, causing a maculo-papular rash. If therapy is discontinued, desensitisation or rechallenge under antihistamine cover should be attempted, unless the rash was accompanied by systemic symptoms or mucosal involvement. Prophylactic doses of co-trimoxazole can also cause neutropenia, but this is very uncommon and routine monitoring of blood counts is not necessary. If co-trimoxazole cannot be tolerated, then

Prevention of opportunistic infections The best way to prevent opportunistic infections is to improve the CD4 count with ART. However, infections continue to occur in the ART era as CD4 counts take time to improve if ART is initiated in patients with profound immune suppression, immune reconstitution on ART is often suboptimal, and CD4 counts may decline because antiretroviral resistance develops. Preventing exposure The best method for avoiding infection is to prevent exposure to the infectious agent. This is possible only for a few opportunistic infections, however. Furthermore, many opportunistic infections occur after reactivation of latent/dormant infection after prior exposure; examples include herpes simplex virus, zoster (shingles), CMV, toxoplasmosis, cryptococcosis and the endemic mycoses. Safe water and food Cryptosporidiosis, microsporidiosis and cystoisosporiasis may be water-borne. If there is no access to safe water, then water should be boiled before drinking. Food-borne illnesses are also important in HIV infection, notably Salmonella species. Toxoplasma exposure is related to eating raw or undercooked meat. People living with HIV infection need to be informed about food hygiene and the importance of adequately cooked meat. Tuberculosis Preventing exposure to tuberculosis is important when there is an infectious case in the household, in clinics and in hospitals. Adequate ventilation, masks and safe coughing procedures reduce the risk of exposure. Malaria vector control All HIV-infected individuals living in malarious areas should practise vector control, as malaria occurs more frequently and is more severe in HIV-infected people. The most cost-effective way to achieve this is by using insecticide-impregnated bed nets. Other modalities of vector control that are of benefit to the community, such as reducing standing water and spraying with residual insecticides and larvicides, should also be implemented.

12.15 Opportunistic infections reduced by co-trimoxazole • Pneumocystis jirovecii pneumonia • Cerebral toxoplasmosis • Bacterial pneumonia • Bacteraemia • Cystoisosporiasis • Malaria

12.14 Approximate incidence ratio of virus-related cancers compared to the general population

Viral cancers Incidence ratio Human herpesvirus 8-related Kaposi's sarcoma

Epstein-Barr virus-related Non-Hodgkin lymphoma

Hodgkin lymphoma

Human papillomavirus-related Cervical cancer

Vulval cancer

Anal cancer

Penile cancer

Hepatitis B/C virus-related Hepatocellular carcinoma

324 • HIV INFECTION AND AIDS immune. In the UK, the following additional vaccines are also recommended: • hepatitis A: in those at risk • human papillomavirus: in people < 40 years old • measles, mumps and rubella (MMR): in those with negative measles serology • meningococcus: in people < 25 years old, those with asplenia or complement deficiency, during outbreaks • diphtheria/tetanus/acellular pertussis (dTaP)/inactivated poliovirus vaccine (IPV): meeting general indications • chickenpox: if seronegative; those who are seropositive should receive the shingles vaccine. Bacille Calmette-Guérin (BCG) is contraindicated in all HIV-infected people. Antiretroviral therapy ART has transformed HIV from a progressive illness with a fatal outcome into a chronic manageable disease with a near-normal life expectancy. The goals of ART are to: • reduce the viral load to an undetectable level for as long as possible • improve the CD4 count to over 200 cells/mm³ so that severe HIV-related disease is unlikely • improve the quantity and quality of life without unacceptable drug toxicity • reduce HIV transmission. Many of the antiretroviral drugs that were initially used have largely been abandoned because of toxicity or poor efficacy. The drugs that are currently recommended are shown in Box 12.17, and their targets in the HIV life cycle in Figure 12.1. Selecting antiretroviral regimens The standard combination antiretroviral regimens are two NRTIs together with an NNRTI, protease inhibitor (PI) or integrase inhibitor. Dual NRTI combinations are usually emtricitabine or lamivudine (they have the same mechanism of action and so are never combined), together with one of abacavir, tenofovir or zidovudine. It is possible to construct effective regimens without NRTIs if there is intolerance or resistance to the NRTIs. Currently used PIs should always be administered with ritonavir, which dapsone 100 mg daily should be substituted. Dapsone is equally effective at reducing the incidence of *P. jirovecii* pneumonia, but has little or no effect on reducing the other opportunistic infections prevented by co-trimoxazole. Tuberculosis preventive therapy Trials in patients not on ART showed that preventive therapy, either with isoniazid or combinations of rifamycins with isoniazid, reduces the risk of tuberculosis only in HIV-infected patients with a positive tuberculin skin test. In HIV infection, induration of 5 mm or more on a Mantoux test is regarded as positive. Recent evidence indicates that tuberculin skin tests do not predict benefit in patients starting ART or established on ART in high tuberculosis prevalence settings. There is no CD4 count or clinical threshold for starting or stopping tuberculosis preventive therapy. It is important to rule out active tuberculosis before starting preventive therapy, and symptom screening has been shown to be adequate to achieve this (Box 12.16). The usual duration of isoniazid preventive therapy is 6 months but this does not provide long-term reduction in the risk of tuberculosis. Isoniazid for 36 months has been shown to be much more effective in people with a positive tuberculin skin test. Rifampicin or rifapentine combined with isoniazid for 12 weeks has been shown to be at least as effective as 6–12 months of isoniazid. Mycobacterium avium complex prophylaxis In high-income countries, a macrolide (azithromycin or clarithromycin) is recommended to prevent MAC in patients with a CD4 count below 50 cells/mm³, which can be discontinued once the CD4 count has risen to over 100 cells/mm³ on ART. MAC is uncommon in low- and middle-income countries and primary prophylaxis

is thus not warranted. Preventing cryptococcosis Serum cryptococcal antigen test should be done in patients with a CD4 count below 100 cells/mm³. If this is positive, pre-emptive therapy with fluconazole should be commenced. Immunisation There are significant problems associated with vaccination in HIV infection. Firstly, vaccination with live organisms is contraindicated in patients with severe immune suppression, as this may result in disease from the attenuated organisms. Secondly, immune responses to vaccination are impaired in HIV-infected patients. If the CD4 count is below 200 cells/mm³, then immune responses to immunisation are very poor. Therefore it is preferable to wait until the CD4 count has increased to more than 200 cells/mm³ on ART before immunisation is given, and essential if live virus vaccines are used. All patients should be given a conjugate pneumococcal vaccine and annual influenza vaccination. Hepatitis B vaccination should be given to those who are not

12.17 Commonly used antiretroviral drugs

Classes	Drugs
Nucleoside reverse transcriptase inhibitors (NRTIs)	Abacavir, emtricitabine, lamivudine, tenofovir, zidovudine*
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz*, rilpivirine (only if viral load < 100 000)
Protease inhibitors (PIs)	Atazanavir, darunavir, lopinavir*
Integrase inhibitors	Raltegravir, dolutegravir, elvitegravir
Chemokine receptor inhibitor	Maraviroc

*These drugs are no longer recommended as first-line options in high-income countries due to their toxicity.

12.16 Symptom screen for tuberculosis before isoniazid preventive therapy

All of the following must be absent:

- Active cough
- Weight loss
- Night sweats
- Fever

Antiretroviral therapy • 325

CD4 counts are generally monitored every 6 months together with the viral load, but there is little point in repeating the CD4 count in patients who maintain virological suppression and whose CD4 count is > 350 cells/mm³. The CD4 count increases rapidly in the first month, followed by a more gradual increase. In the first year, the CD4 count typically increases by 100–150 cells/mm³, and about 80 cells/mm³ per annum thereafter until the reference range is reached, provided the viral load is suppressed. However, CD4 responses are highly variable: in about 15–30% of patients the CD4 count does not increase despite virological suppression, and in a similar proportion of patients the CD4 response is good despite the presence of virological failure. If ART is stopped, the CD4 count rapidly falls to the baseline value before ART was commenced.

Antiretroviral resistance

Reverse transcription is error-prone, generating a large number of mutations. If the viral load is suppressed on ART, viral replication is suppressed and resistance mutations will not be selected. If ART is taken and there is ongoing replication, due to either resistant mutations or suboptimal adherence, mutations conferring resistance to antiretroviral drugs will be selected. Antiretroviral drugs differ in their ability to select for resistant mutations. Some drugs (e.g. emtricitabine, lamivudine, efavirenz) have a low genetic barrier to resistance, rapidly selecting for a single mutation conferring high-level resistance. PIs and some NRTIs (e.g. zidovudine) select for resistance mutations slowly, and multiple resistant mutations often need to accumulate before the drug's efficacy is lost. Patients who develop antiretroviral resistance may transmit resistant virus to others and will eventually develop clinical failure. Antiretroviral resistance is assessed by sequencing the relevant viral genes to detect mutations that are known to confer resistance. The patient must be taking ART when the test is performed, as otherwise the wild-type virus will predominate and resistant mutations will not be detected. The resistant proviral DNA is archived in latent CD4 cells and will re-emerge rapidly on re-exposure to the antiretroviral. In regions where resistance testing is affordable, it is recommended at baseline (to detect primary resistance) and at every confirmed virological failure, in order to select the most appropriate antiretrovirals in a new

regimen. ART complications Immune reconstitution inflammatory syndrome Immune reconstitution inflammatory syndrome (IRIS) is a common early complication of ART, especially in patients who start ART with CD4 counts below 50 cells/mm³. IRIS presents either with paradoxical deterioration of an existing opportunistic disease (including infections that are responding to appropriate therapy) or with the unmasking of a new infection. The clinical presentation of IRIS events is often characterised by an exaggerated immune response, with pronounced inflammatory features. For example, patients with CMV retinitis developing IRIS on ART develop a uveitis; inflammatory haloes occur around KS lesions. Paradoxical tuberculosis IRIS events are common but it is important to exclude multidrug resistance, which could be responsible for the deterioration. IRIS is associated with a mortality of around 5% but this is higher when it complicates CNS infections. itself is a PI that is toxic in therapeutic doses. Low doses of ritonavir dramatically increase the concentrations and elimination half-lives of other PIs by inhibiting the efflux pump P-glycoprotein and the cytochrome P450 isoenzyme CYP3A. Most guidelines from high-income countries, including the UK, allow clinicians to choose a starting regimen of dual NRTIs combined with an NNRTI, or a PI or an integrase inhibitor, as these three regimens have similar efficacy. Subsequent ART regimen switches for virological failure are guided by the results of resistance testing (see below). For low- and middle-income countries, the WHO recommends a public health approach to using ART with standardised first-line (NNRTI plus dual NRTIs) and second-line (ritonavir-boosted PI plus dual NRTIs) regimens. NNRTIs are preferred by the WHO in first-line regimens, as they are cheaper than PIs and better tolerated. Furthermore, NNRTIs need to be given with two fully active NRTIs because they have a low genetic barrier to resistance (see below), whereas PI-containing regimens are effective even when there are some mutations conferring resistance to the NRTIs. PIs in second-line regimens are therefore preferable in settings where resistance testing is not widely available. The public health approach to using ART can be implemented by nurses and has been successfully applied in resource-poor settings. Criteria for starting ART Guidelines now recommend starting ART in all people with confirmed HIV infection, irrespective of CD4 count or clinical status. Early initiation of ART, compared with the previous strategy of deferring ART until CD4 thresholds or clinical disease occurs, has been shown to reduce morbidity and mortality, and has the additional benefit of reducing the risk of transmission. It is seldom necessary to start ART urgently. Several consultations are required to give patients insight into the need for life-long ART, to stress the importance of adherence and to formulate a personal treatment plan. Disclosure of HIV status, joining support groups and using patient-nominated treatment supporters should be encouraged, as these have been shown to improve adherence. Recognition and management of depression and substance abuse is also important. In patients with major opportunistic infections, ART should generally be started within 2 weeks, with two important exceptions: in cryptococcal meningitis, ART should be deferred for 5 weeks, as earlier initiation increases the risk of death; and in tuberculosis, ART should be deferred until 8 weeks (except if the CD4 count is < 50 cells/mm³), as earlier initiation increases the risk of the immune reconstitution inflammatory syndrome (see below). Monitoring efficacy The most important measure of ART efficacy is the viral load. A baseline viral load should be measured prior to initiating treatment. Viral load measurement should be repeated 4 weeks after starting ART, when there should be at least a 10-fold decrease. The viral load should be suppressed after 6 months. Once the viral load is suppressed, measurement should be repeated 6-monthly. Failure of ART is defined by the viral load becoming detectable after suppression. In most guidelines, a viral load threshold is used to define virological failure, e.g. more than 200 (UK) or more than 1000 (WHO) copies/mL. Adherence support should be enhanced if virological failure is detected, and measurement of the viral load repeated to confirm failure before

switching to a new ART regimen.

326 • HIV INFECTION AND AIDS population. Although not yet fully resolved, the current weight of evidence is that fat gain on ART is a return to normal by treating HIV infection. Hypersensitivity rashes These are common but must be differentiated from the other causes described on page 314. The NRTI abacavir typically causes a systemic hypersensitivity reaction, which is limited to people with HLA-B5701, *about 50% of whom will develop a hypersensitivity reaction. HLA testing should be done before abacavir is given and the drug should not be prescribed for people who are HLA-B5701-positive*, which is rare in people of African descent. Rechallenge must never be attempted after abacavir hypersensitivity, as fatal reactions may occur. Drug rashes are very common with NNRTIs. When the NNRTI rash is mild and not accompanied by systemic involvement, the suspected drug is often continued and antihistamines are administered. The rash usually resolves. If it worsens or if systemic features develop, the NNRTI should be discontinued. Other adverse effects The NNRTI efavirenz causes insomnia, agitation, euphoria or dysphoria in many patients but tolerance to its neuropsychiatric effects develops in a few weeks in most patients. The NRTI zidovudine can cause anaemia and neutropenia, and tenofovir may cause nephrotoxicity and loss of bone mineral density. Some PIs are associated with dyslipidaemias and may increase the risk of myocardial infarction. ART in special situations Pregnancy All pregnant women should have HIV testing at an early stage in pregnancy. The CD4 count falls by about 25% during pregnancy due to haemodilution. The course of HIV disease progression is not altered by pregnancy. In the pre-ART era, the rate of mother-to-child transmission was 15–40%, with rates being influenced by several factors (see Box 12.3). ART has dramatically reduced the risk of mother-to-child transmission of HIV to less than 1%. All pregnant women should start ART at the beginning of the second trimester, unless they have advanced disease, when ART should be started in the first trimester. Caesarean section is associated with a lower risk of mother-to-child transmission than vaginal delivery, but the mode of delivery does not affect transmission risk if the viral load is suppressed on ART. HIV is also transmitted by breastfeeding. In high-income countries, exclusive formula feeding is generally recommended. In resource-poor settings, however, formula feeding is associated with a risk of infant morbidity and mortality, which may negate the benefit of not transmitting HIV to the infant. There is minimal risk of transmitting HIV by breastfeeding in women with a suppressed viral load on ART. Furthermore, providing antiretrovirals to infants (usually nevirapine monotherapy) while they are breastfeeding has been shown to reduce the risk of transmission. Breastfeeding is therefore now encouraged in resource-poor settings. Infants should be exclusively breastfed for the first 6 months, as mixed The management of IRIS is to continue ART and to ensure that the opportunistic disease is adequately treated. Symptomatic treatments are helpful. Glucocorticoids are often used for more severe IRIS manifestations but they should not be given to patients with KS, as this can result in rapid progression of KS lesions. Lipodystrophy Long-term use of ART is associated with changes in body fat distribution called lipodystrophy, which can present either with fat accumulation (e.g. visceral fat, ‘buffalo hump’) or with subcutaneous fat loss (‘lipoatrophy’, Fig. 12.16), or with both fat loss and accumulation. The thymidine analogue NRTIs (stavudine and, to a lesser extent, zidovudine) are associated with fat loss. Switching to the non-thymidine NRTIs, abacavir or tenofovir, will result in very gradual improvement of lipoatrophy. Previously, PIs were thought to be the cause of fat accumulation. However, recent studies have shown that all classes of antiretrovirals are associated with fat gain to a similar extent, and visceral adiposity is similar to that seen in the general Fig. 12.16 Fat loss complicating long-term use of the thymidine analogue NRTIs stavudine and zidovudine. 12.18 HIV

infection in old age • Epidemiology: the HIV-infected population is ageing due to the life-prolonging effects of ART. • Immunity: age-related decline increases the risk of infections. CD4 counts decline more rapidly as age extends beyond 40 years, resulting in faster disease progression. CD4 responses to ART decrease with increasing age. • Dementia: HIV causes cerebral atrophy and neurocognitive disorders; dementia is therefore more common and more severe than in the HIV-uninfected elderly. • Vascular disease: HIV is associated with an increased risk, exacerbated by some antiretrovirals that increase the risk of vascular disease by causing dyslipidaemia or insulin resistance. • Polypharmacy: treatment of co-morbidities is complex due to the many drug interactions with antiretrovirals.

Further information • 327 Further information Websites with updated clinical guidelines
aidsinfo.nih.gov AIDSinfo, a service of the US Department of Health and Human Services (HHS).
bhiva.org British HIV Association. who.int/hiv/pub World Health Organisation. feeding (with formula or solids) is associated with a higher risk of transmission. Diagnosis of HIV in infancy requires the detection of HIV RNA by PCR, as maternal antibodies to HIV, which persist for up to 15 months, will give a false-positive result on antibody assays. PCR should ideally be carried out within 6 weeks of birth to facilitate early ART initiation. If the baby is breastfed, the PCR should be repeated 2 weeks after weaning. Prevention of HIV An effective HIV vaccine remains elusive due to the extensive genetic diversity of HIV and the lack of a safe attenuated virus. Measures for the prevention of HIV transmission are shown in Box 12.19. Pre-exposure prophylaxis Pre-exposure prophylaxis (PrEP) with daily tenofovir plus emtricitabine has been shown to reduce the risk of HIV acquisition in people at ongoing high risk (e.g. from sex or injecting drug use) and is well tolerated. Regular HIV testing should be done in people on PrEP. Post-exposure prophylaxis Post-exposure prophylaxis (PEP) is recommended when the risk is deemed to be significant after a careful risk assessment, in both occupational and non-occupational settings. The first dose should be given as soon as possible, preferably within 6–8 hours. There is no point in starting PEP after 72 hours. Tenofovir together with emtricitabine is the most widely used dual NRTI combination, together with either a PI or an integrase inhibitor. PEP should not be given if the exposed person is HIV-infected. HIV antibody testing should be performed at 3 months after exposure. 12.19 Prevention measures for HIV transmission Sexual • Sex education programmes in schools • Easily accessible voluntary counselling and testing centres • Promotion of safer sex practices (delaying sexual debut, condom use, fewer sexual partners) • Effective ART for HIV-infected individuals • Pre-exposure prophylaxis for high-risk groups • Male circumcision • Post-exposure prophylaxis Parenteral • Blood product transmission: donor questionnaire, routine screening of donated blood • Injection drug use: education, needle/syringe exchange, avoidance of ‘shooting galleries’, methadone maintenance programmes Perinatal • Routine ‘opt-out’ antenatal HIV antibody testing • Measures to reduce vertical transmission (see text) Occupational • Education/training: universal precautions, needlestick injury avoidance • Post-exposure prophylaxis

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