

8.5.23 HIV AIDS 901

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8.5.23 HIV/AIDS 901 HCV may clear the virus spontaneously within the first 3 months, treatment is advocated for acute HCV as it is very effective. It should be started between 12 and 24 weeks of infection. This allows sufficient time to assess whether spontaneous resolution has occurred, without losing the clinical benefit of early treatment. Genotype does not affect response and historically cure rates as high as 80–95% can be achieved with 6 months of pegylated interferon monotherapy. It may be that short treatments of the oral directly acting antiviral agents for less than 8 weeks will be as effective in eradicating HCV in the acute setting. Area of uncertainty or controversy The degree of resolution of severe fibrosis and the risk of hepatocellular carcinoma after effective cure with directly acting antiviral agents will need further study, in particular to define at what point screening for primary liver cancer might no longer be necessary. Also, to what extent the immune system recovers from the immunomodulation created during chronic infection is not known. The best strategy to identify and treat all patients with costly directly acting antiviral agents has yet to be identified and represents an important public health challenge. Although pre-existing or emergent drug resistance to directly acting antiviral agents does not appear to be a common problem currently, the potential emergence of drug resistance means this will require close monitoring over time. Likely developments over the next 5–10 years The development of new DAA combinations and rescue regimens which are active against a range of genotypic variants and rare subtypes is important as drug resistance is likely to be a problem in a small proportion of patients. Access to more accurate HCV gene sequencing will also be important when targeting drug resistance. Accessibility and affordability of the newer HCV treatments on a global scale is essential if cirrhosis and hepatocellular carcinoma are to be prevented in most of the world's HCV infected population. Further development of current prophylactic vaccine approaches will depend on the outcome of current clinical trials in at-risk groups. FURTHER READING Afghal N, et al. (2014). Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med*, 370, 1889–98. Benvegnu L, et al. (2004). Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. *Gut*, 53, 744–9. Duggal P, et al. (2013). Genome wide association study of spontaneous resolution of hepatitis C virus infection *Ann Intern Med*, 158, 235–45. Feld JJ, Hoofnagle JH (2005). Mechanism of action of interferon and ribavirin in treatment of hepatitis C. *Nature*, 436, 967–72. Foster GR, et al. (2015). Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alpha in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. *Gastroenterology*, 149, 1462–70. Gee I, Alexander G (2005). Liver transplantation for hepatitis C virus related liver disease. *Postgrad Med J*, 81, 765–71. Heim MH, Thimme R (2014). Innate and adaptive immune responses in HCV infections. *J Hepatol*, 61, S14–25. Johnson RJ, et al.

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8.5.23 HIV/AIDS
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ESSENTIALS Since its discovery in 1983, the human immunodeficiency virus (HIV) has been associated with a global pandemic that has affected more than 78 million people and caused more than 39 million deaths. Globally, 36.9 million (31.1 million–43.9 million) people were living with HIV at the end of 2017. An estimated 0.8% of adults aged 15–49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions. Sub-Saharan Africa remains most severely affected, with nearly 1 in every 20 adults living with HIV and accounting for nearly 71% of the people living with HIV worldwide. The impact of HIV in some African countries has been sufficient to reverse population growth

902 section 8 Infectious diseases and reduce life expectancy into the mid-thirties, although HIV incidence has recently declined in some of these high-prevalence countries. However, there are large-scale epidemics of HIV elsewhere (e.g. India, the Russian Federation, and Eastern Europe). By the end of 2017, globally, 21.7 million (19.1–22.6 million), 59% (44–73%) of all people living with HIV were accessing antiretroviral therapy, while 1.8 million people became newly HIV infected and 940 000 (670 000–1.3 million) died from HIV-related illnesses; a fall of 49% from the peak in 2004. Transmission Worldwide, the principal mode of transmission is heterosexual intercourse. Other risk factors for acquisition of HIV include unprotected sex between men, injecting drug use, transfusion of contaminated untested blood products, and mother-to-child transmission. Cellular biology HIV-1 (derived from a simian immunodeficiency virus in the chimpanzee) and HIV-2 (animal reservoir the sooty mangabey monkey) belong to the lentivirus subfamily of retroviruses. The viral genes in infectious particles are carried as RNA, but upon infection of the host cell, reverse transcriptase catalyses the synthesis of a double-stranded DNA viral genome that is inserted into the chromosomal DNA of the infected cell by viral integrase. Genomic structure—HIV has only nine genes: (1) gag—encoding the core proteins p17, p24, and p15; (2) pol—encoding the enzymes protease, reverse transcriptase, and integrase; (3) env—encoding envelope glycoproteins (gp120 and gp41); (4) two major regulatory genes—tat and rev—encoding proteins that are not assembled into the virus but are essential for replication in the cell; (5) four accessory genes, whose functions are not clearly understood. HIV receptors and cellular tropism—CD4 is the cell-surface receptor for HIV, which binds to it via gp120; gp41 is then thought to effect membrane fusion. However, another cellular component Page: 621 or coreceptor is required, and different substrains of HIV (even those isolated from the same patient) exhibit specific tropisms for different cell types in culture, dependent on the ability of each particular substrain to bind to

particular chemokine receptor family coreceptors. Sexual HIV transmission is usually with a CCR5-using viral variant, and with advanced untreated disease this tends to transition to CXCR4 using species. Naturally occurring deletions in the host genome encoding CCR5 (delta-32 base pair deletion) confers natural resistance to HIV susceptibility. Knowledge of the cell biology of HIV has facilitated the development of pharmacological agents that have transformed the disease from a uniformly fatal illness to a chronic condition in those countries able to provide antiretroviral treatment. Diagnostic tests and screening Reliable tests that detect HIV antibodies and antigen are used for diagnosis and screening. In all countries, around a quarter of the people living with HIV are unaware of their HIV status. For those unaware of their status, therefore not accessing antiretroviral therapy, there remains an increased risk of sexual and perinatal transmission. Targeted screening programmes are needed to encourage HIV testing for this unreached group to achieve zero HIV-related deaths and zero new infections. Due to viral heterogeneity diagnostic tests for HIV focus on the detection of HIV-specific antibodies rather than viral detection itself. Point-of-care technology has transformed uptake of HIV diagnosis and is now commonly used in many countries and is increasingly available for self-testing using finger prick blood drops or oral swab testing. HIV antibody testing misses the diagnosis of acute infection, prior to the development of detectable levels of antibodies. In such cases, combination antigen (p24) antibody testing is performed on venous blood samples and detection of HIV RNA or DNA polymerase chain reaction may also be used. HIV antibody/antigen combined testing is used for confirmation of point-of-care tests. Clinical features Primary HIV infection—a few weeks after acquisition of HIV, many people develop a nonspecific influenza-like illness (seroconversion illness/acute retroviral syndrome), often accompanied by a transient macular or maculopapular rash affecting the upper body. Rarely, there are neurological complications and severe immunodeficiency with secondary opportunistic infections. Most do not seek medical help, and diagnosis is often missed. Nonspecific symptoms can be mistakenly attributed to influenza, upper respiratory tract infections, or glandular fever. Several such indicator diseases should trigger the offer of an HIV test, particularly among men-having-sex-with-men and those from high-prevalence regions. The natural history of untreated HIV disease was referred to as a period of ‘Clinical latency’ typically lasting 8–10 years before development of further illness. This period is often asymptomatic, but some individuals have persistent generalized lymphadenopathy, and may develop minor opportunistic conditions affecting the skin and mucous membranes (e.g. viral warts, oropharyngeal candidiasis, and oral hairy leucoplakia). During this period, in the absence of antiretroviral therapy there is progressive immune destruction, particularly depleting circulating CD4+ T cells from normal levels (>900 cells/cc3 to <200 cells/cc3. Once the CD4 count has fallen to less than 350 cells/cc3 there is an associated significant risk of HIV-related opportunistic disease and AIDS. Progression to symptomatic HIV disease (AIDS)—the value of making a distinction between AIDS and HIV infection in the era of antiretroviral therapy is no longer relevant: It is more useful to consider untreated progressive HIV disease as a continuous spectrum. Complications of late-stage HIV disease include (1) opportunistic infections—for example, pneumocystis pneumonia, oesophageal candidiasis, cerebral toxoplasmosis, and cytomegalovirus retinitis; (2) opportunistic tumours—for example, Kaposi’s sarcoma and non-Hodgkin’s lymphoma; and (3) direct HIV effects—for example, HIV-associated neurocognitive disorders. Clinical management and prognosis CD4+ T-lymphocyte count (CD4 count) and plasma HIV-1 viral load are the two laboratory markers with the best prognostic value: (1) CD4 count—this is an indicator of HIV-related immune impairment, with decline to below

200/cc3 associated with the risk of life-threatening opportunistic infection; based on the findings from recent trial data (START trial) antiretroviral treatment is currently recommended for all people living with HIV irrespective of CD4 count or clinical stage. (2) Viral load—quantitative estimation of HIV RNA in the blood plasma is the key tool in monitoring the effectiveness of therapy,

8.5.23 HIV/AIDS 903 which aims to maintain suppression of viral RNA at undetectable levels (<20–40 copies/ml, depending on the assay). The choice of initial antiretroviral regimen should take into account the results of baseline genotypic resistance testing, comorbidity, coinfections, and drug interactions as well as cost. Prognosis—the outlook for people with HIV infection has been transformed since the late 1990s by the advent of highly active anti-retroviral therapy, but access to antiretroviral drugs continues to be difficult in less-resourced countries (see Chapter 8.5.24). Antiretroviral therapy (ART) for effective viral suppression requires combinations of three drugs from more than 20 agents that are now available: a minimum of three, drawn from at least two drug classes, is required. Initial regimens usually include (1) a backbone of two nucleoside analogues (inhibitors of HIV reverse transcriptase), for example, tenofovir and emtricitabine or abacavir and lamivudine with either (2) a nonnucleoside reverse transcriptase inhibitor (e.g. efavirenz), (3) an integrase inhibitor (e.g. Raltegravir or Dolutegravir), (4) or a boosted protease inhibitor (e.g. Darunavir and ritonavir). Factors considered when selecting the initial antiretroviral combination include potential drug interactions with other medications, presence of renal or hepatic dysfunction, the presence of cardiovascular risk factors and coinfections with other viruses, in particular hepatitis B and C, and avoidance of predictable drug toxicities. An important development has been the availability of simplified regimens involving small numbers of coformulated tablets taken once daily. Adherence to treatment and avoidance of suboptimal therapy (such as regimens involving fewer than three active agents, or use of agents in the presence of HIV mutations conferring resistance) are important in avoiding treatment failure. Other drugs for HIV—(1) New agents in established drug classes—these have activity against HIV despite mutations conferring resistance to other drugs in the class, for example, etravirine and (integrase inhibitors) elvitegravir and dolutegravir. Also, tenofovir alafenamid, a better tolerated, less toxic compound with activity comparable to tenofovir DF, has become available and has been shown to have significantly less renal and bone toxicity. In addition, novel fusion inhibitors currently in phase I and II clinical trials and long-acting injectable formulations are under trial. Adverse reactions to antiretroviral drugs—are relatively common and include: (1) short-term reactions—gastrointestinal disturbances, rashes, and neuropsychiatric reactions that might require early adjustments to the treatment regimen; (2) longer-term reactions—metabolic complications include (a) mitochondrial toxicity; (b) disturbances of lipid and glucose metabolism associated with a risk of cardiovascular disease including myocardial infarction—the absolute risk is small but requires consideration in patients with pre-existing cardiovascular risk factors; (c) renal impairment (e.g. with tenofovir); (d) metabolic bone disease. (3) Paradoxical reactions—called immune reconstitution syndromes—these can occur in up to 20% of patients starting treatment, in particular those with severely impaired immune function prior to therapy, and include new or worsening inflammatory symptoms, especially in patients who have opportunistic infections such as tuberculosis. Earlier HIV diagnosis and initiation of antiretroviral therapy will reduce the cases of immune reconstitution syndromes. Recent clinical trials have identified a clinical benefit of initiation of antiretroviral therapy irrespective of CD4 T-cell count at the time of HIV diagnosis and this has been incorporated in the most recent World Health Organization antiretroviral therapy guidelines of 2015. Coinfections involving HIV and tuberculosis, hepatitis B, or hepatitis C are

common and require specialized treatment due to drug interactions and cotreatment requirements. Integrase inhibitors have limited drug interactions with tuberculosis treatments and are the preferred agents in the presence of tuberculosis. Hepatitis B treatment includes the use of tenofovir plus emtricitabine for most coinfecting patients, enabling easier treatment of both HIV and hepatitis B. When to start antiretroviral therapy—Historically there has been an important balance between the potential drug related toxicities and the individual clinical benefit of treatment. As antiretroviral therapy has become less toxic, easier to take (currently many effective regimens are one coformulated pill once a day) clinical trials have explored the risks vs. benefits of starting antiretroviral therapy at higher CD4 count thresholds. The recently reported START trial identified in a large international randomized controlled study that immediate antiretroviral therapy for patients with CD4 T-cell counts greater than 500 cells/cc³ still conferred overall individual clinical benefit compared with deferral until a CD4 threshold of 350 cells/cc³. The results of this trial have now been incorporated into the World Health Organization and many national antiretroviral therapy guidelines and have resulted in the recommendation of immediate initiation of antiretroviral therapy for all people living with HIV, irrespective of CD4 count. HIV prevention Strategies to raise awareness and provide education, and promote risk reduction, underpin HIV control programmes worldwide. HIV viral load is the most critical determinant of onward HIV transmission. Reduction of HIV viral load using antiretroviral therapy for people living with HIV has been shown to be highly effective at preventing sexual transmission within both heterosexual and men who have sex with men. In addition, the use of antiretroviral therapy or components of it for HIV exposed, but uninfected individuals as postexposure prophylaxis or pre-exposure prophylaxis are also highly effective at preventing establishment of infection among high-risk exposed individuals. Control of coexistent sexually transmitted genital ulcers and other genital infections reduces HIV transmission. Similarly, mother-to-child transmission can be reduced to below 1% if antiretroviral treatment is administered to the mother during pregnancy, delivery is by planned caesarean section (vaginal delivery can be an option if HIV viral load is below the detection threshold), and breastfeeding is avoided. Despite decades of research, an effective HIV vaccine is not available.

Introduction Acquired immunodeficiency syndrome was first recognized in 1981 in the United States of America, when outbreaks of pneumocystis pneumonia and Kaposi's sarcoma were reported in men who have sex with men in New York and California. The variety of unusual infections and other conditions declared a new form

904 section 8 Infectious diseases of cellular immunodeficiency and was described as the acquired immune deficiency syndrome (AIDS). In 1983, the causative retrovirus was isolated and subsequently named human immunodeficiency virus (HIV). At the time of its discovery, HIV was already widespread, the earliest infections probably having occurred before the 1950s. In 1986, a second retrovirus causing AIDS, HIV-2, was identified in West Africa. It remains largely confined to this region, while HIV-1 is the cause of the world pandemic of AIDS. HIV infection may be regarded as a zoonosis: HIV-1 is derived from a simian immunodeficiency virus in the chimpanzee (*Pan troglodytes troglodytes*), and the animal reservoir for HIV-2 is the sooty mangabey monkey (*Cercocebus atys*).

Epidemiology The global HIV-1 pandemic has had the greatest impact in developing countries (see Chapter 8.5.24). The World Health Organization (WHO) estimated that in 2010, 33.3 million people were living with HIV worldwide, of whom 22.5 million were in sub-Saharan Africa (Fig. 8.5.23.1). Worldwide, the WHO estimated there were 2.6 million new HIV infections in 2009, of which 1.8 million were in sub-Saharan Africa. Globally, AIDS caused 1.8 million deaths of which 1.3 million were in sub-Saharan Africa. New HIV infections have fallen by

35% since 2000. Worldwide, 2 million (1.9–2.2 million) people became newly infected with HIV in 2014, down from 3.1 million (3.0–3.3 million) in 2000. New HIV infections among children have declined by 58% since 2000. Worldwide, 220 000 (190 000–260 000) children became newly infected with HIV in 2014, down from 520 000 (470 000–580 000) in 2000. In North America, Western Europe, and Australasia the epidemic began among men who have sex with men and injecting drug users. However, in these regions the proportion attributable to heterosexual transmission subsequently increased. In 2015, over 100 000 people were living with HIV in the United Kingdom, nearly a quarter of whom were unaware of their diagnosis. The proportion of newly diagnosed cases in the United Kingdom attributed to heterosexual transmission rose steadily from 1999 onwards, largely due to increased numbers arriving from countries with high prevalence, and increased HIV detection through routine antenatal testing. However, injecting drug use, unprotected sex between men, and unprotected paid sex remain important modes of transmission in Europe, as well as in Asia and Latin America. Fig. 8.5.23.1 World distribution of HIV, 2013. Copyright © WHO 2014.

8.5.23 HIV/AIDS 905 In contrast, HIV transmission in regions with the highest prevalence rates, such as sub-Saharan Africa, is predominantly heterosexual and perinatal. The estimated overall adult prevalence there is 6%, rising to between 20 and 30% in some countries such as Botswana and Zimbabwe, where AIDS has curtailed population growth and life expectancy had fallen into the mid-30s. Swaziland (population 1 million) is the country with the highest adult seroprevalence, of 33%. The country with more infected people than any other is believed to be South Africa (6.4 million adults living with HIV, adult seroprevalence 20%), although in India, where prevalence data are less easily accessible, the overall numbers might be similar (despite adult seroprevalence below 1%). The overall prevalence of HIV has risen worldwide in recent years because new transmissions exceed AIDS-related deaths, and because successful antiretroviral treatment has reduced mortality. However, there have been notable declines in some high-prevalence countries such as Kenya, Zimbabwe, and parts of India, and a leveling off in other parts of sub-Saharan Africa, attributable to prevention efforts. Uganda is seen as one of the best examples of a country where prevalence has declined significantly, believed to be, at least in part, due to the timely government campaign of public education, although more recently this reduction in incidence has not been sustained. The global distribution of HIV is currently characterized by very variable rates of prevalence and scattered areas of very high transmission in epidemics. Consequently, the risk of acquisition of HIV is also highly variable from region to region. In some countries, such as Russia and Ukraine, HIV has caused large-scale epidemics and transmission rates remain high. The risk of onward transmission is especially high soon after sexual acquisition of HIV, when plasma viral load is high, and the virus is present in genital secretions in sexually active people, often unaware of their changed HIV status. Therefore, it is particularly important to detect primary HIV infection in population screening programmes. HIV transmission continues at a high level in many countries because of poverty, low condom usage, high rates of other sexually transmitted infections, and higher risk behaviour such as unprotected paid sex and use of nonsterile injecting drug equipment. HIV-2 is endemic in parts of West Africa and is also prevalent in Angola, Mozambique, France, and Portugal. In other parts of the world, the prevalence is very low, although it is present in India. The clinical features of HIV-2 are similar to those of HIV-1, but some patients with HIV-2 appear to progress much more slowly than those with HIV-1 for unknown reasons. Most of the currently available antiretroviral therapies (ART) are not effective against HIV-2. Variation of HIV-1 RNA sequences has been identified, leading to a classification of 11 sequence subtypes (or clades), A to

K, of the main group M, and N (new) and O (outlier) as two quite distinct groups in west central Africa. The subtypes have varying geographical distributions. For instance, subtypes A and D are found in central Africa, B in North America and Europe, and E in Thailand. More people are infected with clade C virus than any other, being the predominant clade of virus in southern Africa as well as India. A new group, P, was designated after the discovery of a novel HIV strain in a female from Cameroon in France in 2009, which was closely related to the simian immunodeficiency virus found in gorillas. Study of the genetic and geographical divergence of subtypes has shed light on the emergence and global spread of HIV.

Cellular biology of HIV

The viral replication cycle HIV-1 (Fig. 8.5.23.2) and HIV-2 belong to the lentivirus subfamily of retroviruses. Retrovirus implies a 'backwards' step in biological information during viral replication attributable to its enzyme, reverse transcriptase. As with all retroviruses, the viral genes in infectious particles are carried as RNA, but upon infection of the host cell, reverse transcriptase catalyses the synthesis of a double-stranded DNA viral genome (Fig. 8.5.23.3). Insertion of the DNA genome into the chromosomal DNA of the infected cell is effected by viral integrase. The integrated provirus may remain latent, particularly in resting lymphocytes. In actively infected cells, however, RNA transcripts and proteins are synthesized, leading to the formation of new virus particles. The core proteins derived from the gag and pol genes are made as large polypeptides that are then cleaved into smaller components representing the enzymes and building blocks of the virus. This cleavage is achieved by the viral protease. The unique reverse transcriptase and protease are targets of antiretroviral therapy (see next). Reverse transcriptase inhibitors such as abacavir and lamivudine affect an early step in HIV replication, whereas the protease inhibitors, such as darunavir, block a late stage of virus assembly (Fig. 8.5.23.3). Compounds that inhibit any stage of HIV replication, without being too toxic to the infected person, are potential antiviral drugs. Agents have been developed to block viral entry (e.g. fusion entry inhibitors and CCR5 receptor antagonists) and integration into the host cell DNA (integrase inhibitors). Although regarded as a complex retrovirus, HIV has only nine genes (Fig. 8.5.23.4). The three structural genes are gag, pol, and env, encoding the core proteins p17, p24, and p15, the enzymes (protease, reverse transcriptase, and integrase), and the envelope glycoproteins (gp120 and gp41), respectively. The major regulatory genes tat and rev encode proteins that are not assembled into the virus but are essential for replication in the cell. The Tat protein acts in positive feedback to enhance transcription of viral RNA from the DNA provirus, while the Rev protein helps the efficient transport of

Fig. 8.5.23.2 Electron micrograph of HIV-1. Reproduced by courtesy of H. Gelderblom.

906 section 8 Infectious diseases viral RNA from the nucleus to the cytoplasm. Either of these proteins could be a suitable target for antiviral therapy, particularly Tat, because the synthesis of all the other viral proteins depends on its activity. The functions of the four accessory genes of HIV are less well understood. Vif encodes a protein assembled in virus particles that appears necessary for the infectivity ('viral infectivity factor') at a stage soon after entry. Vif binds and hastens the degradation of the cellular protein APOBEC which, in the absence of Vif, hypermutates HIV, thereby disabling it. Nef also affects an early postentry function; it is not needed by laboratory-adapted HIV strains or if virus enters via endosomal vesicles rather than fusing with the outer cell membrane. It also down-regulates surface expression of the primary cell-surface receptor for HIV, the CD4 antigen, by drawing CD4 into clathrin-coated pits. Vpu similarly interacts with CD4, promoting its degradation by directing it to the ubiquitin-proteasome pathway. Vpr has dual functions; first, it directs the preintegration complex of the virus, containing the newly synthesized DNA, into the nucleus so that it can integrate into chromosomal DNA; second, it blocks cell proliferation in the G2

phase of the cell cycle, thereby enhancing the amount of viral progeny released per cell. Unlike HIV-1, HIV-2 and the simian immunodeficiency viruses (SIV) lack *vpu*, but have an alternative gene, *vpx*. HIV-2 *Vpr* leads the viral genome into the cell nucleus, but does not arrest the cell cycle. These proteins presumably recognize cellular proteins and some of these interactions are species-specific. Thus, the *Vpr* and *Vif* proteins in SIV of African green monkeys do not function in human cells, while the equivalent proteins of SIV from sooty mangabey monkeys work well in human cells. This could explain why sooty mangabey SIV was able to infect humans and become HIV-2, whereas the more widespread African green monkey SIV has not led to a zoonosis. Another difference is that HIV-1 incorporates the cellular protein cyclophilin A (the target of the drug ciclosporin A) into virus particles, where it may cooperate with *Vif* and is required for steps early in the infection. In contrast, HIV-2 does not contain cyclophilin A and replicates well without it. HIV receptors and cellular tropism CD4 is the cell-surface receptor for HIV; it is expressed on T-helper lymphocytes, the cells that become depleted in AIDS. CD4 is also expressed (to a lesser extent but sufficient to permit infection) on macrophages, Langerhans dendritic cells in mucous membranes, and brain microglial cells. These are the other target cells for HIV infection. CD4 is necessary to initiate HIV infection but is not sufficient to allow the virus to fuse with host cell membranes: another cellular component or coreceptor is required. Different substrains of HIV, even those isolated from the same patient, exhibit specific tropisms for different cell types in culture. All isolates can infect primary CD4 lymphocytes, but only some infect macrophages while others can infect cell lines established from CD4⁺ leukaemic cells. Macrophage-tropic strains predominate early in the course of HIV infection, and may be more transmissible from person to person. They do not cause CD4 lymphocytes to fuse together in culture and hence are referred to as non-syncytium-inducing (NSI) strains. In contrast, many HIV isolates established from late-stage infection rapidly adapt in culture to infect T-cell lines and are syncytium-inducing (SI). Approximately 50% of patients with AIDS develop SI strains in addition to NSI strains. The differences in cellular tropism and SI/NSI phenotype occur in all HIV subtypes or clades, which appear to reflect geographical variation of HIV rather than specific biological properties of the virus. The complex cellular tropism of HIV has been explained by the discovery that different members of the chemokine receptor family act as coreceptors to CD4 for HIV entry into cells. Chemokines are chemoattractant, locally acting hormones or cytokines that bind to one or more receptors which are structurally related to olfactory and neurotransmitter receptors. Following binding to the CD4 receptor, primary NSI strains use CCR5, the chemokine receptor for macrophage-inhibitory proteins (MIP-1 α , MIP-1 β) and RANTES. In contrast, the SI strains of HIV use the CXCR4 coreceptor, the receptor for another chemokine, stromal-derived factor-1 (SDF-1). Other receptors such as CCR3 (the receptor of eotaxin) can be used by some NSI strains. High levels of MIP-1 α or - β in the blood correlate with relative resistance to HIV infection. Some exposed yet uninfected individuals are homozygous for an inherited defect of the CCR5 receptor involving a 32 bp deletion in the CCR5 gene. This mutation is present in approximately 20% of white people (approximately 1% of white people are homozygous), but is not found in African and Asian populations. Individuals who are homozygous for the deletion are healthy, indicating that the CCR5 receptor is not essential for the development of immune competence, probably because MIP-1 and RANTES

RNA Fig. 8.5.23.3 Replicative cycle of HIV. HIV-1 LTR GAG POL VIF VPR VPU TAT REV ENV NEF LTR
HIV-2 LTR GAG POL VIF VPR VPX ENV NEF LTR TAT REV kbp 0 1 2 3 4 5 7 6 8 9 Fig. 8.5.23.4 HIV genome map.

8.5.23 HIV/AIDS 907 people are homozygous), but is not found in African and Asian populations. Individuals who are homozygous for the deletion are healthy, indicating that the CCR5 receptor is not essential for the development of immune competence, probably because MIP-1 and RANTES

can also bind to alternative receptors. However, homo-zygotes are genetically resistant to infection by NSI strains of HIV, and the few homozygotes with $\Delta 32$ deletions who are HIV-positive appear to have been infected with SI strains that utilize CXCR4 instead. Other, more subtle, mutations in the promoter region of the CCR5 gene allowing only low levels of coreceptor expression may confer relative resistance to HIV infection and also, if infection occurs, slower the progression to AIDS. A blood group antigen on red blood cells, the Duffy antigen receptor for chemokines (DARC), was shown to be another non-human leukocyte antigen (HLA) genetic factor influencing HIV transmission and disease progression. In addition to forming a receptor for certain HIV-suppressive and proinflammatory chemokines such as RANTES, DARC serves as the red cell receptor for *Plasmodium vivax* malaria and consequently nonexpression of DARC on red cells (Duffy negative phenotype) confers complete resistance to *P. vivax*. As a result of selection pressure from malaria, most West Africans and two-thirds of African Americans do not express DARC on red cells (although expression is preserved on endothelial cells). The DARC-negative red cell phenotype is associated with an increased risk of acquisition of HIV-1; however, it is also associated with slower HIV-related disease progression. The outer envelope glycoprotein, gp120, is the molecule on HIV that binds to CD4 and subsequently to the coreceptor. Gp120 is anchored to the viral envelope via gp41, the viral protein that is thought to effect membrane fusion. The gp120-gp41 is present in the viral envelope as a trimeric complex. SI strains Page: 625 have a gp120-gp41 structure that is less stable than NSI strains, readily undergoing conformational change on binding to CD4. This property makes SI strains more sensitive to neutralization by gp120 antibodies and also to inactivation by soluble forms of recombinant CD4, which were once seen as promising therapeutic agents. NSI strains, however, are more resistant. Mutations in the V3 loop of gp120 can convert NSI strains to SI strains. These mutations arise naturally during progression to AIDS and may allow HIV to switch to infect different cell types via new coreceptors. The natural chemokines act as competitive inhibitors of HIV entry; certain chemically modified chemokines and chemical analogues act as strong HIV inhibitors without triggering the downstream signalling of the receptor. This has led to a new class of anti-HIV drugs, called CCR5 receptor antagonists.

Diagnosis of HIV infection Following seroconversion, antibody to envelope protein persists indefinitely in the serum and forms a highly specific test for HIV infection. Most laboratories use one or more sensitive enzyme immunoassay tests that detect HIV-1 and HIV-2 antibodies and p24 antigen as the initial screening test. Positive screening tests are usually referred to a specialist laboratory for additional tests to confirm the presence of HIV antibodies. Most seroconversions occur within 3 months of infection, and very rarely up to 6 months. Routine diagnostic tests, if negative, should be repeated 6 to 12 weeks after the last possible exposure. Additional tests using HIV RNA and DNA can also detect acute infection more accurately. If primary infection is suspected, or after high-risk exposure, additional tests may be indicated (see 'Primary HIV infection', next). Point-of-care HIV testing is now a standard testing technology globally and involves a finger prick sample or oral swab. This has dramatically increased uptake of HIV testing especially in high-prevalence resource-limited settings where task shifting away from clinically trained healthcare facility testing has enabled enhanced uptake of HIV testing. In many settings HIV self-testing using oral swab testing or in some settings finger prick sampling or testing is also available. Globally around 25% of people living with HIV are unaware of their HIV infection; in the United Kingdom the estimated number of people with undiagnosed HIV infection has reduced from 13 300 in 2015 to around 10 400 in 2016, with most of the decline seen in gay and bisexual men in London, and in black African heterosexual women. Detection of HIV is important for timely intervention with antiretroviral treatment, to reduce HIV-related morbidity and mortality and reduce the risk of

perinatal transmission, and to promote behavioural change to protect sexual partners. Unfortunately, HIV remains a stigmatized condition and acceptance of testing is limited by potential distress and disruption of domestic, social, and professional lives. Psychological support and counselling may be needed, especially around the time of diagnosis. However normalization of HIV testing and the availability of immediate treatment might serve to enhance acceptability of testing. Many industrialized countries are developing strategies to increase HIV detection. In the United Kingdom, it is standard practice that all patients attending sexual health clinics for screening or treatment for sexual infections are offered HIV testing, and 'opt out' testing in genitourinary medicine (GUM) clinics and antenatal settings has dramatically improved testing rates. It is recommended that HIV testing should be considered in all general medical admissions to hospital, particularly in individuals from high-risk groups and those presenting with 'indicator' conditions such as Epstein-Barr virus, cytomegalovirus (CMV) upper respiratory tract infections, and pneumonia. Testing should also be considered for all adults registering with a general practice if the HIV prevalence in the local population exceeds 2 in 1000 (typically larger cities). In the United States of America, where more than 25% of those infected are unaware of their HIV infection, the Centers for Disease Control and Prevention (CDC) has recommended that HIV testing should be routinely offered in all healthcare settings. In patients with unexplained symptoms that could be caused by HIV, testing is essential for diagnosis so that appropriate treatment can be provided. If the patient is too ill to give consent, testing is justified on the grounds of being in the patient's best interest. As there is still stigma associated with HIV, confidentiality must be maintained; disclosure of HIV-positive status is acceptable only in the medical interests of the patient and in general with their knowledge and consent. Patients unwilling to inform their sexual partners should be advised of the possible legal implications of nondisclosure if transmission occurs. In the United Kingdom, there have been successful prosecutions of individuals knowingly exposing their partners to HIV.

908 section 8 Infectious diseases Transmission of HIV Viral transmission across a mucosal membrane is relatively inefficient when compared to other sexually transmitted infections (gonorrhoea or syphilis) but once established, dissemination to the local, and then regional lymph nodes occurs rapidly, within a few days. Transmission occurs usually with a clonal infection which rapidly diversifies due to the lack of fidelity of the reverse transcriptase enzyme into a new quasi-species. The clonality of recently transmitted virus can be used in research studies to estimate how recently the infection occurred. Infected antigen presenting cells and CD4+ T cells rapidly traffic to regional and local lymph nodes carrying virus with them and the lymph node is the active site of viral transfer to uninfected CD4-bearing cells. For this reason postexposure prophylaxis (PEP) must be initiated as soon as possible after exposure to optimize efficacy although current guidelines still recommend prescription up to 72 hours after exposure. Mucosal delivery of ART agents through vaginal rings impregnated with antiretroviral agents is under trial as a prevention tool. Clinical presentation and features Primary HIV infection Between 2 and 6 weeks after exposure to HIV, 50 to 70% of those infected develop a transient, often mild, nonspecific illness (sometimes called seroconversion illness or acute retroviral syndrome) similar to infectious mononucleosis, with fever, malaise, myalgia, lymphadenopathy, and pharyngitis. However, unlike infectious mononucleosis, over 50% of people develop a rash, typically erythematous, maculopapular, and affecting the face and trunk. Other rashes and patterns of distribution, and oral and genital ulcers have also been reported. The illness begins abruptly and usually lasts for 1–2 weeks, but may be more protracted. Most cases are so mild that patients do not seek medical help.

In addition, abnormal liver function tests are common and neurological complications can occur and include acute encephalitis, lymphocytic meningitis, and peripheral neuropathy. Severe or long-lasting illness and neurological involvement are associated with accelerated progression to AIDS and a bad prognosis, which might be influenced by immediate antiretroviral therapy. A transient decrease in CD4 lymphocytes is usual during primary illness. Occasionally, this can be substantial and associated with opportunistic infections such as oral or oesophageal candidiasis, and rarely pneumocystis pneumonia (PCP). There are few data on primary infection features associated with HIV-2. Diagnosis requires a high index of suspicion. Primary HIV infection is a time of high viraemia (typically 10⁵–10⁶ viral particles/ml) during which antibodies to HIV may initially be absent (Fig. 8.5.23.5). However, combined antigen-antibody fourth-generation tests can detect p24 antigen as well as HIV antibodies and can often detect p24 antigen in advance of antibody early in primary infection. Serum antibodies to the core and surface proteins of the virus usually appear within 2 to 6 weeks. However, if primary infection is suspected and the initial antibody test is negative, additional tests may be required; rapid diagnosis can be provided by detecting HIV viraemia using tests for HIV RNA or proviral cDNA (by polymerase chain reaction, PCR), which might confirm HIV infection before antibodies become detectable. Aggressive therapy of primary HIV infection with antiretroviral drugs does not eradicate the infection but, on theoretical grounds, might alter the natural history. After primary infection, in the absence of intervention, the viral load becomes relatively stable after 6 to 9 months at an average level of 30 000 HIV RNA copies/ml plasma (Fig. 8.5.23.5). The plasma HIV RNA level at this virological steady state or 'set point' is of prognostic importance. Starting ART in primary HIV infection confers a better chance of immune recovery.

Fig. 8.5.23.5 Natural history of HIV infection showing changes in viral and immune parameters. Reproduced from Cohen MS et al. (2011). Acute HIV-1 Infection. NEJM, 364, 1943–54, Copyright © 2011 Massachusetts Medical Society.

8.5.23 HIV/AIDS 909 function normalization in terms of CD4 count recovery as well as CD4:CD8 ratio. Early HIV infection Following the primary illness or subclinical seroconversion, there usually follows an asymptomatic period lasting an average of 10 years without antiretroviral therapy. Although a time of clinical latency, there is intense viral turnover: 10⁹ to 10¹⁰ viral particles are replaced daily and the half-life of circulating CD4 lymphocytes is substantially reduced. During the asymptomatic period, physical examination may be normal, but about one-third of patients have persistent generalized lymphadenopathy. The enlarged nodes, caused by a reactive follicular hyperplasia, are usually symmetrical, mobile, and non-tender. The cervical and axillary nodes are most commonly affected. Nodes that are markedly asymmetrical, painful, or rapidly enlarging should be biopsied to exclude tumours such as lymphoma and opportunistic infections such as tuberculosis. Symptoms of progressive HIV infection can be prevented by antiretroviral treatment. In the absence of treatment, patients often develop minor opportunistic conditions affecting the skin and mucous membranes. These are also common throughout the later stages of HIV disease. They include a range of infections: fungal (e.g. tinea, pityrosporum), viral (e.g. warts, molluscum contagiosum, herpes simplex, herpes zoster), and bacterial (e.g. folliculitis, impetigo); and also eczema, seborrhoeic dermatitis, and psoriasis. Oral hairy leucoplakia usually appears as corrugated greyish-white lesions on the lateral borders of the tongue in homosexual

men. The condition is symptomless and nonprogressive, but can be a clue to HIV seropositivity. Epstein-Barr virus DNA has been demonstrated in these lesions. One of the characteristic clinical presentations of HIV disease is a sore mouth and throat due to oropharyngeal candidiasis (oral thrush) (Fig. 8.5.23.6). This is a sign of worsening immunodeficiency and might be recurrent. *Candida albicans* is usually responsible, but other species (e.g. *Candida glabrata*) are sometimes implicated. There is an increased incidence of peri-dontal disease in those with untreated HIV, including inflammation of the gums (gingivitis) and the more serious and extensive periodontitis that can lead to loss of teeth. Two distinctive forms are associated with HIV: a linear gingival erythema that causes a typical red band along the gum line, and in advanced immunosuppression, necrotizing ulcerative periodontitis which may require extensive debridement and antimicrobials. Recurrent oropharyngeal aphthous ulceration is common and can be painful. Recurrent ulcers can occur in the oesophagus and other parts of the gastrointestinal tract. They usually respond to local or systemic corticosteroid therapy. Resistant cases may respond to thalidomide. The availability of antiretroviral therapy has reduced the need for specific treatment. Later on in the course of untreated HIV infection, intermittent or persistent nonspecific constitutional symptoms might develop, which include lethargy, anorexia, diarrhoea, weight loss, fever, and night sweats. These symptoms can presage severe opportunistic infections or tumours. Generally, disease progression is slow in HIV-2 infections and has a much longer period of clinical latency. The rate of CD4 count decline is much slower. Progression to symptomatic HIV disease (AIDS) Various staging systems for HIV infection and case definitions of AIDS were developed and modified as understanding of the pathogenesis and natural history increased (Fig. 8.5.23.7). The CDC in the United States of America listed a range of specific diseases and other criteria, such as a CD4 lymphocyte count of less than 200/mm³ ($0.2 \times 10^9/\text{litre}$), as indicative of AIDS. AIDS-defining illnesses were essential for surveillance when HIV status was frequently unknown, the natural history of HIV infection was poorly understood (the proportion developing opportunistic complications was uncertain), and disease-modifying drugs were not available. Antiretroviral therapy improves the clinical condition and survival, even when started after progression to AIDS. These factors have undermined the epidemiological value and prognostic value of the CDC criteria. Fig. 8.5.23.6 Oral candidiasis. By courtesy of the late Dr B. E. Juel-Jensen. 1.00 0.75 0.50 0.25 0 Cumulative survival probability Pre-ART period ART period 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 Time from seroconversion (years) Fig. 8.5.23.7 Natural history of HIV. Estimated proportions of individuals surviving from HIV-1 seroconversion in the pre-ART era. ART, antiretroviral therapy. Reprinted from CASCADE collaboration (2000). Survival after introduction of HAART in people with known duration of HIV-1 infection. The CASCADE Collaboration. Concerted Action on SeroConversion to AIDS and Death in Europe. Lancet, 355, 1158–59, Copyright © 2000, with permission from Elsevier.

910 section 8 Infectious diseases importance of a strict AIDS case definition. Therefore, the current value of making a distinction between AIDS and HIV infection at other stages is questionable, especially in industrialized countries. It is more useful to consider progressive HIV disease as a continuous spectrum. However, clinical criteria to identify symptomatic HIV disease and AIDS were needed in resource-poor countries, if laboratory confirmation of HIV was not possible. The WHO therefore adopted clinical case definitions for AIDS surveillance in resource-limited countries, based on clinical manifestations with or without laboratory confirmation of HIV infection. This approach has been superseded by the WHO clinical staging system, which assumes that an HIV test has been done. Rapid HIV tests can now be done even in field conditions. For surveillance, it is suggested that HIV case reporting should supersede AIDS case reporting, though that may not yet

be possible everywhere. Once clinical progression occurs in HIV-2 infection, the clinical features are similar to those seen in HIV-1. Nonclinical progression The average CD4 decline without treatment is approximately 67 cells/year. Although the average time between infection with HIV and CD4 count less than 200 cells/cc³ or the development of AIDS is about 10 years, approximately 20% of patients progress rapidly to AIDS within 5 years and 10–15% remain clinically well for 15–20 years. Age is an independent risk factor for disease progression; acquisition of HIV in later life is associated with a less favourable prognosis. Long-term healthy survivors previously called ‘nonprogressors’, and this subgroup generally represents the tail end of a normal distribution of progression rates. Ultimately for most individuals previously defined as ‘nonprogressors’ clinical disease does become evident. Although several investigators have reported virological, genetic, and cellular and humoral immunological factors that may be associated with nonprogression, limitations in study design have made it difficult to identify what is responsible. In white cohorts of antiretroviral treatment-naïve, HIV-infected persons who show unusually successful control of HIV to levels of below 50 copies/ml plasma, more than 50 to 90% express one or both of the HLA class I alleles *HLA-B*5701* and *HLA-B*2705*. The protective value of these HLA class I alleles is related to the importance of the CD8⁺ T-cell response in successful immune control of HIV, and in particular where the CD8⁺ T-cell response includes broad targeting of epitopes in the conserved internal Gag protein. Infected persons expressing the HLA class I alleles *HLA-B*3502* or *B*5802* tend not to make Gag-specific CD8⁺ T-cell responses, and progress to AIDS significantly more rapidly. In addition to defining the nature of the CD8⁺ T-cell response, the particular HLA alleles expressed have important influences on the natural killer cell response against HIV, also affecting rates of progression to HIV disease. Non-HLA genes that affect rates of progression include the macrophage chemokine receptor CCR5 gene mutation (see ‘Cellular biology of HIV’,) associated with nonprogression in the heterozygous state. In the setting of universal ART, the distinction of ‘nonprogressors’ has now become clinically less relevant. However, a better understanding of natural viral control is still of great interest in terms of HIV cure.

Late complications and their management

Pneumocystis jirovecii pneumonia (See Chapter 8.7.5.) *P. jirovecii* (previously *Pneumocystis carinii*) pneumonia (PCP), one of the hallmarks of AIDS, is now less common because of primary prophylaxis and antiretroviral therapy. Some 85% of cases occur in patients with CD4 counts below 200/mm³, and mostly at counts below 100/mm³. Symptoms typically include increasing shortness of breath, dry cough, and fever, usually developing subacutely over a few weeks. Malaise, fatigue, weight loss, and chest pains, or tightness may occur. Chest signs are usually minor (crackles) or absent. The characteristic chest radiograph shows bilateral mid-zone interstitial shadowing (Fig. 8.5.23.8), but can be normal. Other appearances include localized infiltrates or consolidation, upper lobe shadows resembling tuberculosis, nodular lesions, and pneumothorax; effusions are very rare. The arterial oxygen saturation is usually less than 95% at rest or falls after exercise. Infection with *P. jirovecii* is associated with an interstitial inflammatory infiltrate and progressive impairment of lung function. The diagnosis can sometimes be confirmed by microscopy of sputum, which is induced by nebulized saline in properly ventilated isolation rooms (to read more about reducing the risk of tuberculosis transmission, see ‘Multidrug-resistant tuberculosis’, next). *P. jirovecii* cysts and trophozoites are visualized by the use of special stains. If the result is negative, fiberoptic bronchoscopy with bronchial lavage is indicated (Fig. 8.5.23.9); other causes of lung disease or coexistent infection might also be diagnosed by this technique, including tuberculosis, fungal infections, and Kaposi’s sarcoma. Immunofluorescence using monoclonal antibodies, or DNA amplification by PCR, may improve diagnostic sensitivity when compared with conventional staining techniques. In a minority of patients with Fig. 8.5.23.8 Chest

radiograph: *Pneumocystis jirovecii* pneumonia.

8.5.23 HIV/AIDS 911 *P. jirovecii* pneumonia the diagnosis is not confirmed but treatment is given empirically. High-dose co-trimoxazole (120 mg/kg daily in divided doses) for 3 weeks is the first-line treatment for pneumocystis pneumonia. Oral therapy is often adequate, but in moderate and severe cases the drug should be given intravenously. A switch to oral therapy can be made if fever, symptoms, and oxygenation have improved after 7–10 days. Adverse reactions to co-trimoxazole—especially neutropenia, anaemia, rash, and fever—occur in up to 40% of patients, usually after 6–14 days. Intravenous pentamidine (4 mg/kg per day) is the second-line choice for patients who do not tolerate co-trimoxazole. Patients intolerant of co-trimoxazole and pentamidine can be treated with clindamycin plus primaquine or dapsone plus trimethoprim. These regimens have only been evaluated in patients with mild to moderate pneumocystis pneumonia, as has atovaquone, an antiprotozoal drug that is active against *P. jirovecii*. Although slightly less effective than co-trimoxazole, atovaquone causes fewer adverse effects. In patients with moderate or severe pneumocystis pneumonia, adjunctive high-dose corticosteroids reduce morbidity and mortality. If the arterial partial pressure of oxygen (P_{aO_2}) is less than 9.3 kPa or the alveolar–arterial oxygen gradient is greater than 4.7 kPa, oxygen, intravenous methylprednisolone or oral prednisolone should be given for 5 to 10 days. Patients who develop respiratory failure require ventilatory support. After treatment for pneumocystis pneumonia has been completed, secondary prophylaxis should be given to prevent recurrence. This can be discontinued if there is a good response to antiretroviral treatment, with a rise in the CD4 count sustained above 200/mm³.

Bacterial pneumonia The risk of bacterial pneumonia is increased in HIV, especially if the CD4 count is below 200/mm³. The most common cause is *Streptococcus pneumoniae*, although *Haemophilus influenzae* and *Moraxella catarrhalis* are also relatively common, and *Staphylococcus aureus*, *Klebsiella* spp., and other Gram-negative rods are important causes in advanced HIV disease. Rare causes include *Nocardia* spp. and *Rhodococcus equi*. The presentation might be atypical, and radiological appearances frequently include diffuse infiltrates that resemble pneumocystis pneumonia, as well as more typical segmental or lobar patterns. Cavitation with abscess formation, pleural effusion, and empyema can occur. HIV predisposes to recurrent invasive pneumococcal infections with bacteraemia; recurrent bacterial pneumonia in a 12-month period is an AIDS-defining condition. Chronic lung damage with bronchiectasis and colonization by *Pseudomonas aeruginosa* have been reported. Other pulmonary complications

Disseminated fungal infections, including *Cryptococcus* spp., can involve the lungs (see Chapter 8.7.2). In endemic areas, histoplasmosis, coccidioidomycosis, and disseminated *Talaromyces marneffei* infection need to be considered (see next). Invasive *Aspergillus fumigatus* infections can occur in patients with advanced HIV disease who have additional risk factors such as severe neutropenia. Patients usually have severe systemic illness. The radiographic appearances in all these fungal infections are usually nonspecific. Bronchoalveolar lavage might be needed for diagnosis. HIV-associated lymphocytic interstitial pneumonitis (LIP) causes diffuse abnormalities, usually in children but occasionally in adults. Increasingly recognized are chronic lung abnormalities in adolescents who were infected vertically with HIV. Cryptogenic organizing pneumonia is a steroid-responsive cause of lung infiltrates, probably a tissue response to various underlying conditions, which has also been reported in HIV and may be confused with pneumocystis pneumonia. Tuberculosis (See Chapter 8.6.26.) The interaction between HIV and tuberculosis (TB) was recognized early in the HIV epidemic. Studies in central Africa in the mid-1980s showed that more than 60% of newly diagnosed tuberculosis patients were HIV positive at a time when the

background seroprevalence of HIV in the population was much lower. Injecting drug users were shown to have an increased risk of developing active tuberculosis if they were HIV positive. After decades of progressive decline in the incidence of tuberculosis in the United States of America, notifications increased during the mid-1980s, soon after the emergence of the HIV epidemic. A similar trend was subsequently observed in Western Europe. Globally, tuberculosis remains the most frequent life-threatening opportunistic infection in AIDS. Most cases of tuberculosis in HIV-positive individuals represent reactivation of dormant bacilli. However, molecular typing of isolates of *Mycobacterium tuberculosis* by restriction fragment length polymorphism analysis suggests that up to 40% are new infections. The WHO estimates that one-third of the world's HIV-positive population is coinfecting with tuberculosis. In communities where *M. tuberculosis* is endemic those who are immunosuppressed by HIV have an increased risk of relapsing or contracting new infections. Where the background prevalence of tuberculosis is low, the disease is uncommon in HIV-positive patients unless they become exposed (e.g. through travel). Testing for HIV should be done in all patients presenting with active tuberculosis, and tuberculosis should be considered as a cause of unexplained symptoms in patients with HIV. Active tuberculosis can occur at any time during the course of HIV infection. In early-stage HIV, it is more likely to present with the typical clinical features: subacute history of cough, fever, and Fig. 8.5.23.9 *Pneumocystis jirovecii* cysts in bronchoalveolar lavage aspirate.

912 section 8 Infectious diseases weight loss, upper lobe cavitory disease and/or pleural disease on chest radiographs, and a positive skin test to tuberculin. In late-stage HIV, infected patients are more likely to present atypically with unusual chest findings, extrapulmonary involvement, and cutaneous anergy. The chest radiograph might be normal in up to 40% of cases and, when abnormal, upper lobe involvement is less common. Sputum smears should be examined for acid-fast bacilli, but are less likely to be positive in HIV. Blood cultures can sometimes be positive for *M. tuberculosis*. Patients with HIV and TB are more likely to relapse after completion of therapy and to die prematurely if their HIV disease is not treated. Patients with advanced HIV infection are more likely to develop extrapulmonary tuberculosis involving lymph nodes, pericardium, liver, bone marrow, or meninges. Diagnosis can be difficult and frequently relies on invasive procedures to obtain appropriate specimens. The role of interferon- γ release assays (IGRA) in the diagnosis of HIV-associated TB is uncertain. The standard 6-month regimen of four antituberculosis drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) is generally effective in patients with HIV, unless there is resistance to one or more of these first-line drugs. The drug regimen might need to be adjusted once in vitro sensitivity results are known. For fully sensitive organisms, after 2 months on four drugs, isoniazid and rifampicin should be continued for a further 4 months. It should be noted that rifampicin interacts with many of the antiretroviral drugs, particularly protease inhibitors, and these interactions need to be considered in deciding on drug regimens. Patients with pulmonary tuberculosis should, ideally, be isolated initially. Contact tracing is important; HIV-positive contacts of a smear-positive TB case are at particular risk and should be offered isoniazid preventive therapy (unless the index case has multidrug-resistant TB). The tuberculin skin test might be negative, especially if the CD4 count is low, as might interferon- γ release assays (IGRA). Up to 20% of patients with HIV experience adverse reactions to antituberculosis drugs. In HIV-positive patients with tuberculosis in Africa, the sulpha-based drug thiacetazone has been associated with serious skin reactions, including toxic epidermal necrolysis and fatal cases of Stevens-Johnson syndrome. Whereas response rates for conventional short-course tuberculosis treatment in industrialized countries are similar to those achieved in HIV-

negative patients, in resource-limited countries and where compliance is less easily achieved, cure rates are lower and there is a risk that resistance will develop. Several countries have adopted a 'directly observed therapy' strategy to address this problem. Supervised drug administration is a component of this strategy but political commitment, secure drug supply, and good organization are needed for this to be effective. The optimal timing of the initiation of antiretroviral treatment in patients presenting with HIV-associated TB has been controversial. Early initiation of ART increases the pill burden and risks immune reconstitution inflammatory syndromes (IRIS), whereas starting too late risks HIV disease progression. However, recent studies have clarified this area and have shown that in patients with TB and HIV whose initial CD4 count is less than 50/mm³, ART and TB therapy should be started together. Although the incidence of IRIS reactions is increased, this does not increase mortality. Concomitant administration of prednisolone in this setting might reduce the risk of IRIS. For patients with CD4 counts greater than 200/mm³, antiretroviral therapy can be deferred for 8 to 12 weeks. HIV therapy should not be delayed beyond 12 weeks, however. It should be noted that these studies were mainly carried out in patients with pulmonary TB and a study in TB meningitis showed no benefit with immediate ART and an increased frequency of severe adverse effects.

Multidrug-resistant tuberculosis Over 15 outbreaks of multidrug-resistant tuberculosis (MDR-TB) have been reported since the late 1980s. MDR-TB isolates are resistant to at least two first-line antituberculosis drugs, most commonly isoniazid and rifampicin, and are often resistant to several agents. Most have occurred in HIV units in hospitals, but there have been outbreaks in prisons, drug treatment centres, and nursing homes. Most documented outbreaks have been in the United States of America. Elsewhere, over 200 people were involved in Buenos Aires, Argentina, and another outbreak affected over 100 people in Lisbon, Portugal. In MDR-TB outbreaks, healthcare workers are at risk of becoming infected. Initially, the mortality among HIV-positive patients was very high (up to 93%), but the outcome has subsequently improved because of more rapid diagnosis and treatment with at least four drugs to which the *M. tuberculosis* isolate is sensitive in vitro. More recently, extensively drug-resistant TB (XDR TB) in HIV-infected patients in South Africa has caused outbreaks, with 100% mortality in those with HIV. To prevent outbreaks of MDR-TB, special precautions are required when HIV-positive patients with possible tuberculosis are admitted to hospitals. Diagnosis must not be delayed, appropriate treatment must be started as soon as possible, and drug resistance identified, although this can be difficult in resource-limited settings. Precautions include the isolation of patients in negative-pressure rooms, use of respiratory protection for staff, and special care during certain procedures such as bronchoscopy or nebulized pentamidine administration. With effective treatment, patients rapidly become noninfectious, but precautions need to be continued until the sputum is repeatedly culture-negative.

Mycobacterium avium complex In the absence of antiretroviral treatment, patients with advanced HIV infection and CD4 counts below 50/mm³ are at high risk of disseminated *Mycobacterium avium* complex (MAC) infection, particularly in industrialized countries where historically it was reported to develop in up to 40% of patients with AIDS. *M. avium* is a ubiquitous environmental organism of low pathogenicity that can be isolated from domestic water supplies. Infection is likely to be through the gastrointestinal tract. MAC infection becomes widely disseminated in those with advanced HIV and causes fever, night sweats, weight loss, diarrhoea, abdominal pain, anaemia, disturbed liver function, and reduced overall survival. The organism can usually be cultured from blood or bone marrow, or might be recognized as acid-fast bacilli in tissue biopsies (e.g. from lymph node, small bowel, or liver). It is unclear why the diagnosis is uncommon in low-income countries; high mortality from other opportunistic infections at earlier stages of immunosuppression could be partly responsible. MAC infection is intrinsically resistant to most first-

line antituberculosis drugs. Comparative trials suggest that initial therapy should be with two or three drugs: clarithromycin or azithromycin and ethambutol should be used, and additional rifabutin or a quinolone (e.g. ciprofloxacin) considered. In severely ill patients, intravenous amikacin might be useful as the third agent.

8.5.23 HIV/AIDS 913 In the absence of antiretroviral treatment, lifelong treatment is required to prevent relapse; but if immunity is restored by highly active antiretroviral therapy, such maintenance therapy can be discontinued. Early studies in the pre-ART era showed some benefit with azithromycin prophylaxis in those with low CD4 counts but now it is more appropriate to use ART to improve the immune system. Other nontuberculosis mycobacteria Other mycobacteria, notably *Mycobacterium kansasii*, *Mycobacterium genavense*, and *Mycobacterium celatum*, can cause opportunistic infections in those with HIV. *M. genavense*, which colonizes pet birds, was discovered in European patients with HIV and causes fever, diarrhoea, and severe weight loss. HIV does not seem to affect the incidence or natural history of leprosy (*Mycobacterium leprae*). Gastrointestinal disease Oesophageal candidiasis Oesophagitis presents with retrosternal pain on swallowing, and in patients with HIV is most commonly caused by *C. albicans*. Oesophageal candidiasis indicates advanced immunosuppression and is an AIDS-defining condition. The diagnosis should be suspected in a patient with oral candida and dysphagia, and may be supported by barium swallow or confirmed by endoscopy and biopsy. Treatment is with oral azole antifungal agents such as fluconazole. It might recur and in patients with severe immunosuppression, and in the absence of antiretroviral treatment, candida can become resistant to prolonged azole treatment. Resistance tends to develop gradually and can be monitored by in vitro testing. Such patients require treatment with high doses of fluconazole or one of the newer azoles. Azole-resistant oro-oesophageal candidiasis has become rare since the advent of antiretroviral therapy. Echinocandins or amphotericin can be used in such cases. The differential diagnosis of oesophageal candidiasis includes oesophagitis caused by cytomegalovirus (CMV) or herpes simplex virus (HSV), which require specific antiviral therapy, and aphthous ulceration, which might respond to oral prednisolone or thalidomide. Intestinal infections Some infections are much more common in HIV disease than in other settings. *Cryptosporidium parvum* can lead to cholera-like diarrhoea. An ascending cholangitis might occur with fever, pain, and jaundice and have the imaging appearance of sclerosing cholangitis. Other protozoan parasites, such as *Cystispora belli* and *Cyclospora cayetanensis*, may also cause diarrhoea, as can microsporidia. Cytomegalovirus can cause an acute colitis with pain and bloody diarrhoea. Sigmoidoscopy shows ulceration and biopsies show characteristic CMV inclusions. Tuberculosis can also present as intestinal disease or peritoneal infection. HIV enteropathy Many patients with HIV, especially in the tropics, present with diarrhoea and malnutrition leading to wasting in the absence of detectable gastrointestinal opportunist infections. Biopsies often show villous blunting and increased inflammatory cells in the lamina propria of the small bowel and functional tests suggest increased bowel permeability. The pathogenesis of this enteropathy is poorly understood, but might involve cytokine activation secondary to HIV infection. HIV and the nervous system (See Chapter 24.11.4) The nervous system is a major site of involvement for direct and indirect complications of HIV at all stages of infection. All parts of the nervous system may be affected. In advanced HIV, opportunistic infections and tumours (lymphoma), and tissue damage caused by HIV replication in the brain and spinal cord, are important and relatively common during progressive HIV disease. Cerebral toxoplasmosis (See Chapter 8.8.4.) Cerebral infection with the intracellular protozoan *Toxoplasma gondii* is the most frequent infection of the central nervous system in AIDS, occurring

when the CD4 count is below 200/mm³. It usually results from reactivation of toxoplasma cysts in the brain, leading to the formation of focal lesions that are typically multiple but may be single. Symptoms develop subacutely and include focal neurological disturbance, headache, confusion, fever, and convulsions. On computed tomography (CT) scan the lesions appear as ring-enhancing masses with surrounding oedema (Fig. 8.5.23.10). MRI is more sensitive and frequently detects lesions not visible on CT. Serum antibodies to toxoplasma spp. are usually detectable; their absence makes the diagnosis unlikely but does not exclude it. Detection of toxoplasma DNA in cerebrospinal fluid by PCR is being evaluated as a diagnostic test. The principal differential diagnosis is primary cerebral lymphoma; other causes of focal brain lesions in AIDS include cryptococcoma, cerebral abscess (including infection with nocardia spp.), tuberculoma, progressive multifocal leukoencephalopathy, and neurosyphilis. Brain biopsy is required for a definitive diagnosis, but is rarely performed. As toxoplasmosis is by far the most common treatable cause of focal cerebral lesions in HIV, it is standard practice to treat for this and only consider biopsy if there is no clinical improvement in 7–10 days. Fig. 8.5.23.10 Cerebral toxoplasmosis: ring enhancement and surrounding cerebral oedema (CT with contrast).

914 section 8 Infectious diseases The condition responds well if treatment is started early; a combination of sulfadiazine at 4 to 6 g/day and pyrimethamine at 50–75 mg/day is the treatment of choice. More than 40% of patients experience adverse effects, especially rash and nephrotoxicity caused by sulfadiazine. The haematological toxicity of pyrimethamine might be reduced by adding folinic acid (10 mg/day). If sulpha drugs are not tolerated, clindamycin with pyrimethamine is an effective alternative. Corticosteroids can be used to reduce cerebral oedema in patients with large lesions and serious mass effects, but this is controversial. Treatment is usually given for 3 to 6 weeks, and in the absence of effective antiretroviral treatment, relapse is common after stopping. In these circumstances, lifelong maintenance treatment is usually required using pyrimethamine (25–50 mg/day) with a sulpha drug or clindamycin. However, these can be discontinued if antiretroviral treatment leads to sustained immunological recovery. The use of primary prophylaxis against PCP also reduces the risk of toxoplasmosis. Cryptococcal meningitis (See Chapter 8.7.2.) Although infection of the central nervous system with *Cryptococcus neoformans* can occur in the absence of immunodeficiency, it most commonly arises in association with HIV infection. Before the widespread use of azole antifungals for mucosal candidiasis, it accounted for 5 to 10% of opportunistic infections in patients with AIDS. The presentation is usually subacute and may be subtle and nonspecific with headache, vomiting, and mild fever, and few neurological signs. Less frequently, psychiatric disturbance, convulsions, cranial nerve palsies, truncal ataxia, or focal intracerebral lesions can occur. Neck stiffness is unusual. The diagnosis is made by detecting cryptococci in the cerebrospinal fluid by India ink staining, detection of cryptococcal antigen in the cerebrospinal fluid (uniformly positive), and culture. Cryptococcal antigen is also usually detectable in serum. *C. neoformans* in patients with AIDS causes minimal inflammation, so the white cell count of the cerebrospinal fluid is often only mildly raised and the protein and glucose levels of the cerebrospinal fluid may be normal. A randomized, controlled trial showed that the combination of amphotericin B and flucytosine was superior to amphotericin B alone or fluconazole alone for the treatment of cryptococcal meningitis. Amphotericin B and flucytosine together lead to more rapid sterilization of the cerebrospinal fluid, but are not as well tolerated as fluconazole. Resistance of cryptococci to fluconazole is very rare. Adverse reactions to amphotericin are frequent, especially fever, myalgia, renal impairment, and electrolyte disturbances. Close monitoring is required. Lipid formulations of amphotericin are increasingly used and have become

the standard of care. Raised intra-cranial pressure is associated with clinical deterioration and the risk of blindness: repeated lumbar punctures and, sometimes, lumbar or ventricular shunting are needed in these circumstances. Steroids have been shown to be ineffective and possibly deleterious. Without secondary prophylaxis, cryptococcal meningitis relapses in 50 to 80% of patients with HIV in the absence of antiretroviral treatment. Oral fluconazole (200 mg/day) is effective for maintenance, and can be discontinued when antiretroviral treatment leads to sustained immunological recovery. A recent trial has found that oral fluconazole is safe and effective as primary prophylaxis against cryptococcal disease in patients awaiting or starting antiretroviral therapy in Uganda.

Progressive multifocal leukoencephalopathy Progressive multifocal leukoencephalopathy is a progressive demyelinating condition of advanced HIV disease caused by JC virus, a polyomavirus cytopathic for oligodendroglia. It presents with focal neurological deficits, personality changes, or ataxia; headache and mass effects are absent. Brain MRI, the investigation of choice, usually shows multiple white matter lesions. JC virus is detectable in cerebrospinal fluid by PCR, but this is not usually necessary for diagnosis. There is no specific treatment. Survival of less than 6 months is usual, but progression might sometimes be halted or reversed by highly active antiretroviral therapy. The other human polyomavirus, BK virus, is a very rare cause of encephalitis and interstitial nephropathy in AIDS.

Primary cerebral lymphoma These are B-cell non-Hodgkin lymphomas that are associated with Epstein-Barr virus, which is usually detectable in the cerebrospinal fluid by PCR. Lymphoma of the central nervous system may present in a manner similar to toxoplasmosis, with focal signs or seizures. CT or MRI of the brain often reveals a single space-occupying lesion but the disease is typically multifocal. Without treatment the prognosis is only a few weeks. Treatment with radiotherapy and steroids, with or without chemotherapy, and antiretroviral therapy, prolongs the median survival to several months, but longer-term survival is exceptional.

HIV-associated neurological disorders (HAND) HIV can infect the nervous system directly, leading to a variety of clinical problems. The virus targets macrophages in the nervous system but can also infect astrocytes, but nonproductively. Most patients dying of AIDS show histological evidence of brain involvement including neuronal loss. It is estimated that up to 50% of those with HIV have some form of neurological disorder. So-called HAND (HIV-associated neurological disorder) is split into three types. The most common is asymptomatic neurocognitive impairment where individuals have abnormalities demonstrated by neuropsychological testing. Some of these abnormalities can be moderately severe and impact on daily living, including the ability to adhere to treatment regimens. A smaller subset, up to 12% of those with HIV in one study, have more marked problems, termed mild neurocognitive disorder. These individuals have worse scores on testing and usually have symptoms and functional impairment. At the extreme are those with HIV-associated dementia (HAD), previously called AIDS dementia complex or HIV encephalopathy. Risk factors for HAND include a lower nadir CD4 count and older age at time of infection. Other comorbidities also play a role, such as cardiovascular disease, but no clear genetic influences have been identified. Diagnosis is largely clinical, along with neuropsychological testing when available. Although abnormalities in the cerebrospinal fluid have been reported, such as elevated protein levels, lymphocytosis, and detectable virus, none of these are consistent or diagnostic. Virus levels in the cerebrospinal fluid do not correlate with disease.

8.5.23 HIV/AIDS 915 There has been a lot written about ART and the effect on HAND. The CASCADE study showed that the incidence of HAD had diminished with the advent of ART but had not disappeared completely. Nevertheless, it is not clear that asymptomatic neurocognitive im-

pairment is affected much by treatment. Various ART drugs have been assessed to have better central nervous system penetration efficacy (CPE), such as tenofovir, emtricitabine, and dolutegravir but it is not really clear if choosing drug combinations with good CPE affects outcomes. There are examples of patients developing neurocognitive problems while on ART who have detectable virus in the cerebrospinal fluid that is resistant to the ART, but these are very rare. Other psychological/psychiatric problems include anxiety, panic attacks, and depression. Psychotherapy might be helpful. Antidepressants are needed in severe cases. Acute psychosis is rare. Dystonic reactions to various drugs, such as metoclopramide, are more common in patients with HIV. In the late stages of HIV disease, the differential diagnosis of HIV-associated dementia includes cytomegalovirus (CMV) encephalitis. This usually presents with rapidly progressive confusion and dementia, impaired consciousness, fever, cranial nerve lesions, and convulsions. MRI shows necrotizing periventriculitis; protein levels in cerebrospinal fluid might be elevated and CMV DNA is detectable in the cerebrospinal fluid by PCR. Ganciclovir and other anti-CMV agents might reduce progression. Peripheral neuropathy and myelopathy Peripheral neuropathy can occur at any stage of HIV infection, even with primary infection, but is most common in advanced disease, when 10 to 15% of patients have a distal symmetrical sensorimotor neuropathy of axonal type causing pain and paraesthesia that can limit walking and, less often, distal weakness and atrophy. Mononeuritis multiplex and acute inflammatory demyelinating polyneuropathy resembling the Guillain-Barré syndrome are also described, generally at an earlier stage. Drugs used in patients with HIV, including stavudine, didanosine, and vincristine, might cause or exacerbate peripheral neuropathy. HIV-related autonomic neuropathy can cause postural hypotension, diarrhoea, impotence, impaired sweating, and bladder symptoms. CMV infection in patients with AIDS presents with a lumbosacral polyradiculopathy causing sacral paraesthesias and numbness, lower limb weakness, and urinary retention that might progress to flaccid paraparesis if untreated. HIV can involve the spinal cord directly, causing a vacuolar myelopathy. This usually presents with bilateral leg weakness and sensory symptoms, usually paraesthesias, and might progress to spastic paraparesis, ataxia, and incontinence. Rarely, a myopathy can occur. Ocular disease Cytomegalovirus retinitis Without antiretroviral therapy, up to 30% of patients with AIDS (and a CD4 lymphocyte count below 50/mm³) develop reactivation of CMV in the form of a destructive and blinding retinitis. This is rare in other types of immunosuppression. It usually presents with blurring of vision, scotomas, floaters, or flashing lights. The characteristic retinal changes are patches of irregular retinal pallor, caused by oedema and necrosis, and haemorrhages in a perivascular distribution (Fig. 8.5.23.11). The retinitis usually starts peripherally and progresses rapidly to involve the macula and whole retina, leading to blindness. Complications include retinal detachment, branch retinal artery occlusion, persistent iritis, and cataract. CMV retinitis should not be confused with cotton wool spots (HIV retinopathy)—small, pale retinal lesions without haemorrhages that commonly occur in patients with HIV. These are benign and often come and go. The diagnosis of CMV retinitis is clinical, based on the characteristic retinal appearance (see Chapter 25.1). CMV viraemia may be detectable by PCR, and high or rising CMV viral load is associated with an increased risk of developing retinitis and other CMV disease. Anti-CMV drugs (ganciclovir, foscarnet, cidofovir) are virustatic. Before the availability of antiretroviral drug therapy, the aim of treatment was to stop progression rather than to cure disease. First-line treatment is with intravitreal ganciclovir injection or implant; oral valganciclovir is often given in conjunction with intravitreal ganciclovir as patients treated without systemic therapy may develop contralateral or extraocular CMV disease. Oral valganciclovir alone may be used as an alternative in patients without sight-threatening disease. Other effective treatments include intravenous

ganciclovir, foscarnet, or cidofovir. Intravenous ganciclovir and foscarnet require administration via a central vein, whereas foscarnet can be given via a peripheral vein. The main adverse effects of ganciclovir are bone marrow suppression, in particular neutropenia, central nervous system symptoms, abnormal liver function tests, fever, and rash. Foscarnet is associated with decreased renal function, electrolyte abnormalities, and infusion-related nausea. With the advent of ART, CMV retinitis is much less common in developed countries. Sustained suppression of HIV viral load and improvement in immune status can allow discontinuation of maintenance treatment. New manifestations of ocular CMV, such as vitritis, have been reported in patients starting ART (see 'Immune reconstitution syndromes', next). Other ocular syndromes Acute retinal necrosis is a rare condition originally reported in reactivation of varicella zoster virus in otherwise healthy adults. In patients with advanced HIV infection, it is usually preceded by dermatomal herpes zoster and typically presents with blurring of vision and pain in the affected eye. Progressive necrotizing retinitis leads to visual deterioration that may be associated with uveitis. An outer retinal necrosis syndrome with little ocular inflammation also occurs in patients with AIDS. There is a high risk of visual loss and retinal detachment. Both eyes can be affected. Suspected acute retinal necrosis should be treated with intravenous aciclovir. Acute toxoplasma chorioretinitis can resemble CMV retinitis, but the retinal scarring that follows treatment is distinctive. The disease is more common in countries such as Brazil and France where the background prevalence of toxoplasmosis is much higher than in the United Kingdom. Chorioretinitis is also a rare complication of histoplasmosis and cryptococcosis, and uveitis can occur in syphilis. HIV-related tumours HIV is an oncogenic virus and even for individuals with high CD4 counts (>500 cells/cc³) there appears to be an increased risk of developing cancer compared to uninfected individuals. In the recently reported START trial where individuals were randomly allocated to immediate or deferred ART initiation with CD4 counts greater than 500, those in the deferred arm had an increased risk of cancer. Kaposi's sarcoma Kaposi's sarcoma characteristically presents as multiple, purplish, nodular skin lesions (Fig. 8.5.23.12). Lesions start as small, pink, deep purple, or brown macules, and develop into nodules or plaques that may ulcerate. They also occur on mucosal surfaces, most commonly on the hard palate. Local or regional oedema and lymph node enlargement may occur. Mucocutaneous lesions are cosmetically and psychologically important but are rarely of clinical importance (Fig. 8.5.23.13). However, visceral disease, which most commonly affects the lungs and gastrointestinal tract, is an important cause of morbidity and even mortality. Lung lesions cause dyspnoea, cough, or haemoptysis, and gut involvement may cause abdominal pain, bleeding, or a rare protein-losing enteropathy. Extensive visceral involvement can cause constitutional symptoms such as fevers, night sweats, and weight loss. Kaposi's sarcoma rarely affects the central nervous system. In industrialized countries, Kaposi's sarcoma is over 2000 times more common in HIV-infected individuals than in the general population. Classic Kaposi's sarcoma in HIV-negative individuals occurs in middle-aged and older men of Eastern European or Mediterranean origin. Endemic Kaposi's sarcoma in Africa has been known for decades. It is predominantly a disease of older men that has a fairly indolent course. HIV-related Kaposi's sarcoma, on the other hand, is a more aggressive disease and occurs mostly in those people who have acquired HIV via a sexual route, namely gay and bisexual men and in younger African men and women. The epidemic of Kaposi's sarcoma in Central and East Africa exactly mirrors the HIV epidemic in these regions. Kaposi's sarcoma is rare in intravenous drug users and very rare in recipients of blood products, including those with haemophilia. These epidemiological features suggested a sexually

916 section 8 Infectious diseases vision and pain in the affected eye. Progressive necrotizing retinitis leads to visual deterioration that may be associated with uveitis. An outer retinal necrosis syndrome with little ocular inflammation also occurs in patients with AIDS. There is a high risk of visual loss and retinal detachment. Both eyes can be affected. Suspected acute retinal necrosis should be treated with intravenous aciclovir. Acute toxoplasma chorioretinitis can resemble CMV retinitis, but the retinal scarring that follows treatment is distinctive. The disease is more common in countries such as Brazil and France where the background prevalence of toxoplasmosis is much higher than in the United Kingdom. Chorioretinitis is also a rare complication of histoplasmosis and cryptococcosis, and uveitis can occur in syphilis. HIV-related tumours HIV is an oncogenic virus and even for individuals with high CD4 counts (>500 cells/cc³) there appears to be an increased risk of developing cancer compared to uninfected individuals. In the recently reported START trial where individuals were randomly allocated to immediate or deferred ART initiation with CD4 counts greater than 500, those in the deferred arm had an increased risk of cancer. Kaposi's sarcoma Kaposi's sarcoma characteristically presents as multiple, purplish, nodular skin lesions (Fig. 8.5.23.12). Lesions start as small, pink, deep purple, or brown macules, and develop into nodules or plaques that may ulcerate. They also occur on mucosal surfaces, most commonly on the hard palate. Local or regional oedema and lymph node enlargement may occur. Mucocutaneous lesions are cosmetically and psychologically important but are rarely of clinical importance (Fig. 8.5.23.13). However, visceral disease, which most commonly affects the lungs and gastrointestinal tract, is an important cause of morbidity and even mortality. Lung lesions cause dyspnoea, cough, or haemoptysis, and gut involvement may cause abdominal pain, bleeding, or a rare protein-losing enteropathy. Extensive visceral involvement can cause constitutional symptoms such as fevers, night sweats, and weight loss. Kaposi's sarcoma rarely affects the central nervous system. In industrialized countries, Kaposi's sarcoma is over 2000 times more common in HIV-infected individuals than in the general population. Classic Kaposi's sarcoma in HIV-negative individuals occurs in middle-aged and older men of Eastern European or Mediterranean origin. Endemic Kaposi's sarcoma in Africa has been known for decades. It is predominantly a disease of older men that has a fairly indolent course. HIV-related Kaposi's sarcoma, on the other hand, is a more aggressive disease and occurs mostly in those people who have acquired HIV via a sexual route, namely gay and bisexual men and in younger African men and women. The epidemic of Kaposi's sarcoma in Central and East Africa exactly mirrors the HIV epidemic in these regions. Kaposi's sarcoma is rare in intravenous drug users and very rare in recipients of blood products, including those with haemophilia. These epidemiological features suggested a sexually

transmissible aetiological agent. (d) (c) (b) (a) (e) Fig. 8.5.23.12 Kaposi's sarcoma. (a, b) cutaneous Kaposi's sarcoma in a white man; (c, d), cutaneous Kaposi's sarcoma in a Zimbabwean; (e) invasive Kaposi's sarcoma in a Kenyan. Copyright D. A. Warrell.

8.5.23 HIV/AIDS 917 In 1994, a new herpesvirus, human herpesvirus 8 (HHV-8), was found in HIV-related Kaposi's sarcoma and was soon detected in the lesions of all forms of Kaposi's sarcoma. Seroepidemiological studies show that HHV-8 is common only in certain geographical regions, corresponding to where Kaposi's sarcoma was endemic before the era of HIV. HHV-8 is detectable in saliva but less often in semen. This might explain why both sexual and other routes of transmission occur. In Africa, where HHV-8 infection is common, it is transmitted perinatally from mother to child. Kaposi's sarcoma lesions are characterized by proliferating spindle cells of lymphatic and blood vascular endothelial origin, thin-walled slit-like vascular spaces, infiltration by lymphocytes and plasma cells, and extravasated red cells. Multiple lesions appear synchronously in widely dispersed areas. The clonality of Kaposi's sarcoma lesions has not been fully resolved. Although some studies have suggested a monoclonal origin, others have shown a mixed picture and the lesions may be reactive proliferative rather than truly cancerous. HHV-8 is detectable in spindle cells and flat endothelial cells lining the vascular spaces of Kaposi's sarcoma lesions. It is likely that the virus triggers the release of cellular and virus-encoded cytokines that promote the proliferation of spindle cells. Antiretroviral therapy has led to a dramatic reduction in the frequency and mortality of Kaposi's sarcoma in developed countries. In early Kaposi's sarcoma, the progression is often halted or reversed by starting antiretroviral treatment alone. Otherwise, cutaneous lesions may be left untreated or treated with local radiotherapy, cryotherapy, or intralesional vinblastine. Widespread skin or visceral disease is usually treated by systemic chemotherapy, usually with a liposomal anthracycline such as daunorubicin or doxorubicin, which are more effective than the previously used combination of vincristine and bleomycin. Paclitaxel, a taxane, is potentially more toxic than liposomal anthracyclines, but can be useful as a second-line agent after treatment failure. Treatment of disseminated Kaposi's sarcoma has not been considered to be curative, but remissions might be induced by a combination of ART and systemic chemotherapy.

Non-Hodgkin's lymphoma Non-Hodgkin lymphoma develops in 3 to 10% of HIV-positive patients, an incidence 60 to 100 times higher than in the general population. Most tumours are extranodal and, histologically, 60% are large cell B-cell lymphomas; 30% are Burkitt's type and the rest are of T-cell or non-B-, non-T-cell origin. Some 50% are associated with Epstein-Barr virus infection and are more aggressive with a shorter survival. A minority of HIV-related lymphomas are associated with HHV-8. They present as body cavity lymphomas, causing pleural or peritoneal effusions (primary effusion lymphoma). Patients on highly active antiretroviral therapy have a reduced risk of developing non-Hodgkin lymphoma, and consequently the incidence of HIV-related lymphomas in developed countries has declined in recent years. HIV-associated lymphoma outside the central nervous system may respond well to standard lymphoma chemotherapy regimens, in addition to antiretroviral therapy. Response is better in those who are less immunosuppressed (CD4 above 200/mm³ and no previous AIDS diagnosis). Opportunistic infections cause many deaths during chemotherapy. Lower dose or less toxic chemotherapy protocols are sometimes advocated for patients with more advanced HIV disease.

Non-AIDS-defining cancers It is now apparent that HIV increases the frequency of several cancers other than those that have been categorized as AIDS-defining (i.e. Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical carcinoma), and non-AIDS-defining cancers cause a high proportion of deaths in HIV patients in industrialized countries (50% in a recent study from France). These include Hodgkin's disease, particularly of the mixed

cellularity type and associated with Epstein–Barr virus. Disseminated disease with a poor prognosis seems to be more frequent than for HIV-negative Hodgkin’s disease. Other cancers that arise with higher frequency than in HIV- negative individuals include hepatocellular carcinoma (caused by hepatitis C and hepatitis B); lung carcinoma; skin tumours (basal cell carcinoma, squamous cell carcinoma, and malignant melanoma); and cancers of the head and neck, probably associated with human papillomavirus (HPV), especially type 16. There is an increased incidence of squamous cell carcinoma of the conjunctiva in patients with HIV infection, especially in Africa. HPV is also associated with a higher incidence of cervical intraepithelial neoplasia (CIN) and predisposition to cervical carcinoma in HIV-infected women, and the higher incidence of vulvar intraepithelial neoplasia in women; and also anal carcinoma and its precursor anal intraepithelial neoplasia, which occurs at a greatly increased frequency in HIV-positive gay men. Other cancers that might arise with greater frequency, but where this is less clear cut, include colorectal cancer, testicular cancer, myeloma, and acute myeloid leukaemia. Cancers that do not arise with greater frequency include prostate, bladder, and breast. It should be noted that even when ART is started at high CD4 counts, the incidence of malignancy seems not to change, suggesting that HIV itself is associated with an increased risk of cancer. Fig. 8.5.23.13 Palatal Kaposi’s sarcoma. Copyright D. A. Warrell.

918 section 8 Infectious diseases Miscellaneous conditions Castleman’s disease Castleman’s disease (angiofollicular lymph node hyperplasia) is a lymphoproliferative condition that can be HHV-8 related and, in the multicentric form, is associated with HIV. It can sometimes be difficult to distinguish from Kaposi’s sarcoma. Bacillary angiomatosis Disseminated infection with *Bartonella henselae*, the principal agent of cat-scratch disease, is the cause of bacillary angiomatosis, an HIV-associated condition that typically causes multiple sub-cutaneous vascular lesions, fever, liver lesions (bacillary peliosis hepatis), and osteolytic bone lesions. The skin lesions are usually purplish nodules that may be mistaken for Kaposi’s sarcoma, but the histology is distinct—acute neutrophilic inflammation and capillary proliferation, and clusters of bacilli revealed by modified silver staining. The organism may be cultured from blood. A similar syndrome in HIV-positive patients can be caused by the agent of trench fever, *Bartonella quintana*. Bacillary angiomatosis usually responds to treatment with a macrolide antibiotic. Cats and cat fleas form a reservoir for *B. henselae*, and patients who develop bacillary angiomatosis frequently have a history of contact with cats. Disseminated fungal infections In regions where invasive fungal infections are endemic (such as *Histoplasma capsulatum* in the Mississippi river region, *Coccidioides immitis* in the southern United States of America, and *Talaromyces marneffei* in South East Asia) or where there is a relevant travel history, disseminated fungal infection should be considered in HIV-positive patients presenting with fever, weight loss, anaemia, pulmonary infiltrates, lymphadenopathy, and hepatosplenomegaly. Papular skin lesions might be seen in disseminated histoplasmosis and *T. marneffei* infection. Similar lesions resembling giant molluscum (see next) might occur with disseminated cryptococcosis. Blood or bone marrow cultures or direct identification by the use of special stains on tissue obtained from skin lesions, bone marrow, or liver are required for diagnosis. Initial therapy is generally with intravenous amphotericin; itraconazole (for histoplasmosis and *T. marneffei*) or fluconazole (for coccidioidomycosis) might be adequate for subsequent maintenance treatment. Leishmaniasis (See Chapter 8.8.12.) HIV-associated disseminated leishmaniasis is mostly reported from the Mediterranean littoral, South America, and Africa. It is caused by dissemination of *leishmania* spp., protozoan parasites transmitted by sandflies. A high index of clinical suspicion is required, because although the classic features are fever, weight loss, anaemia, and hepatosplenomegaly, a high proportion of patients have fever alone. The disease may

present months or years after exposure in an endemic country. Leishmania can be transmitted by shared needles in injecting drug users. Most cases can be diagnosed by bone marrow examination or splenic aspirate; serology may be helpful. Treatment is with lipid formulations of amphotericin B. Haematological conditions Thrombocytopenia is relatively common (5–15%) in HIV infection and may be how the disease first presents. It is associated with antiplatelet antibodies. Symptomatic thrombocytopenia is uncommon but more likely in the later stages of HIV infection. Life-threatening bleeding is rare. Thrombocytopenia is not a marker for HIV progression and spontaneous remissions are frequent. Antiretroviral treatment is first-line when the CD4 count is low; zidovudine is known to increase platelet production. When specific treatment for thrombocytopenia is required, the principles and response are similar to those that apply in the treatment of HIV-negative immune thrombocytopenia, and include the use of prednisolone, intravenous immunoglobulin, and splenectomy. Anaemia is common in patients with advanced HIV infection, and is frequently related to medications (such as zidovudine). Human (B19) parvovirus infection is a reversible cause of chronic anaemia in HIV infection. Bone marrow biopsy typically shows an absence of erythroid development with occasional giant pronormoblasts, and B19 parvovirus is detected by PCR. The anaemia might respond to treatment with intravenous immunoglobulin. Mild neutropenia is common in HIV-positive patients at all stages of infection, and may be partly responsible for the increased risk of pyogenic bacterial infections; however, profound neutropenia (below $0.5 \times 10^9/\text{litre}$) is rare. Antineutrophil antibodies might be present. Drugs (such as co-trimoxazole, ganciclovir, and antiretrovirals) may increase the incidence and severity of neutropenia. In selected HIV-positive patients with refractory or life-threatening bacterial or fungal infection and severe neutropenia, the addition of recombinant human granulocyte colony-stimulating factor to the treatment regimen might improve the outcome. Skin conditions in advanced HIV In the later stages of HIV infection, several infections have atypical cutaneous manifestations. All have become rare in settings where antiretroviral treatment is available to prevent advanced immunosuppression. These conditions include giant molluscum contagiosum, characterized by large, flesh-coloured, nontender umbilicated lesions often affecting the face in homosexual men. In advanced HIV disease, genital herpes simplex infection may cause painful chronic genital or anal ulcers that can become resistant to aciclovir and related compounds; intravenous foscarnet or cidofovir are effective. Aciclovir-resistant varicella zoster virus also occurs in AIDS; and reactivation of varicella zoster virus can take an unusual form, with a subacute course and dissemination causing scattered vesicular lesions in the absence of dermatomal zoster. CMV is a cause of chronic perianal ulceration that can be treated with ganciclovir. Atypical cutaneous presentations of syphilis can occur at any stage of HIV infection. HIV-associated nephropathy (HIVAN) HIV can directly infect glomerular and tubular epithelial cells and renal disease is relatively common in HIV-infected patients, most commonly caused by a collapsing focal segmental glomerulosclerosis, also known as HIV-associated nephropathy (HIVAN). This typically presents as a nephrotic syndrome, but with minimal oedema. It appears to be more common in Africans and African Americans than in the white population. Renal function usually improves with

8.5.23 HIV/AIDS 919 the use of antiretroviral medication, but some patients progress to chronic renal failure and require renal replacement therapy or transplantation. Other renal diseases are described in HIV including membranoproliferative glomerulonephritis associated with hepatitis C, immune complex glomerulonephritis with IgA deposits, and membranous nephropathy. Drug toxicity is an important cause of renal impairment in HIV patients, including drugs used to treat opportunistic infections (e.g. cidofovir, amphotericin B, pentamidine). Antiretroviral treatment (e.g.

tenofovir) may cause Fanconi's syndrome due to tubular damage; atazanavir and indinavir may induce renal calculi and a nephropathy). Renal impairment caused by concurrent conditions such as diabetes or hypertension can also arise in patients with HIV infection. HIV and hepatitis virus coinfections Because of common risk factors for blood-borne virus infections, there are increasing numbers of individuals with HIV who are coinfecting with either hepatitis C (HCV) or hepatitis B (HBV) virus, or both. Over the past few years, new data have become available on the size of this problem and some management strategies have emerged. HIV/HCV coinfection HCV coinfection occurs in up to a third of those with HIV. The group with the highest prevalence is the haemophilic population, but the group most at risk now is injecting drug users (IDU). Anywhere between 50 and 75% of IDU with HIV are coinfecting. More recently, there is an awareness that growing numbers of men who have sex with men are acquiring HCV sexually. HCV/HIV coinfection increases the risk of liver disease progression compared to HCV infection by itself. In addition, the treatment of HIV with antiretrovirals might carry an increased risk of hepatotoxicity in those with coinfection. The impact of HCV on HIV progression is less clear but it might blunt CD4 recovery with ART. Treatment aimed at clearing HCV in those with coinfection initially used combinations of pegylated interferon and ribavirin, but were less likely to lead to a sustained virological response compared to treating those with HCV infection alone. However, the advent of directly acting antiviral drugs (DAA) for HCV infection has revolutionized the management of coinfecting patients (see Chapter 8.5.22). In HIV-negative patients with HCV, these new drugs have produced cures of greater than 90% and similar results are seen in those with HIV coinfection. The optimum DAA combination for those with coinfection is yet to be determined and will depend on the HCV genotype. It is important to be aware of drug interactions with ART and, in some circumstances, the ART might need to be altered to get the best chance of clearing the HCV infection. HIV/HBV coinfection The scale of the HIV epidemic in Africa and, now, in Asia means that up to 90% of those with HIV will have evidence of past or current HBV infection. Estimates vary, but up to 10% of those with HIV may be HBV carriers. Unlike with HCV, there is no evidence that liver disease due to HBV is worse in HIV coinfecting individuals. Although HBV DNA levels are higher in HIV coinfection, there is evidence that there is less liver injury. New HBV infections in HIV-positive individuals are less likely to cause acute hepatitis and jaundice, but are more likely to result in chronic HBV carriage. HBV infection does not seem to affect the progression of HIV disease. Treatment of HBV coinfection is less well defined than treatment of HCV coinfection. Although pegylated interferon might be useful, there are no large trials of its efficacy in HIV. Lamivudine monotherapy is more likely to lead to resistant HBV with the 'YMDD' mutant in the presence of HIV. Drugs currently used to treat HBV in the absence of HIV coinfection also have anti-HIV activity, particularly lamivudine, emtricitabine, and tenofovir. Caution must be used in treating HBV with these agents in coinfecting patients as monotherapy with these drugs will lead to resistant HIV. A recently introduced drug to treat HBV, entecavir, was thought not to have activity against HIV but had now been shown to have an anti-HIV effect and this can also lead to HIV resistance. By contrast, if HBV coinfecting patients require antiretroviral therapy, a combination of lamivudine and tenofovir, or emtricitabine and tenofovir, is recommended as part of the antiretroviral regimen to decrease HBV replication and avoid the onset of resistance. Management of HIV infection and prognosis The advent of antiretroviral therapy (ART) in the mid-1990s led to marked reductions in morbidity and mortality attributable to HIV and its complications. A decline in the incidence of opportunistic infections, notably pneumocystis pneumonia, disseminated M. avium complex (MAC) infection, CMV retinitis, cerebral toxoplasmosis and cryptococcal meningitis, and associated mortality was reported from the United States of America and Europe after the introduction of treatment based on a minimum

of three antiretroviral drugs. HIV infection in adults in resource-rich countries is now almost exclusively managed on an outpatient basis. Antiretroviral treatment has transformed HIV/AIDS from a uniformly fatal disease to a long-term condition. Although the prognosis is variable and influenced by adherence to ART, a large-scale study of mortality in HIV-infected adults in Europe has shown that in patients who are stable on treatment the standardized mortality ratio (SMR) approaches normal (1.05) and nearly half of patients have SMR less than 2, which is lower than for type 1 diabetes. In industrialized countries, ART has also influenced the proportion of deaths from non-AIDS causes, which now exceed AIDS-related deaths and typically include non-AIDS-defining cancers, cardiovascular disease, and liver disease. The recent changes in WHO and many national ART guidelines recommending immediate initiation of ART for all HIV+ individuals irrespective of CD4 count will, in the long term, enhance clinical outcomes further. This carries a burden of clinical management and cost of drug provision for the lifetime of all HIV+ individuals. However, these costs are offset by the significantly improved clinical benefit and also by the reduction in the risk of onward viral transmission. Initial assessment and management Ideally, HIV infection should be identified at the asymptomatic stage. At the time of diagnosis, patients should undergo a baseline assessment that includes taking a detailed history, including a sexual history, and determination of risk factors for HIV

920 section 8 Infectious diseases infection. An assessment of cardiovascular risk factors should be made, including smoking and family history. A detailed physical examination should be performed with attention to the skin and mucous membranes, blood pressure, and body mass index, fundoscopy, and should include a search for lymphadenopathy and signs of liver disease. Initial investigations include full blood count, biochemical screen including liver profile, bone profile, and estimated glomerular filtration rate, lipids, chest radiography, and serological screening for infections that may require additional treatment (hepatitis B and C, syphilis) or which can reactivate during immunosuppression (CMV and toxoplasma and TB). Baseline investigations include CD4 lymphocyte (T-helper cell) count (lymphocyte subsets profile), quantitative estimation of HIV RNA in the blood plasma (viral load), and HIV genotypic resistance testing; and should include tissue typing for HLA-B*5701, a marker for abacavir hypersensitivity. In women, cervical cytology screening is indicated at annual intervals. All HIV+ individuals should be referred for appropriate TB screening. Following initial assessment, hepatitis B immunization can be provided to susceptible individuals, and pneumococcal vaccine can be offered. Consideration should also be given to HPV vaccination in women and in men who have sex with men. Psychological support and counselling are often needed. There should be a discussion about who should be informed about their HIV status, including the primary care physician, and family members and friends for support. The issue of disclosure to sexual partners should also be raised, with advice on reducing risk of transmission (including the importance of barrier methods such as condoms). Antiretroviral treatment of the HIV-infected partner reduces risk of transmission to their HIV-negative sexual partner, although safe sex counselling should still be provided. The CD4 lymphocyte count and HIV viral load are the two laboratory markers that have the best prognostic value. The CD4 count is a reliable indicator of HIV-related immune impairment. CD4 counts, normal at or above 900/mm³, vary considerably, even in the absence of HIV infection. A fall in the CD4 lymphocyte count to below 200/mm³ is associated with a risk of opportunistic infections of about 80% over 3 years without antiretroviral treatment. However, progression is variable and a minority remain well for several years with stable low CD4 counts. This variability is explained partly by differences in HIV viral load. The level of CD4 lymphopenia generally determines the spectrum of potential infections (Table 8.5.23.1). For

instance, whereas oral and oesophageal candidiasis and pneumocystis Table 8.5.23.1 Principal complications of untreated HIV infection Infections Neoplasms Direct HIV effects Early/intermediate HIV infection (CD4 >200/mm³) Herpes zoster Non-Hodgkin's lymphoma Persistent generalized lymphadenopathy Oral hairy leucoplakia Cervical intraepithelial neoplasia Atopy; eczema Oral candidiasis; candidal vaginitis Anal intraepithelial neoplasia Recurrent aphthous ulcers (oral and gastrointestinal tract) Pulmonary tuberculosis Immune thrombocytopenia Bacterial pneumonia, especially pneumococcal Neutropenia Bacteraemia, especially pneumococcal and salmonella Neuropathy (mononeuritis multiplex; Guillain-Barré syndrome) Bacillary angiomatosis HIV-associated nephropathy (HIVAN) Lymphocytic interstitial pneumonitis (LIP) Late HIV infection (CD4 <200/mm³) Pneumocystis pneumonia Kaposi's sarcoma HIV enteropathy Candidal oesophagitis Primary cerebral lymphoma Peripheral neuropathy (distal, axonal) Cerebral toxoplasmosis Hodgkin's lymphoma Autonomic neuropathy Cryptococcal meningitis Conjunctival carcinoma Myelopathy Chronic cryptosporidial diarrhoea ? Cervical carcinoma HIV dementia Chronic isosporiasis, microsporidiosis ? Anal carcinoma Wasting syndrome Chronic HSVa ulceration Cardiomyopathy Extrapulmonary tuberculosis Disseminated M. avium complex (MAC)a CMV (retinitis and disseminated)a Progressive multifocal leukoencephalopathy Recurrent bacterial pneumonia Recurrent bacteraemia, especially salmonella Disseminated histoplasmosis, and P. marneffei a AIDS-defining conditions; incomplete list. ? Signifies suspected but unproven association. Many of the early/intermediate manifestations also occur in late-stage HIV disease; non-Hodgkin's lymphoma is more common during the later stages.

8.5.23 HIV/AIDS 921 pneumonia can occur at CD4 counts of 100 to 200/mm³, disseminated MAC infection and CMV retinitis are rarely seen until the CD4 count is below 50/mm³. The prognostic value of measuring HIV RNA in plasma was re-reported from the United States of America in 1996. In HIV-positive men, in a subgroup of the Multicenter AIDS Cohort Study, only 8% with less than 5000 copies of HIV RNA/ml progressed to AIDS over 5 years, whereas 62% with viral loads above 35 000 developed AIDS. For a given level of CD4 lymphocytes, variations in viral load broadly predict the risk of progression. The most useful prognostic information was therefore derived from the CD4 count and viral load taken together (Fig. 8.5.23.14). Based on the findings from the START trial it is now recommended that ART is initiated for all HIV+ individuals irrespective of CD4 count or viral load as long-term clinical benefit has been shown. In industrialized countries, HIV viral load measurements are widely available. Techniques include reverse transcription followed by amplification by the polymerase chain reaction (RT-PCR), branched DNA (bDNA) signal amplification, and nucleic acid sequence-based amplification. Highly sensitive tests with very low detection limits (20 copies/ml) are generally used. Development of point-of-care viral load measurements are currently in progress and development of technology that can be transferred to resource-limited settings is under investigation. Such use of viral load measurement for monitoring will make CD4 count monitoring for stable virally suppressed patients on ART irrelevant, although initial CD4 count testing at the time of HIV diagnosis remains an important tool to direct OI prophylaxis assess the potential risk of IRIS for those starting therapy and plan preventive vaccination courses. The treatment of HIV-2 infections is comparatively complex, largely because of a paucity of data. The rate of progression is highly variable and not all who are infected progress to disease. There are no data on when to start treatment in this group but there is consensus that those with symptomatic disease should be treated with antiretrovirals, as should pregnant women. Additionally, lower than normal CD4 counts or detectable HIV-2 viraemia might be indications to start treatment. However, measuring HIV-2 RNA in the blood is not an assay that

is widely available and commercial tests to quantitate the RNA are not available. Antiretroviral therapy Nucleoside analogues Knowledge of the viral lifecycle (Fig. 8.5.23.3) led to the development of several antiretroviral compounds with clinically useful activity against HIV (Table 8.5.23.2). The forerunner of these was zidovudine (AZT or ZDV), first shown to be active against HIV in vitro in 1985. Zidovudine, a nucleoside analogue that inhibits HIV reverse transcriptase, slowed down the rate of disease progression over a 12-month period in patients with AIDS and improved short-term survival, well-being, body weight, and neurological features. However, clinical progression associated with viral resistance to the drug was observed after a year or two of therapy. When early treatment with zidovudine was compared to deferred zidovudine, there was no difference in survival or disease progression after 3 years. The clinical failure of monotherapy prompted combination therapy in an attempt to reduce the development of drug resistance. Double nucleoside combinations proved superior to zidovudine monotherapy, especially in patients without prior exposure to zidovudine. Treatment with at least three drugs is more effective and has become the standard of care. In general, two nucleoside drugs are used with either a nonnucleoside reverse transcriptase inhibitor, an integrase inhibitor, or a protease inhibitor. A nucleotide agent, tenofovir, has similar properties and is usually grouped in the same category as the nucleoside analogues. Nonnucleoside reverse transcriptase inhibitors The prototype of the class is nevirapine, a potent and selective inhibitor of HIV reverse transcriptase. When nevirapine is given alone, resistance develops rapidly; this drug is of limited effectiveness in double therapy or when added to failing regimens. However, in antiretroviral-naïve patients without AIDS (CD4 200–600/mm³), over 50% of patients treated with nevirapine plus two nucleosides (zidovudine and didanosine) had undetectable 0.8 0.6 1.0 0.4 0.2 0.0 Proportions of AIDS-free patients 0 2 4 6 8 10 0 2 4 6 8 10 Years after measurements V (70) IV (20) 0.8 0.6 1.0 0.4 0.2 0.0 Proportions of AIDS-free patients Years after measurements V (141) I (110) II (180) III (237) IV (202) 0 to 200 CD4+ cells/mm³ (n = 100) 500 CD4+ cells/mm³ (n = 870) (b) (a) Fig. 8.5.23.14 Curves showing AIDS-free survival with time among groups with different baseline CD4 lymphocyte counts, according to HIV-1 RNA category.

The five categories were (copies/ml): I, 500 or less; II, 501–3000; III, 3001–10 000; IV, 10 001–30 000; and V, above 30 000. (Sample sizes are shown in brackets.)

922 section 8 Infectious diseases plasma HIV RNA after 1 year of therapy, compared with 12% for zidovudine/didanosine only. Efavirenz and etravirine are other nonnucleoside reverse transcriptase inhibitors (NNRTIs) with similar properties to nevirapine. The most recently licensed NNRTI, rilpivirine, has been shown to be as effective as efavirenz in treatment-naïve patients who have HIV viral loads of less than 100 000 copies/ml but was not noninferior at higher viral loads. NNRTIs are not active against HIV-2. Protease inhibitors The HIV-encoded protease (or proteinase) is required for the production of mature infectious viral particles. This enzyme cleaves several structural proteins and enzymes from the polyprotein precursors produced by translation of the gag and gag-pol genes. Inhibitors of HIV protease act synergistically with nucleoside drugs and are potent inhibitors of HIV replication. In early studies, indinavir, in combination with two nucleoside analogues (zidovudine/lamivudine or stavudine/lamivudine) produced good results in a large controlled trial with clinical endpoints (ACTG 320 clinical trial). Similar results were subsequently reported for combination therapy with other protease inhibitors (PIs). The PIs in current use are generally 'ritonavir-boosted', that is, they are used in combination with low-dose ritonavir to improve pharmacokinetics (via cytochrome P450 interactions) of the principal PIs (especially lopinavir, atazanavir, and fosamprenavir). A recently developed drug, cobicistat, interacts with the

cyp450 system in a manner analogous to ritonavir and can be used to boost PIs. Cobicistat has no direct antiviral activity. PIs have a higher threshold for development of resistance mutations compared to NNRTIs, so that when resistance does occur it is more likely to be due to poor absorption and suboptimal blood levels. Nevertheless, PI mutations do occur and can be a problem in drug-experienced patients. Newer PIs, such as tipranavir and darunavir, are active against some of the PI-resistant isolates and have an increasing role in therapy, including for salvage therapy.

Entry inhibitors HIV entry inhibitors are a relatively new class of antiretroviral drugs that target viral entry into cells. This class contains two subgroups, fusion inhibitors and coreceptor antagonists. The fusion inhibitor enfuvirtide (T-20) stops the HIV glycoprotein gp41 from effecting fusion of the viral and cellular membranes, and thereby prevents HIV entry into host cells. This drug is licensed for use in treatment-experienced patients in combination with other drugs. It must be given by subcutaneous injection and is associated with a high rate of injection site reactions. Coreceptor antagonists act as functional antagonists of the chemokine receptor CCR5 and are active against the R5-tropic subgroup of HIV-1 viruses. Maraviroc is the first to be licensed from this subgroup, but others, such as cenicriviroc, are in clinical trials. These drugs are not effective against strains of virus using CXCR4 (more common in late disease), so tropism assays to determine the type of coreceptor usage of a patient's virus are needed before these drugs are used. The place of these agents in HIV therapy is yet to be determined.

Integrase inhibitors This class of drugs inhibits an essential enzyme that catalyses the integration of HIV proviral DNA into the host cell genome. The enzyme, integrase, is also involved in viral assembly and is not a feature of host cells. The first drug to be licensed in this group, raltegravir, is a potent inhibitor of HIV replication which currently should only be used in combination with other active antiretrovirals in patients. More recently developed integrase inhibitors, dolutegravir

Table 8.5.23.2 Principal antiretroviral agents

Nucleoside reverse transcriptase inhibitors	Nonnucleoside reverse transcriptase inhibitors	Protease inhibitors	Entry inhibitors
Zidovudine (AZT/ZDV)	Nevirapine	Lopinavir	Fusion inhibitor
Lamivudine (3TC)	Efavirenz	Ritonavir	Enfuvirtide
Emtricitabine (FTC)	Etravirine	Atazanavir	Rilpivirine
Abacavir (ABC)	Lersivirine ^b	Saquinavir (obsolete)	CCR5 antagonists ^b
Didanosine (ddI) (obsolete)	Fosamprenavir	Maraviroc	Stavudine (d4T) (rarely used)
Indinavir (obsolete)	Cenicriviroc ^b	Nelfinavir (obsolete)	Nucleotide reverse transcriptase inhibitor
Tipranavir	Integrase inhibitors	Tenofovir (TDF)	Tenofovir (TAF)
Darunavir	Raltegravir	Elvitegravir ^b	Dolutegravir ^b

Other compounds (not shown) are at earlier phases of development and evaluation. ^a Given with low-dose ritonavir for pharmacokinetic enhancement. ^b Experimental, in advanced clinical trials. Development discontinued due to poor results in recent clinical trials.

8.5.23 HIV/AIDS 923 and elvitegravir, have a higher resistance threshold and can be given once daily. Integrase inhibitors, because they are well tolerated and have few drug interactions, are rapidly becoming the preferred agents in HIV infection. Other drugs There is a need for new drug classes for use after development of drug resistance, allowing additional options for switching after treatment failure or drug intolerance, and also to provide compounds that avoid the long-term toxicities associated with current antiretrovirals. Immunotherapy with interleukin-2 (IL-2), which raises CD4 lymphocyte counts and is given by subcutaneous injection, has been shown to be clinically ineffective. Recent studies have involved the use of depot injections of long-acting integrase inhibitors. Such developments might be useful for those unable or unwilling to take tablets long term. The role of these preparations for treatment and prevention are being investigated.

HIV-2 Treatment Although HIV-2 can cause disease, there are fewer data on how to treat this virus. HIV-2 is intrinsically resistant to NNRTI and to the fusion inhibitor, enfuvirtide.

Protease inhibitors are variable in their potency. Generally, lopinavir or darunavir are preferred to the others available. Nucleoside reverse transcriptase inhibitors and integrase inhibitors have good activity. Advice should be sought from an expert in treating HIV-2.

When to start antiretroviral treatment

The optimum time to start antiretroviral therapy is now known. A major trial (Strategic Timing of Anti-Retroviral Treatment, START) compared clinical outcomes for individuals with HIV and CD4 counts greater than 500 cells/cc³ who were randomly allocated to either start immediate ART or defer according to local guidelines (CD4 <350 cells for most sites). This trial reported a significant benefit of starting immediate ART greater than 500 cells and this has now become incorporated into revised WHO and many national guidelines. The decision to start treatment should also take into account how quickly ART should be implemented and will include assessment of age and presence of coinfection with TB, hepatitis B or C. Patients who are clinically well after starting ART should be seen for follow-up at intervals of 3–6 months for regular viral load measurements.

What to start with Antiretroviral therapy

consists of at least three drugs from two different drug classes, usually a backbone of two nucleosides with either a nonnucleoside reverse transcriptase inhibitor, an integrase inhibitor, or a protease inhibitor (see Table 8.5.23.3). For improved pharmacokinetics, the protease inhibitor is usually combined ('boosted') with a second protease inhibitor (i.e. low-dose ritonavir or a newer drug, cobicistat). Several initial regimens have equivalent efficacy. Current recommendations are based on viral efficacy, tolerability, and cost with a preference given to regimens that are taken only once a day. The most important cause of treatment failure is inadequate treatment, which may relate to failure to take the drugs regularly (i.e. non-adherence, lack of availability of drugs, or poor absorption). Before starting treatment it is, therefore, important to discuss the patient's views about taking medication regularly. Simplified regimens with combination single tablet, once daily formulations have helped with adherence (see next). Several other factors also influence the selection of the initial regimen, including potential drug interactions (e.g. with antituberculosis treatment), toxicity, ease of administration, presence of renal or hepatic dysfunction, female gender. HIV viral load and CD4 count should be checked within 2 months. The aim of initial treatment is to achieve a sustained reduction in viral load to undetectable levels (<20 copies/ml) within 2–3 months of starting treatment.

Patient adherence

A substantial proportion of all patients, including those with HIV, struggle to follow treatment recommendations. Reasons for non-adherence include poor communication, the complexity of drug regimens and number of tablets, disruption of life (including timing and food restrictions), side effects, concerns about long-term effects, and lack of confidence in noncurative treatments of indefinite duration. Adherence to treatment requires a high level of understanding and motivation in the patient. This is of particular concern in HIV therapy because of the risk of developing drug-resistance mutations during suboptimal therapy. The recent development of simplified regimens (one or two tablets taken once or twice daily) has helped. Patients can be helped to be adherent by skilled support from trained professionals such as counsellors or pharmacists.

Changing therapy

The principal reasons for changing antiretroviral treatment are treatment failure, toxicity, and poor adherence. There is no agreed definition for treatment failure. Patients whose viral load is not suppressed to less than 40 copies/ml within 3 months, or was initially suppressed and subsequently rises, should be considered for changing to a completely new regimen of at least three drugs. This should be guided by a resistance test (see next). Continuing viral replication in the presence of antiretroviral treatment should be avoided because of progressive accumulation of resistance mutations which can compromise future treatment options. If adherence is poor or likely to be the cause of treatment failure, changing to a combination that is simpler to take should be considered (e.g. based on once or twice daily dosage

and low pill burden). Poor absorption of protease inhibitors might sometimes cause treatment failure related to low blood levels, without development of resistance; measurement of blood levels can be useful in this context. Table 8.5.23.3 Initial antiretroviral regimens Examples Comment

TDF/FTC + integrase inhibitor Preferred regimen TDF/FTC + PI with RTV Preferred regimen TDF/FTC + EFV Alternative if no contraindications to EFV 3TC/ABC + PI with RTV ABC contraindicated if HLA-B57.01 3TC/ABC + integrase inhibitor 3TC/ABC + EFV Only appropriate if viral load <100 000 3TC, lamivudine; ABC, abacavir; FTC, emtricitabine; PI, protease inhibitor; TDF, tenofovir; RTV, ritonavir; EFV, efavirenz. TDF/FTC + integrase inhibitor. TDF/FTC + PI with RTV. See British HIV Association guidelines: <http://www.bhiva.org> for latest UK guidelines.

924 section 8 Infectious diseases If treatment needs to be changed because of drug toxicity (e.g. a severe rash), a single drug substitution can be made if the responsible agent is identified.

‘Salvage’ therapy Salvage therapy is generally defined as treatment following exposure to multiple antiretroviral drugs. In this situation, numerous drug-resistance mutations are usually present and the likelihood of achieving sustained viral suppression below the detection level is much lower than for patients who have limited or no previous antiretroviral exposure. This is especially true if drugs from all three major classes have previously been used. Studies using clinical endpoints suggest that declines in viral load correlate with improvements in clinical outcome, even if suppression to below the detection limit is not achieved. Several factors may be considered when selecting a treatment regimen in these circumstances, including the history of drug classes to which the patient has not been exposed and the results of tests for viral resistance. It might be possible to recycle some drugs with less likelihood of resistance, or to include new drugs active against resistant isolates (e.g. darunavir) or new classes of drugs (e.g. maraviroc). When initiating salvage therapy it is important to use at least two new drugs to which the patient has not been exposed in order to reduce the risk of further resistance developing.

Drug resistance Viral resistance is a major factor in treatment failure. Resistant mutants can arise spontaneously even in the absence of antiretroviral therapy; however, the selection of drug-resistance mutants occurs rapidly when HIV replicates in the presence of subtherapeutic levels of antiretroviral drugs, and is eliminated when HIV replication is completely suppressed by a potent drug combination. Extensive genotypic variation of HIV occurs because of very high viral turnover and transcription errors by the reverse transcriptase enzyme, so that all possible single point mutations are likely to occur over time. Although mutations causing resistance to single agents may arise before antiretroviral treatment is started, on statistical grounds it is unlikely that specific combinations of multiple mutations will be present. Control of viral replication with a highly potent treatment regimen limits the appearance of resistant HIV mutants. Genotypic and phenotypic assays have been developed to test for drug resistance in HIV isolates. Genotypic assays that identify codon mutations correlating with in vivo resistance to antiretrovirals are relatively easy to perform, inexpensive, and most widely used. Phenotypic assays that measure the ability of the virus to grow in increasing concentrations of drugs are time-consuming and expensive, but provide more direct evidence of resistance to a particular drug. Resistance assays are widely used in the selection of drug regimens and investigation of treatment failure. Interpretation of resistance patterns is increasingly difficult as the number of drugs and mutations involved increases. Resistance mutations to antiretroviral agents in newly acquired HIV, indicating transmitted drug resistance, are identified in approximately 10% of recent seroconverters in Europe. However, the presence of a mutation does not necessarily denote clinical resistance. In the absence of therapy, wild-type virus predominates, and resistance mutations may be undetectable though present in small copy

numbers. This can lead to treatment failures with the resistant mutants increasing as wild-type virus is eradicated by drugs. For this reason, baseline resistance testing at diagnosis is now advocated in an attempt to identify resistance mutations at the outset. Drug toxicity and interactions

Adverse reactions to antiretroviral agents are relatively common and may lead to the patient stopping their therapy (Table 8.5.23.4). Minor gastrointestinal disturbances (nausea, vomiting, and diarrhoea), rashes, and headache are common, but some adverse reactions are serious. Drug interactions must be considered when prescribing antiretroviral drugs, especially in advanced HIV disease. Antiretroviral agents can interact with each other and with other drugs. For example, phenytoin drastically reduces plasma levels of efavirenz. Ritonavir, a potent inhibitor of cytochrome P450, is especially prone to raising blood levels of other drugs and should not be given with most antiarrhythmics, anxiolytics, and antihistamines. Caution is required with several analgesics, anticonvulsants, and other categories of medication.

Metabolic complications Metabolic problems, especially mitochondrial toxicity and disturbances of lipid and glucose metabolism, have emerged as important adverse effects of antiretroviral therapy. Mitochondrial toxicity is associated with nucleoside drugs (especially didanosine and stavudine, which are now rarely prescribed) and might result in neuropathy, myopathy, pancreatitis, hepatic steatosis, hyperlactataemia, and lactic acidosis. Lactic acidosis causes nonspecific symptoms, including malaise, gastrointestinal disturbance, and liver function abnormalities, and can progress to death, particularly if antiretrovirals are not stopped. There is no evidence that routine monitoring of lactate levels is helpful. Nucleoside drugs are thought to cause mitochondrial dysfunction by inhibiting mitochondrial DNA polymerase- γ . In addition, lipid abnormalities are commonly seen in the face of antiretroviral therapy, leading to raised triglycerides and cholesterol. Hyperlipidaemia has been particularly associated with the use of protease inhibitors, as has insulin resistance. A syndrome of lipodystrophy (progressive loss of fat from face and limbs) is associated with thymidine analogue nucleoside drugs, especially stavudine, and to a lesser extent zidovudine. Truncal fat accumulation, has also been associated with protease inhibitors.

Cardiovascular disease After the introduction of antiretroviral treatment, early reports suggested a possible increase in cardiovascular disease in patient with HIV. Several variables potentially affect the risk of myocardial infarction and other cardiovascular events in this patient group. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D.) study group has shown an association with antiretrovirals and cardiovascular events. The relative risk of myocardial infarction may be increased by about 10% when other factors, such as lipid levels, are taken into account. The INITIO trial showed an increased incidence of the metabolic syndrome with antiretroviral treatment, with an associated increased risk of cardiovascular disease. Although there is still some controversy, it seems that the nucleoside analogue abacavir is more commonly associated with an increased cardiovascular risk than other antiretrovirals, though the mechanism remains unclear. A variety of studies have tried to quantitate the risk of cardiovascular disease in HIV and to analyse the pathogenesis. Investigation of the intima media thickness in the carotid artery shows increased thickening in those with HIV compared to

8.5.23 HIV/AIDS 925 noninfected matched controls. Assessments of coronary calcification and plaque disease again point to slightly worse measures in HIV. Whether these observations correlate with outcome is uncertain. More recently attention has focused on the role of chronic inflammation due to HIV infection causing arterial endothelial dysfunction. Studies have shown elevated levels of C-reactive protein and proinflammatory cytokines, such as IL-6, in HIV. There may also be abnormalities in coagulation that contribute to an

Table 8.5.23.4 Principal toxicities

of antiretroviral drugs Nucleoside reverse transcriptase inhibitors (NRTI) Class effects GI disturbances, raised liver enzymes, hepatic steatosis, lactic acidosis Zidovudine (AZT) Headache, nausea (usually resolve within 2–4 weeks) Anaemia (avoid if anaemic at baseline) Macrocytosis (benign) Nail pigmentation Myopathy (rare on lower dosages 500–600 mg/day) Lipodystrophy with facial wasting (long-term effect, unknown incidence) Abacavir (ABC) Hypersensitivity 5%; may be fatal if rechallenged (closely associated with HLA-B*57.01) Didanosine (ddI) Pancreatitis, peripheral neuropathy—no longer used Stavudine (d4T) Lipodystrophy with facial wasting; peripheral neuropathy; rarely used Lamivudine (3TC), Emtricitabine (FTC) No major toxicities Nucleotide RTI Tenofovir disoproxil fumarate (TDF) Renal failure (case reports, rare, incidence unknown) renal protein and phosphate leak; osteoporosis Tenofovir alafenamide (TAF) Diarrhoea; rash Reduced incidence of renal or bone adverse effects compared to TDF Nonnucleoside RTI (NNRTI) Efavirenz Neuropsychiatric disturbances (8%)—vivid dreams, impaired concentration, mood changes (usually transient, <4 weeks duration); rash Nevirapine Rash (20%, severe 6%); rarely Stevens–Johnson syndrome; hepatitis (esp. in women with CD4 >250/mm³ or men with CD4 >400/mm³—avoid) abnormal LFT Etravirine Rash with eosinophilia; toxic epidermal necrolysis Rilpivirine Insomnia, Neuropsychiatric disturbances; rash; osteonecrosis Protease inhibitors (PI) Class effects GI disturbances; hyperlipidaemia, truncal fat accumulation, diabetes, bleeding in haemophiliacs, raised liver enzymes Lopinavir Diarrhoea Ritonavir Circumoral and peripheral paraesthesiae (unusual in low dosage) Saquinavir Rash, peripheral neuropathy; no longer used Nelfinavir Diarrhoea; no longer used Indinavir Renal calculi, haemolysis; no longer used Atazanavir Hyperbilirubinaemia, jaundice Tipranavir Rash (caution in sulphonamide allergy), liver dysfunction Darunavir Diarrhoea, rash (caution in sulphonamide allergy) Entry inhibitors Fusion inhibitors Enfuvirtide Injection site reactions (painful, erythematous nodules); headache, dizziness, nausea, eosinophilia CCR5 antagonists Maraviroc Cough, muscle and joint pain, diarrhoea, sleep disturbance, raised liver enzymes (and possibly hepatitis) Integrase inhibitors Raltegravir Nausea, diarrhoea, headache, insomnia; raised creatine kinase (CK) in some patients Dolutegravir Hypersensitivity reactions; diarrhoea, raised CK Elvitegravir Rash, diarrhoea, dyspepsia

926 section 8 Infectious diseases increased cardiovascular risk. Levels of D-dimer tend to be higher in HIV infection compared to controls. The absolute risk is very small when compared to the risks associated with smoking, diabetes mellitus, and male gender. Nevertheless, increasing attention is being paid to modifying cardiovascular risk factors in those on HIV therapy, such as smoking cessation programmes, treatment of hypertension, and managing hyperlipidaemia. Statins are slightly less effective lipid-lowering agents in those with HIV and there are no data at present to show that statins are clinically effective in HIV in preventing cardiovascular events. It should be noted that some statins, such as simvastatin, have significant interactions with some antiretrovirals. Current guidelines suggest avoiding the use of abacavir if there are significant cardiovascular risk factors present in an individual. In addition, it may be prudent to change from a protease inhibitor to an integrase inhibitor or to a nonnucleoside reverse transcriptase inhibitor, such as rilpivirine, in patients with hyperlipidaemia and risk factors. Recent attention has also focused on changes in bone metabolism. HIV-infected patients have an increased risk of osteoporosis and bone fractures, which are often multifactorial. Antiretroviral therapy seems to be a factor with tenofovir DF being particularly implicated as it can lead to urinary phosphate wasting. The use of tenofovir alafenamide might reduce this risk. Proinflammatory cytokines might also play a role in a manner analogous to the cardiovascular risks but other contributing causes include smoking, vitamin D deficiency, low testosterone levels in males, low oestrogen levels in

postmenopausal women, and increasing age. Hepatitis C infection is associated with osteoporosis and may contribute significantly in coinfecting patients. Patients on HIV therapy also have an increased incidence of avascular necrosis (osteonecrosis) of the femoral head. Although guidelines have been produced for screening for bone disease in HIV, the merits of intervening outside of the existing guidance for non-HIV-infected individuals are not clear.

Treatment interruptions In general, once treatment is started it is continued indefinitely. For individuals who do choose to interrupt treatment, the virus will rebound in plasma within 2-6 weeks. There has been recent interest in whether interrupting treatment (in supervised or structured treatment interruptions) might be beneficial. In theory, it was postulated that ART interruptions might enhance immune responses, reduce long-term drug toxicity, or reduce resistant virus by allowing repopulation with wild-type virus. A large trial (SMART) was stopped early because of a paradoxical result. The study randomized patients with stable disease on therapy to continuing therapy or to stopping (and restarting if the CD4 count fell below 250). Not only were there more HIV complications in the stopping group, but this group, surprisingly, also had a higher incidence of cardiovascular disease. It is postulated that the increased cardiovascular risk is related to endothelial inflammation secondary to uncontrolled viraemia. It is thus unlikely that treatment interruption will be a sensible management strategy and patients should be counselled about the need for long-term treatment.

Interruption of ART is a common occurrence for multiple reasons: drug stock-outs, patient travel, intercurrent illness, toxicities and treatment fatigue. Whilst the SMART trial identified a significant risk to stopping ART amongst individuals with low nadir CD4 counts when ART was initiated in chronic disease, the SPARTAC trial, where short course ART was used in primary HIV infection and restarted later by CD4 threshold, did not see any similar mortality or morbidity. It can be hypothesized that ART interruption, whilst not recommended, might be safer in individuals with preserved immune function. Similarly, in the context of the HIV remission/cure trial setting with very careful viral load monitoring, this approach might be necessary to test ultimately if an intervention has led to viral control off therapy.

Immune reconstitution inflammatory syndrome (IRIS) Since the introduction of antiretroviral therapy, there have been reports of unusual symptoms and signs appearing in patients some weeks to months after starting therapy. Because these clinical problems arise in the face of increasing CD4 counts, the syndrome has been called the immune reconstitution inflammatory syndrome (IRIS) or immune reconstitution disease. In the absence of HIV, paradoxical clinical responses have been described in tuberculosis and in leprosy. In the setting of HIV, IRIS often takes the form of an exacerbation of a previously treated opportunist infection or an unusual clinical presentation of an opportunist infection that was subclinical at the time ART was started. The incidence of IRIS is difficult to determine, particularly as there is no currently agreed definition, but it might occur in up to 20% of patients starting ART. Usually, IRIS starts within a few months of starting ART and is temporally related to a rise in CD4 count. A proposed definition includes (1) new or worsening symptoms of an infection or inflammation after starting antiretrovirals, (2) symptoms not explained by a new infection or the expected course of an infection previously diagnosed, and (3) a decrease in viral load by at least one log₁₀. The pathogenesis of IRIS is poorly understood, but many patients have been found to have raised IL-6 levels, possibly related to a brisk Th-1 lymphocyte response. The most common opportunistic infections complicated by IRIS are tuberculosis, *M. avium* (MAC) infections, pneumocystis pneumonia, cryptococcal meningitis, and cytomegalovirus. IRIS complicating tuberculosis is probably the most common problem. Patients can develop fever or lymphadenopathy or might present with pleural effusions. Bone and joint involvement also occurs. IRIS is possibly more common in those presenting with extrapulmonary tuberculosis and can be

fatal in tuberculous meningitis. IRIS can occur in those receiving treatment for MAC and in one series complicated 30% of cases. The usual problem is lymph node enlargement, which can be massive and might mimic lymphoma. Some cases are complicated by hypercalcaemia. Cryptococcal meningitis, when complicated by IRIS, might present as an apparent relapse with fever, headache, and signs of meningeal irritation. Rapidly expanding cerebral cryptococcomas may lead to fatal increases in intracranial pressure. In parts of the world where this fungus is a common problem, screening patients for cryptococcal antigen (CRAg) is done before ART are started. Cytomegalovirus infections can also be complicated by IRIS with a worsening of signs of retinitis or a more benign vitritis. Rarely, patients have presented with a uveitis some years after starting ART. Some of the common features in the aforementioned conditions are that affected patients often started ART at very low CD4 counts and with very high HIV viral loads. There is no consensus on the best management of IRIS, but there is no rationale for stopping ART and most cases are self-limiting. Steroids and nonsteroidal anti-inflammatory drugs are frequently used, but the use of steroids has only recently been shown to help in TB-associated IRIS.

8.5.23 HIV/AIDS 927 HIV and ageing There are two aspects to the issue of HIV and ageing. The first, and obvious, thing is that with the remarkable success of ART, people with HIV are now living longer and acquiring the noncommunicable diseases and comorbidities of the general ageing population. This has implications for nonspecialists, particularly geratologists, who will need to familiarize themselves with HIV and, in particular, the current therapies. The question is whether these comorbidities occur earlier in those with HIV; that is, does HIV cause premature ageing? The recognized increased cardiovascular risks, neurocognitive disorders, and metabolic changes, including osteoporosis, might suggest that this is the case. However, it is difficult to untangle the effects of ART from the effects of long-term HIV infection. There is some evidence to suggest that chronic HIV infection, even when controlled by ART, leads to increased endothelial inflammation and that this might be responsible for some of cardiovascular complications (and others) seen in HIV. In addition, HIV infection appears to accelerate the exhaustion (and hence, ageing) of the immune system. Children and HIV Paediatric HIV is even more an epidemic of sub-Saharan Africa than is adult infection: approximately 90% of children and 67% of adults with HIV live in sub-Saharan Africa. Furthermore, the shape of the paediatric epidemic is changing, as access to antiretroviral therapy increases and prevention of mother-to-child transmission (PMTCT) programmes decrease transmissions. The combined impact of these changes is that, globally, the overall numbers of children living with HIV is still high (currently estimated at 1.8 m, UNAIDS 2015 Report), and the adolescent epidemic, which previously did not exist, is a growing challenge, bringing with it major issues around ART nonadherence. In Europe and North America, however, numbers of newly HIV-infected children have dwindled to a trickle. Most paediatric infections result from the mother-to-child transmission (MTCT) of HIV, although some children may be infected by blood products or sexual abuse. The risk of MTCT is increased during advanced maternal HIV disease or acute maternal infection during pregnancy, by vaginal delivery, and by breastfeeding (see 'Mother-to-child transmission', next). Diagnosis is important as early as possible because without antiretroviral therapy (ART) approximately 50% of HIV-infected children progress to AIDS during the first year of life; however, HIV antibody detection is not helpful towards diagnosis before 18 months of age, because over this period uninfected children may have maternal HIV antibody. Techniques for virus detection (e.g. HIV DNA by PCR) allow confirmation of HIV infection irrespective of the presence of maternal antibody. Point-of-care testing (by HIV DNA PCR) can successfully diagnose HIV infection in in utero infected infants within hours of birth. The natural

history is very different in resource-rich versus resource-limited countries. In the latter, HIV-infected children without antiretroviral therapy have a mortality rate of 45 to 59% at 2 years. In Europe and the United States of America, about 20% of untreated children would develop AIDS or die in infancy; by 5 years, 40% of children would have developed AIDS and 25% would have died. Without any intervention, the most common AIDS diagnosis in infancy is pneumocystis pneumonia, typically presenting at 10 to 14 weeks of age. HIV encephalopathy is also common in untreated HIV-infected infants, with severe developmental delay occurring in about 10% and more subtle delays in an additional 40%. Although progression to HIV disease is generally much more rapid in infected children than adults, there is a substantial subset of 5–10% of ART-naïve HIV-infected children who maintain CD4 counts that are normal-for-age for HIV-uninfected children. Unlike ‘elite controller’ adults in whom viral replication is suppressed by the HIV-specific immune response to very low levels, viral loads in the paediatric nonprogressors remain at high levels (104–105 copies/ml plasma). This scenario is reminiscent of the natural hosts of SIV infection, such as the sooty mangabey, who are disease-free despite persistent high viral loads of c.105 copies/ml plasma. However, while this is of scientific importance and interest to help direct vaccine development, the current recommendation is to offer ART to all children irrespective of CD4 count and viral load. In particular the high level of HIV viral load observed in these young people confers a significant risk of onward viral transmission. In older children, clinical conditions suggestive of HIV infection include persistent oral candida, parotid swelling, and recurrent or frequent serious bacterial infections including pneumonia, meningitis, and sepsis. Failure to thrive, diarrhoea, fever, lymphadenopathy, and hepatosplenomegaly are more common in HIV-infected infants but are nonspecific and less predictive. HIV dementia and other neurological and developmental problems are associated with a poor prognosis. HIV-related lymphocytic interstitial pneumonitis (LIP) typically occurs in children and is characterized by progressive, widespread, reticulonodular shadowing on chest radiography. LIP develops insidiously and may initially be asymptomatic; chronic lung disease develops with cough, breathlessness, hypoxia, clubbing, and secondary bacterial infections, and bronchiectasis occurring in severe cases. LIP is often associated with other lymphoproliferative manifestations (such as parotitis) and relatively well-preserved immune function, and may be treated with oral prednisolone. The management of HIV-infected children has changed dramatically in recent years. As in adult infection, there has been a move to initiate ART earlier and earlier in the course of infection, but the very high mortality in HIV-infected infants and difficulty to predict sudden declines in infants on the basis of clinical evaluation and measurements of CD4 count and viral load has meant that ART initiation in all infected children aged less than 1 year, irrespective of CD4 count or viral load, has been practised based on WHO guidelines since 2008. In 2013, WHO guidelines moved further to recommend that all HIV-infected children aged less than 5yrs should receive ART irrespective, while in children aged over 5 years the practice has been to start ART based on the same absolute CD4 count and clinical criteria as used in adults. From 2016, recommendations now are that all HIV-infected children should receive ART, irrespective of CD4 count or clinical status. Principles of antiretroviral treatment are similar in children and adults. Particular challenges to the effective use of ART that are specific to children include the need to adjust drug dose as the child grows (to avoid underdosing and drug resistance); the lack of paediatric formulations suitable for infants, fewer drug choices, limited paediatric toxicity data, and nonspecific presentation of drug toxicity in children; reliance of children on caregivers who themselves might have HIV and be ill; and, in adolescents, problems of adherence and coming to terms with an HIV diagnosis. The issue of disclosure, the process by which the child or adolescent learns of the HIV diagnosis,

928 section 8 Infectious diseases is especially challenging, not only because the optimal approach and timing needs to be carefully tailored to each individual setting, but also because there may be some sense of guilt on the parental side. An additional problem in the use of ART in infants, where infected mothers have received single-dose nevirapine (or other antiretroviral therapy during pregnancy to reduce MTCT), is that the transmitted virus in such a setting is usually nevirapine resistant. This should in future not be a problem as current recommendation for all HIV infected pregnant women is to start lifelong ART. However, it is important to note the potential for drug-resistant virus among multiparous HIV-positive women who might have acquired drug-resistant HIV through previous pregnancies. Prevention of opportunistic infections (See Table 8.5.23.5.) The risk of developing an opportunistic infection rises greatly once the peripheral CD4 lymphocyte count falls consistently below 200/mm³. It is standard practice to introduce low-dose co-trimoxazole prophylaxis for pneumocystis pneumonia at this stage. This also reduces the risk of cerebral toxoplasmosis and may prevent bacterial pneumonia. Studies in Africa, in both children and adults, have shown that co-trimoxazole prophylaxis is associated with decreased mortality. The risk of developing active tuberculosis in HIV-positive American intravenous drug users with positive tuberculin skin tests has been shown to be about 8% per year and can be reduced by taking isoniazid for a year. In developing countries, in particular, the risk of active tuberculosis in HIV-positive individuals is high and isoniazid alone or in combination with rifampicin can reduce the risk, but there is a challenge in implementation, which includes addressing the need to exclude active TB. Bacillus Calmette-Guérin (BCG) vaccination does not appear to be protective in HIV. Primary prophylaxis might prevent other conditions, such as CMV retinitis, cryptococcal meningitis, and histoplasmosis, but because of the relatively low incidence and lack of predictors of risk for these conditions, it is not cost-effective. Before the advent of antiretroviral therapy, after treatment of an opportunistic infection the predisposition to the infection usually remained. Thus, in early

Table 8.5.23.5 Prophylaxis of major opportunistic infections in HIV Infection

Indications	Regimens	Comments
First line	Alternatives	Pneumococcal pneumonia All HIV-positive patients Pneumococcal vaccine None Clinical effectiveness unproved; antibody response greater if CD4 >350/mm ³
P. jirovecii pneumonia	CD4 <200/mm ³ ; or symptomatic HIV; or following PCP	Co-trimoxazole 480–960 mg daily (or 960 mg, 3 times per week) Dapsone; dapsone with pyrimethamine; monthly nebulized pentamidine; atovaquone May be stopped if CD4 is sustained

“ 200/mm³ on anti-HIV treatment Cerebral toxoplasmosis CD4 <100/mm³ plus toxoplasma IgG-positive following treatment of cerebral toxoplasmosis As above Dapsone with pyrimethamine Primary prophylaxis usually incidental to that for PCP prophylaxis; pentamidine not protective Sulfadiazine 0.5–1 g, 4 times daily with pyrimethamine 25–75 mg/day, and folinic acid; protects against P. jirovecii as well Clindamycin with pyrimethamine, and folinic acid May be stopped if CD4 is sustained 200/mm³ on anti-HIV treatment Tuberculosis Tuberculin reaction 5 mm induration with no previous BCG; or high-risk exposure to tuberculosis Isoniazid 300 mg/day with pyridoxine 50 mg/day for 6–12 months Rifampicin with isoniazid for 3 months Rifampicin should not be given with protease inhibitors or nevirapine M. avium complex (MAC) CD4 <50/mm³ following treatment of disseminated MAC Clarithromycin 500 mg, twice daily, or azithromycin 1200 mg/week Rifabutin;

rifabutin with azithromycin Primary prophylaxis not recommended
 Clarithromycin 500 mg, twice daily, with ethambutol 15 mg/kg per day with or without rifabutin 300 mg/day Azithromycin with ethambutol, with or without rifabutin May be stopped if CD4 is sustained 200/mm³ on anti-HIV treatment
 Cytomegalovirus (CMV) CD4 <50/mm³ and CMV antibody-positive Valganciclovir 900 mg daily None Primary prophylaxis not recommended Following CMV retinitis or other CMV disease Valganciclovir 900 mg daily; or ganciclovir 5–6 mg/kg IV on 5–7 days/week Foscarnet IV; cidofovir IV; ganciclovir intraocular implant May be stopped if CD4 is sustained 200/mm³ on anti-HIV treatment Cryptococcal meningitis CD4 <50/mm³ following treatment of cryptococcal meningitis Fluconazole 100–200 mg/day orally Itraconazole orally Primary prophylaxis recommended in endemic settings Fluconazole 200 mg/day orally Itraconazole orally; amphotericin B IV weekly or 3 times/weekly Fluconazole superior to itraconazole for secondary prophylaxis May be stopped if CD4 is sustained 200/mm³ on anti-HIV treatment IV, intravenous; PCP, pneumocystis pneumonia. a In circumstances of contact with MDR-TB, specialist advice about prophylaxis should be sought.

8.5.23 HIV/AIDS 929 studies, following an episode of pneumocystis pneumonia, patients had a 50% chance of a further episode within a year. Secondary prophylaxis with co-trimoxazole proved effective. Secondary prophylaxis for pneumocystis and other opportunistic infections, including MAC and CMV, is discontinued if there is a good response to antiretroviral treatment, with CD4 counts sustained above 200/mm³ and low plasma levels of HIV RNA. Simple measures, other than drugs, can reduce the risk of some infections. Avoiding undercooked eggs and poultry may reduce the risk of disseminated salmonella infection and adequate boiling of drinking water can prevent cryptosporidiosis. Stopping cigarette smoking reduces the risk of bacterial chest infections.

Prevention of HIV transmission Sexual transmission Sexual transmission accounts for most new cases of HIV infection. Education to alter behaviour and reduce the risk of HIV infection is a key component of HIV control programmes. Condom promotion in Thailand has made an impact on HIV transmission rates. The presence of other sexually transmitted infections, especially those causing genital ulcers, facilitates HIV transmission. Accordingly, studies in Tanzania and elsewhere have demonstrated that programmes to prevent and treat sexually transmitted infections reduce the incidence of new HIV infections. Herpes simplex virus type 2 (HSV-2) is of particular importance in facilitating HIV-1 transmission, because of its high prevalence worldwide, including developing countries. Aciclovir suppression of HSV-2 infection has been shown to reduce genital shedding of HIV-1 and plasma HIV viral load, but field studies have not demonstrated a consequent reduction in risk of HIV acquisition. This may be a consequence of poor HSV suppressive therapy as well as the overriding driver or transmission of HIV viral load. These studies were undertaken with suboptimal HSV suppression and not in the era of universal ART. The risk of HIV transmission is related to the HIV viral load, and is reduced dramatically by antiretroviral treatment. A systematic review in 2009 showed no transmissions in over 5000 sero-discordant heterosexual couples when the index patient's viral load was less than 400 copies/ml. HIV may be detected in the semen of patients with undetectable viral load and so it should not be assumed that the risk of transmission is zero. These

findings have led to a debate on the potential value of large-scale antiretroviral treatment as a strategy for controlling HIV transmission in populations with high prevalences of HIV. Subsequently two large randomized controlled trial (RCT) have shown a very dramatic reduction in the risk of sexual transmission of HIV where the HIV-positive partner in a sero-different relationship receives suppressive ART. The HPTN052 and PARTNER study both identified a reduction in viral transmission when the HIV-positive partner was on suppressive ART of up to 96% and subsequent follow-up study of couple out to 5 years after the trial reported have shown a sustained reduction in transmission risk of 93% overall. The approach at a population level to implement 'treatment as prevention' has been a focus especially among those at highest risk of transmission. With the adoption of the most recent ART guidelines recommending ART initiation for all HIV-positive individuals irrespective of CD4 count, the secondary impact on reduced viral transmission at a population level is estimated to be very significant. However, the key barrier to population level impact of such a wide spread intervention is knowledge of HIV status. At present slightly over 50% of all people living with HIV in highest burden settings in sub-Saharan Africa are aware of their HIV status and in the developed world this remains around 20%. Until HIV testing can diagnose more than 90% of all people living with HIV, ART initiation will have a limited impact of stopping the epidemic. In 2014 UNAIDS and partners launched an initiative to support a target globally that 90% of all people living with HIV should know their status with repeat annual testing for those testing HIV negative, 90% of all diagnosed HIV-positive individuals should start ART and of these 90% should have an undetectable plasma viral load (90:90:90). The foreskin in males, rich in Langerhans cells, is an important portal of entry for HIV infection. Randomized trials in Africa have confirmed that the risk of acquiring HIV for heterosexual men is reduced by over half in circumcised men compared to uncircumcised men. Adult male circumcision, although not fully protective, may therefore be a valuable addition to HIV prevention programmes in resource-limited countries. A program in high burden settings to encourage voluntary medical male circumcision for HIV-negative men has been supported in many African countries although uptake and resources are limited. Male circumcision will not affect men who have sex with men due to the nature of sexual exposure. Large studies to assess the efficacy of vaginal microbicides in the prevention of sexually transmitted infections and HIV have been disappointing. However, a controlled study to assess the feasibility of using antiretroviral drugs for pre-exposure prophylaxis (PrEP) of sexually acquired HIV yielded promising results using tenofovir and emtricitabine in a daily single tablet. Four RCTs of combined tenofovir and emtricitabine as daily oral prescription have shown effectiveness of between 44 and 75%. The cost-effectiveness and appropriate use of PrEP remain to be determined and are influenced mostly by the cost of drug. New studies have explored alternative agents and routes for prevention that may avoid the need for daily oral dosing; these include monthly injectable agents as prevention, an integrase inhibitor injection (Cabotegravir) as well as infusions of monoclonal antibodies (AMP study HPTN085) or antiretroviral impregnated vaginal rings (Dapivirine). Mother-to-child transmission In the absence of intervention, mother-to-child transmission (MTCT) rates are approximately 25% in nonbreastfed infants (7% in utero and 18% intra-partum) and 40% in breastfed children. The numbers of children infected via MTCT, currently estimated at c.240 000 new infections per year (10–12% of total new infections) have dropped substantially since the advent of effective prevention to mother-to-child transmission (PMTCT) programmes. PMTCT started with the ACTG 076 study in 1994 reporting a 67% reduction in MTCT as a result of AZT monotherapy given through pregnancy and intra-partum, and to the infant for 6 weeks. More recently, all HIV-infected mothers receive ART throughout pregnancy and MTCT rates are down to 1–2% or lower. If viraemia is successfully suppressed by ART through

pregnancy to undetectable levels (<50 copies/ml plasma) transmission rates are zero. The current 1– 2% MTCT rate results either from a failure of HIV testing of the mother, or ART nonadherence, or acute maternal infection during pregnancy. HIV antibody tests are negative during peak viraemia (c.107 HIV copies/ml) and MTCT rates in these settings are 20%.

930 section 8 Infectious diseases In the absence of ART, post-partum transmission through breast-feeding carries the risk of MTCT as described. In resource-limited settings, prior to ART being indicated for all HIV-infected mothers, breastfeeding for 6 months was still recommended because the sub-stantial nutritional and immunological benefits outweighed even the increased risk of HIV infection in the infants. Blood products Screening of blood products began as soon as testing for HIV be- came available, and heat treatment for factor VIII concentrate was also introduced. These measures dramatically reduced the risk of virus transmission by blood and blood products in industrialized countries. However, there may still be a problem in resource-limited countries where screening is not efficient, or where the background seroprevalence of potential donors is so high that HIV-infected blood may be screened as negative when donated by an individual in the ‘window period’ immediately after initial infection (see ‘Diagnosis of HIV infection’, earlier). Injecting drug use Needle exchange programmes and the prescription of controlled drugs to registered addicts can reduce the incidence of new HIV infections in injecting drug users. Major problems still exist in countries such as India and Russia, where injecting drug use is more common and education about the risk and the availability of clean needles is very limited. Occupational exposure and postexposure prophylaxis Based on data from more than 3000 occupational exposures to HIV, the average risk of HIV infection after needlestick injury or other percutaneous exposure was calculated to be 0.3% (about 1 in 325). The risk following mucous membrane exposure has been es- timated to be around 0.1%. The risk of transmission is greatest for deep injuries, if there is visible blood on the device, during proced- ures involving direct cannulation of blood vessels or if the source patient has advanced HIV disease. A small retrospective case-con- trol study demonstrated an 80% reduction in the likelihood of seroconversion in healthcare workers who took zidovudine soon after percutaneous exposure to HIV. In view of the greater activity of antiretroviral drug combinations but without direct evidence, it is currently recommended that high-risk occupational exposures to HIV are treated as soon as possible with two nucleoside inhibi- tors and an integrase inhibitor (such as tenofovir, emtricitabine, and raltegravir) for 1 month. Nevirapine is not recommended in postexposure prophylaxis regimens because of a relatively high rate of adverse reactions. A careful risk assessment should be done, and if a significant risk of HIV transmission is identified, antiretroviral therapy should be offered and started promptly to maximize the chance of success. Following possible sexual exposure to HIV, antiretroviral therapy may reduce the risk of seroconversion, but there are no random- ized studies to confirm this. A comparative study in men who have sex with men in Brazil reported that individuals who took antiretro- viral therapy after sexual intercourse were less likely to acquire HIV infection (0.6% vs. 4.2%). Unprotected receptive anal intercourse (including sexual assault) is associated with the greatest risk (esti- mated up to 3%). After possible sexual exposure to HIV, a risk as- sessment is recommended and antiretroviral therapy should be offered if a significant risk is identified. Treatment should be started as soon as possible and is unlikely to be effective if started more than 72 h after exposure. PEP is no longer recommended for individuals where the exposure is with a known HIV-positive partner on fully suppressive ART as the risk of HIV acquisition remains very low. Vaccine development The high degree of viral variation and immune escape present dif- ficulties for the development of an effective preventive HIV vac- cine. Nonetheless, group-specific

neutralizing antibodies have been identified. In particular, there is evidence that broad CD8+ T-cell responses directed against the relatively invariant, internal p24 Gag 'capsid' protein can be successful in achieving durable immune control of HIV at very low or undetectable (below 50 HIV RNA copies/ ml plasma) levels. Current vaccine efforts are therefore focused principally on inducing broad CD4+ and CD8+ T-cell responses against HIV. These responses, however, would be expected to control rather than eliminate the virus altogether, and might lead to disease modification rather than complete prevention. Although a vaccine capable of inducing broadly neutralizing antibodies against the range of HIV variants would eliminate the virus, no antigen capable of doing so has been identified to date. So far, noninfectious killed whole virus or recombinant subunit vaccines have not been successful in protecting chimpanzees from HIV infection, or macaques from SIV infection and disease. Certain live attenuated strains of SIV, with deletion mutations in *nef* and other regulatory genes, initially appeared to protect adult monkeys from challenge with virulent SIV strains, but subsequently were reported to cause AIDS in neonatal macaques. Human testing of candidate HIV vaccines, including a vaccine made from recombinant fragments of gp120, the surface glycoprotein of HIV that binds to host cell CD4 receptors, has so far not been successful. Large phase III trials in Thailand and the United States of America involving over 5000 uninfected high-risk volunteers showed no protection by a vaccine using recombinant gp120 (VaxGen) that had produced good neutralizing antibodies in pilot studies. Several new approaches are being examined, which may prove more effective in inducing protective humoral and killer T-cell-mediated immunity. These include DNA vaccines, consisting of pieces of HIV DNA incorporated into harmless plasmid DNA from bacteria, and the use of live vectors (e.g. poxviruses such as canarypox and modified vaccinia) to deliver portions of the HIV envelope. A common approach now is to use a 'prime-boost' strategy whereby a DNA vaccine dose is given, followed by a boosting with the DNA incorporated in a vector, such as modified vaccinia. One of the most potent vaccines uses a replication-incompetent adenovirus type 5 as the vector. However, a phase IIb efficacy trial (STEP/HVTN 502) using the adenovirus type 5 vector with *gag*, *pol*, and *nef* genes was stopped prematurely. Not only was no efficacy shown, but there was evidence that those already immune to human adenovirus from natural infection were more likely to become infected by HIV. The reasons for this are not clear, but the National Institutes of Health has stopped or paused other trials using adenovirus vectors as a result. Trials with canarypox and other vectors continue. This approach, using DNA vaccines to stimulate CD8+ responses, is also being evaluated for therapeutic vaccination in

8.5.23 HIV/AIDS 931 HIV-positive patients with suppressed viraemia who are being treated with antiretroviral agents, to determine if vaccination will allow interruption of treatment without loss of virological control. Effective vaccination is likely to hold the greatest promise for controlling HIV infection in the future, but experience to date would indicate that researchers continue to face a formidable challenge. HIV cure While ART has dramatically altered the clinical course of disease and markedly improved survival, ART alone is unable to cure HIV infection. This is a function of an inaccessible pool of latently infected cells, where viral DNA is incorporated into host cell genome. These latently infected cells, termed the HIV reservoir, represent the current barrier to a cure for HIV. There is no evidence that ART alone can ever achieve eradication or 'cure' of HIV. Although HIV may be undetectable in plasma for many years, this long-lived reservoir of infectious virus can be recovered from latently infected (resting) memory CD4 lymphocytes. The half-life of this cell population is long, about 6 months, and it is not known whether HIV can ever be eradicated from this infected cell line. Other compartments exist that are relatively inaccessible to drugs—for

example, in the central nervous system, retina, and testes—and unless viral replication can be successfully prevented at such sites there is also the risk of reinfection of compartments previously cleared by therapy. One pool of latently HIV-infected cells is the gut associated lymphoid tissue which, irrespective of the route of viral transmission, are the first cells infected and remain the largest source of reservoir cells. Recent data suggest that despite plasma viral levels remaining below the limit of detection (<20 copies HIV RNA/ml) on ART, there can be very low level ongoing viral replication (to 1 copy/ml) and for this reason despite years of successful viral suppression cessation of ART is invariably accompanied by viral rebound in the vast majority of individuals. People rapidly initiating ART around the time of acute infection have a much smaller HIV reservoir than individuals starting treatment after years of uncontrolled viral replication. In addition, early treatment, before any significant immune damage has occurred enables normalization of immune function. Among such treated acute HIV-infected individuals there appears to be a greater chance of spontaneous viral control after stopping therapy; so-called viral remission or posttreatment control. Even so, stopping therapy is not recommended given that in most individuals viral recrudescence occurs within 4–8 weeks, and its associated risk of onward transmission and potential increase in inflammatory mediated complications. The Berlin patient There is to date only one man who has been successfully cured of HIV infection; Timothy Brown, the so-called Berlin patient. Having received successful ART for many years with an undetectable HIV plasma viral load he was diagnosed with acute myeloid leukaemia. As treatment for the leukaemia he underwent total body irradiation (including head), chemotherapy, and bone marrow transplantation with homozygous delta-32 base pair deletion in the CCR5 gene from the donor bone marrow. He then experienced graft vs. host disease, relapse of the acute myeloid leukaemia, and the entire process was repeated using a second transplantation from the same Δ32 donor. Subsequently he stopped ART and remained with an undetectable viral load throughout follow up (Fig. 8.5.23.15). Despite multiple large blood sampling, tissue biopsies (including brain) there has been no evidence of HIV DNA or RNA from any site. Therefore, by all available assays, he is cured of HIV infection.

	107	800	100	200	300	400	500	600	101	102	103	104	HIV-1 RNA (cop/ml)	CD4+ T-cells (μl)	
June '06	HIV DNA	env	HIV DNA	LTR	ART	AML diagnosis	AML relapse	2nd allogeneic transplantation	1st allogeneic transplantation	100% chimerism	Limit of detection	Oct '06	Feb '07	Mar '07	Jul '07
Jan '08	Mar '08	Jan '11	105	106	ART	CD4+ T cell count	HIV-1 RNA	Fig. 8.5.23.15 The Berlin patient.							

Adapted from Hütter G et al. (2009). Long-Term Control of HIV by CCR5 Delta32/Delta32 Stem-Cell Transplantation. NEJM, 360, 692–8.

932 section 8 Infectious diseases Several other bone marrow transplant recipient cases have attempted to replicate this initial cure case. None, however, have been successful and viral recrudescence after ART cessation has in most cases been rapid. What represent the key differences between these cases and Timothy Brown is unclear but might be the graft-versus-host disease experienced by Timothy Brown that was not a key feature of other cases. Data from primate experiments point to the fact that for the Berlin patient, either the genetic mutation of the bone marrow donor or the graft-versus-host disease 'played a significant role', in the ultimate cure. Viral remission Since a sterilizing cure for HIV (as seen with Timothy Brown) seems highly unlikely and certainly not scaleable, the concept of a 'functional cure' for HIV, such as used in describing cancer, has been sought. In this scenario, while it is anticipated that detection of viral genome may still be the case, the patient remains aviraemic off ART with preserved immune function (in terms of normal CD4 count, CD4:CD8 ratio). Such cases of viral remission have been reported among very early treated infected infants and treated acute infections where therapy was subsequently stopped. In both groups, viral detection in terms of HIV reservoir (total HIV DNA) from blood and

tissues, as well as very sensitive low copy viraemia from plasma, is still possible but using standard diagnostic viral load tests these remain below the limit of detection off ART. Such cases remain rare but suggest that very early ART may limit the size of the HIV reservoir to such a low level and enable normalization of the immune system that allows spontaneous control of viral replication off therapy. Interventions to activate and eliminate viral reservoir towards HIV remission CD4 bearing cells containing incorporated HIV DNA are the key barrier to a cure for HIV. While ART is highly effective at blocking ongoing viral replication and further infection of uninfected cells, it is unable to remove viral DNA that is present within quiescent resting CD4 cells. These cells, termed the reservoir of HIV latent infection, or their progenitor cells potentially survive the lifetime of an infected individual and for most individuals, despite years of viral suppression, represent the source of rebounding virus when therapy is stopped. Removal or reduction in the frequency of such HIV-infected viral reservoir cells is the goal of any novel 'cure' intervention. A concept termed 'Kick and Kill' is currently under investigation in small 'pilot proof of concept' studies. Here agents that reverse viral latency, which include histone deacetylase inhibitors, immune activators, or monoclonal antibodies act to 'kick' viral replication and the 'kill' aspect of the approach is usually undertaken by targeted primed HIV-specific immune responses, driven by therapeutic vaccination (Fig. 8.5.23.16). FURTHER READING Abdool Karim SS, et al. (2010). Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*, 362, 697–706. Altfeld M, Goulder P (2007). 'Unleashed' natural killers hinder HIV. *Nat Genet*, 39, 708–10. Appay V, Kelleher AD (2016). Immune activation and immune ageing in HIV infection. *Curr Opin HIV AIDS*, 11, 242–9. Anti-CD3 + anti-CD28 co-stimulation IL-2 IL-7 Prostratin HDAC inhibitors Other molecules Integrated provirus Translation and virion assembly mRNA splicing and nuclear export Transcription HIV antigen loading into MHV class I Budding and maturation HIV Env HIV-specific cytotoxic CD8+ T cell Activating latent virus is a necessary step in many HIV cure strategies Cytotoxic molecules induce cell lysis Productively infected CD4+ T cell Latently infected CD4+ T cell Fig. 8.5.23.16 HIV cure 'kick and kill'—various strategies might be invoked to activate latently infected T cells so that drugs and vaccine-induced CD8+ cytotoxic T cells can act to eliminate the infected cell and virus. Adapted with permission of Future Medicine Ltd from Marsden MD and Zack JA (2009). Establishment and maintenance of HIV latency: model systems and opportunities for intervention. *Future Virology*, 5(1), 97–109; permission conveyed through Copyright Clearance Center, Inc.

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