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 therapy, but remains shorter than in high-income countries. For people initiating HIV care with advanced disease, early mortality re- mains high. More work is needed to improve coverage of HIV testing among asymptomatic people, along with effective

linkage to and re- tention in care. Prevention—this requires political commitment to creating an environment that supports education about HIV, prevents stigma and discrimination, and protects the rights of key populations such as sex workers, men who have sex with men, transgender people, and people who inject drugs. Despite overall reduced HIV incidence since the late 1990s, the goal of preventing HIV transmission re- mains elusive in many settings, with HIV incidence rates highest among key populations; gay men and other adolescents, and young women. Major recent advances in HIV prevention science have been demonstration of the powerful preventive effect of antiretroviral therapy through viral load suppression in HIV-positive individuals, thus reducing infectiousness, and in the form of pre- exposure prophylaxis in HIV-negative people. Universal testing of pregnant women linked to lifelong antiretroviral therapy can al- most eliminate mother-to-child transmission. Prevention interventions for general populations should include information and education; promotion of partner reduction and of condoms, which are highly protective against sexual transmission if used correctly and consistently; and encouragement of universal knowledge of HIV serostatus. Targeted interventions should be fo- cused on groups and situations in which HIV transmission is most intense, guided by local epidemiology. Male circumcision has a pro- tective efficacy of almost 60% against heterosexual acquisition of HIV infection in men, but other methods of prevention must still be promoted among circumcised men. No vaccine is available.
Epidemiology The 2018 report from the Joint United Nations Programme on HIV/ AIDS (UNAIDS) and the World Health Organization (WHO) esti- mated that, in 2017, 36.9 million (range 31.1–43.9 million) people were living with human immunodeficiency virus (HIV) infection worldwide. This global pandemic comprises a mosaic of local epi- demics, each with its own characteristics. Variation, both between regions and between groups of individuals affected within one re- gion, is one of the pandemic's striking features. Broadly, there are two patterns: generalized epidemics, established in the general population in most countries in sub-Saharan Africa; and concen- trated epidemics, in specific populations in most other regions. Local epidemiology depends on the relative contribution of the three major routes of HIV transmission to incidence: sexual contact (heterosexual and homosexual); mother-to-child; and exposure to blood or blood products; mortality; and the effect of antiretroviral therapy (ART) on both incidence and mortality. Within sub-Saharan Africa, there have been substantial regional differences in the evolution of the epidemic. The main route of transmission is sex between men and women. Among key populations at increased risk are gay men and other men who have sex with men (MSM), among whom HIV epidemics are expanding in many countries despite falling in- cidence overall. Other key populations include people who inject drugs, and transgender people and, depending on local contexts, migrants, prisoners, and specific occupational groups, such as truck drivers and fisher folk. The HIV epidemic has been most severe in southern Africa; adult HIV prevalence in some parts of southern Africa is almost 30%. The reason for regional differences is not fully understood, but likely contributors include behavioural factors such as young age of sexual debut in women, age-disparate relationships, and transactional sex; biological risk factors including herpes simplex virus type 2 (HSV-2) infection, and lack of male circumcision; and structural factors such as labour migration. Global HIV incidence peaked in the mid-1990s, and has subsequently declined, but the decline is too slow to meet global targets. In 2017, there were an estimated 1.8 million new infections, of which 980 000 were in sub-Saharan Africa. The reduction in HIV incidence is attributed to a range of reasons including maturation of the epidemic; successful prevention campaigns, particularly the prevention of mother-to-child transmission (estimated to have prevented 1.4 million infections between 2010 and 2017); and behaviour change; high mortality among HIV-positive people likely also contributed. HIV prevalence among young people has fallen

in many, but not all, high-prevalence countries, reflecting this reduc- tion in HIV incidence. Adolescent girls and young women remain at disproportionately high risk of acquiring HIV in high prevalence settings such as eastern and southern Africa. In 2017, global deaths due to HIV were estimated at 940 000, and in sub-Saharan Africa at about 570 000; these have fallen since 2006, as ART coverage has increased. The total number of people living with HIV is increasing, reflecting ongoing incidence combined with reduced mortality as ART coverage increases. Prevention of new infections remains the key to controlling the epidemic. Understanding the local epi- demiology, and the performance of treatment and prevention pro- grammes, is essential to guide prevention and control efforts. Prevention Prevention of HIV infection requires political commitment to create an environment that supports education and openness about HIV; prevents punitive laws, stigma, and discrimination; and protects the rights of key populations most at risk for HIV. Involvement of civil society and those living with HIV is especially important. A series of randomized controlled trials, including HPTN 052, START, and several trials of pre-exposure prophylaxis (PrEP), have fundamentally changed the prevention and treatment landscape. HPTN 052 showed that ART reduced heterosexual transmission from an HIV-positive individual to his/her sex partner by 96%. START demonstrated a 57% reduction in severe disease or death in HIV-positive people initiating ART at a CD4 count above 500 cells/μl as opposed to deferring therapy. Several studies in different populations at risk have shown that antiretroviral drugs in the form of PrEP are effective in protecting HIV-negative persons from ac- quiring HIV, although adherence has been a challenge. In 2014 UNAIDS introduced the concept of ‘90:90:90’, aiming to diagnose 90% of persons living with HIV; assuring that 90% of those receive ART; and ensuring 90% of those on ART are vir- ally suppressed. Most recent guidelines from WHO recommend PrEP for groups in which annual HIV incidence is 3% or higher. ‘Combination prevention’ incorporates HIV testing, ART, and PrEP

 as appropriate, behaviour change including partner reduction and correct and consistent use of condoms, male circumcision for men at heterosexual risk, harm reduction for people who inject drugs, and structural interventions. Prevention of sexual transmission The traditional approach has been that of ‘ABC’, standing for Abstinence, Being faithful, and using Condoms if neither abstinent nor monogamous. While abstinence is an appropriate recom- mendation for the youngest age group, there is no evidence that abstinence promotion or education are effective as broader strat- egies. Reduction in the number of sexual partners and avoidance of concordant partnerships are important. Correct and consistent use of condoms is highly protective against acquiring HIV infection, but is difficult to sustain in long-term relationships. Since HIV- positive people aware of their HIV status tend to alter their behav- iour to prevent transmission to others, promoting knowledge of HIV status is important. Concomitant sexually transmitted infec- tions can increase infectiousness as well as susceptibility to HIV, so screening and treatment for sexually transmitted infections should be enhanced. HPTN 052, a randomized trial of immediate ART for the HIV- positive partner in discordant couples where the HIV-positive partner had a CD4 count of 350–550 cells/μl, found a 96% reduc- tion in HIV transmission to the HIV-negative partner. START was a randomized trial comparing immediate vs. deferred ART among HIV-positive people with CD4 greater than 500 cells/μl, and showed a 57% reduction in severe events or death with early treat- ment. Therefore, not only does early ART have prevention benefit, it also benefits individual health. In consequence, and analogous to how we approach syphilis or tuberculosis control, diagnosing and treating persons with HIV are now key priorities and cen- tral to management and prevention of HIV/AIDS. Studies are in progress to assess the impact of early ART on HIV incidence at population level.

Different studies have confirmed the efficacy of oral tenofovir alone or in combination with emtricitabine as PrEP in preventing HIV acquisition among HIV-negative MSM, people who inject drugs, discordant couples, and young heterosexuals. The effective- ness of PrEP is associated with adherence; lack of adherence being the likely explanation for negative findings in two studies among African women. The first study of a tenofovir-based vaginal gel using a pericoital dosing schedule provided 39% protection from HIV ac- quisition. As with oral PrEP, efficacy requires adherence. Extensive research is underway and planned of different dosing schedules, oral and topical PrEP regimens using different drugs, longer-acting injectable agents and sustained release delivery systems, and rectal preparations. Although genital herpes is a risk factor for HIV transmission and acquisition, clinical trials of herpes suppressive therapy have not shown that this intervention reduces HIV incidence. Currently there is no vaccine against HSV-2. Voluntary medical male circumcision has a protective efficacy of almost 60% against heterosexual acquisition of HIV infection in men. The once-only nature of this intervention, its independence from adherence, and its sustained efficacy make it an important public health intervention. Prevention benefit to women is in- direct, there being no evidence of reduced HIV transmission from HIV-positive circumcised men. Medical devices have been intro- duced which can replace surgery for male circumcision, although their uptake has been limited. Complication rates from surgery or devices have been low, and include infection, haemorrhage, and penile deformity. There have been occasional reports of tetanus, usually following unsterile dressing of the surgical wound. Uptake of voluntary medical male circumcision has been greater in East than in southern Africa. Key populations may benefit from special services tailored to their needs in specific venues or using outreach approaches, avoiding stigmatization and healthcare worker disapproval that all too often characterize public healthcare settings. A particular challenge is HIV prevention in adolescents and especially girls and young women, particularly in sub-Saharan Africa. Social grant programmes incorporating cash transfers aim to reduce pressure for transactional sex, older sex partners, teenage preg- nancy and early marriage, and school drop-out. While increased education generally reduces high-risk behaviour in young women, the impact of such programmes on HIV incidence has been mixed. For sex workers and their clients, correct and consistent condom use, and prompt diagnosis and treatment of other sexually trans- mitted infections must be promoted. Important interventions for MSM include HIV counselling and testing, access to correct and consistent condom use and lubricants, and addressing drug use that might lead to unsafe behaviour. The quest continues for an effective HIV vaccine. Prevention of transmission by injecting drug use The public health approach emphasizes harm reduction, whose es- sentials include information and education; access to HIV testing, ART, and PrEP; needle and syringe programmes; treatment for drug dependence including opioid substitution therapy; clin- ical services for associated conditions such as viral hepatitis and skin infections; and interventions to prevent sexual transmission of HIV. Prevention of transmission through blood, blood products, and nosocomial exposures Although eliminated in high-income countries, transmission of HIV by blood transfusion remains a possibility in many countries. Basic measures to prevent transfusion-transmitted HIV include appropriate management of conditions predisposing to the need for transfusion (such as childbirth and malaria), and avoidance of all but essential transfusions. Family and paid donors should be avoided in favour of regular, low-risk donors. All blood destined for transfusion should be screened for HIV, syphilis, and hepatitis B and C and, as far as possible, obtained from centralized services that can assure safe blood. Preventive measures against nosocomial transmission include universal precautions, which treat all body fluids as potentially infectious. Exposure-prone procedures might require other pro- tection in addition to gloves such as masks, gowns, and goggles. Injection safety

requires absolute avoidance of re-use of nee- dles and syringes, and assurance of their safe use and disposal. Healthcare institutions require policies concerning availability of postexposure antiretroviral prophylaxis following occupational exposure.

936 section 8 Infectious diseases Prevention of mother-to-child transmission In industrialized countries, combination ART for pregnant women, elective caesarean section if necessary, and avoidance of breast- feeding have rendered perinatal HIV transmission very rare. A four- pronged integrated approach in low- and middle-income countries, promoted by United Nations agencies, includes primary prevention of HIV infection in girls and young women, prevention of unin- tended pregnancy in HIV-positive women, interventions to prevent transmission of HIV from positive women to their offspring, and diagnosis and care of HIV-positive infants and their mothers. HIV testing should be recommended to all pregnant women. Until 2012, recommendations for preventing mother-to-child transmission offered complex alternatives for maternal and infant prophylaxis, so-called Options A and B. A proposal from Malawi that rapidly became adopted, 'Option B+', recommended immediate and lifelong combination ART for all pregnant women, offering simplicity, protection against transmission during breastfeeding, and protection during subsequent pregnancies. WHO guidelines re- commending ART for all HIV-positive persons also cover pregnant women, who should initiate ART upon diagnosis during pregnancy or breastfeeding and continue it lifelong. Infants born to HIV- positive women should receive 6–12 weeks of prophylaxis using AZT and/or nevirapine according to WHO guidelines. In countries where HIV-positive mothers are recommended to breastfeed; exclu- sive breastfeeding for six months is recommended with introduction of complementary food thereafter; breastfeeding should continue to 12 months, with gradual weaning over one month. Clinical features Acute HIV disease Symptoms associated with primary HIV infection are described in Chapter 8.5.23. Although rarely specifically diagnosed, HIV pri- mary infection is important to consider in the differential diagnosis of an acute febrile illness, particularly in high-prevalence settings. In a study of women in Kenya, the most common symptoms reported by those newly infected were fever, headache, fatigue, and arthralgia, whereas the most strongly associated clinical features were lymph- adenopathy, vomiting, diarrhoea, and fever. Progression from HIV infection to symptomatic disease Data from representative cohorts of people with well-defined dates of seroconversion show that the progression of HIV disease from primary infection to the stage of advanced immunosuppression in low- and middle-income countries is little different from that ob- served in the pre-ART era in high-income countries. Once people reach the stage of advanced immunosuppression, survival is likely to be shorter than in high-income countries if they do not have ac- cess to ART and interventions to prevent and treat opportunistic infections. Symptomatic HIV disease HIV-positive people experience much higher incidence of diseases caused by pathogens common in low- and middle-income countries, such as tuberculosis, pneumococcal disease, and nontyphoidal sal- monella, compared to their HIV-negative counterparts. Tuberculosis is often the first manifestation of HIV disease, although by the time they present with tuberculosis, about half of HIV-positive people will already have a CD4 count below 200 cells/μl. Other early pre- senting symptoms of HIV disease are skin conditions such as gen- eralized pruriginous dermatitis (prurigo) and herpes zoster, both of which have a high positive predictive value for underlying HIV in- fection among populations with high HIV prevalence. Advanced HIV disease When HIV-positive people reach the stage of advanced immuno- suppression, the spectrum of disease varies by geographical re- gion. Tuberculosis, bacterial infections due to pathogens such as Streptococcus pneumoniae, and cryptococcal disease are common worldwide. Disease due to nontyphoidal salmonella species might be more common

where sanitation is poor. Pneumocystis pneu- monia is relatively common in Asia and South Africa but in many countries in sub-Saharan Africa it is less common as a cause of severe respiratory symptoms than bacterial infections and tuber- culosis, perhaps because disease due to these more common patho- gens occurs earlier in the course of HIV disease. The frequency of cerebral toxoplasmosis varies by region, influenced particularly by consumption of undercooked meat. Exposure to some opportun- istic infections is geographically limited. Talaromycosis (formerly penicilliosis), caused by Taralomyces marneffei, is largely confined to Southeast Asia and southern China (Chapter 8.7.6), and exposure to Trypanosoma cruzi, which can reactivate, most often causing cere- bral lesions, is largely restricted to the Americas. Diseases charac- teristic of very advanced immunosuppression, such as those due to cytomegalovirus and Mycobacterium avium intracellulare, have been rare in many low- and middle-income countries, probably be- cause survival with advanced disease in the absence of ART is short. Despite increasing ART coverage, many HIV-positive people still present with advanced disease, and the spectrum of disease among HIV-positive people admitted to hospital continues to reflect ad- vanced immunosuppression, with tuberculosis and severe bacterial infections the leading causes of admission and in-hospital mortality. Tuberculosis (Chapter 8.6.25) Tuberculosis is the most important cause of HIV-related severe morbidity and mortality in low- and middle-income countries. It results both from reactivation of latent infection as well as rapid pro- gression following new or re-infection. Molecular epidemiological studies show that new infections are an important mechanism of recurrence, which is common in HIV-positive people. The diagnosis of tuberculosis is more challenging in low- and middle-income countries. HIV-positive people with tuberculosis are less likely to have symptoms typical of pulmonary disease and to have smear-negative sputum, making the diagnosis harder to con- firm, especially in settings where the main diagnostic test is sputum microscopy. This is a particular problem for people with advanced immunosuppression, where a delay in initiating tuberculosis treat- ment may be fatal. Sputum culture is more sensitive than micros- copy, particularly if liquid culture media are used, but in many low- and middle-income countries facilities for mycobacterial cul- ture are very limited. An automated, nucleic acid amplification-based assay (Xpert MTB/RIF, described in detail in Chapter 8.6.25), which is more

 sensitive than microscopy and provides rapid diagnosis of rifam- picin resistance, is recommended by WHO for HIV-positive people with symptoms suggesting tuberculosis. However, implementation of Xpert MTB/RIF has not improved outcomes for patients with drug-susceptible tuberculosis. In South Africa, where Xpert MTB/ RIF has replaced microscopy as the first test for tuberculosis, the expected increase in tuberculosis case notifications has not been seen in practice, probably because Xpert has provided bacterio- logical confirmation among people who were previously treated for tuberculosis on clinical criteria. Xpert MTB/RIF is increasingly used as the initial test for all people with symptoms suggesting tu- berculosis; however, logistical barriers and cost limit its use in primary care settings. A low-cost lateral flow assay which detects lipoarabinomannan (LAM), a component of the mycobacterial cell wall, in urine has a role in the diagnosis of tuberculosis among hos- pitalized HIV-positive people with advanced immunosuppression. Its low sensitivity among other patient groups limits its wider use. A sensitive, low-cost test for tuberculosis which can be used in pri- mary care settings remains an urgent priority. A particular challenge is posed by drug-resistant tuberculosis. Extensively drug-resistant tuberculosis (defined as resistance to at least rifampicin, isoniazid, any quinolone, and one of the injectable agents: amikacin, capreomycin, or kanamycin) has been identified in every world region. The seriousness of this issue was highlighted by a nosocomially-transmitted outbreak

of extensively drug-resistant tuberculosis in South Africa, identified in 2005–6 in an HIV care facility, with high case fatality. The problem of drug-resistant tubercu- losis is made worse by the paucity of facilities for drug-susceptibility testing in most countries that carry the highest burden of tubercu- losis, making rapid appropriate treatment, and interruption of trans- mission, challenging. Xpert MTB/RIF allows rapid identification of rifampicin resistance, and if widely used will identify more people with drug-resistant tuberculosis, but outcomes for patients will only improve if they can access, and complete, effective treatment. Major gaps persist between the estimated number of people who develop drug-resistant tuberculosis and those who start treatment, and treatment outcomes remain poor. There remains an urgent need for more accessible diagnostic tests for drug resistance, more effective and more tolerable treatment for people with drug-resistant tuberculosis, better linkage to HIV care for HIV-positive people with tu- berculosis, and better infection control in health facilities to prevent nosocomial transmission to both patients and staff. The WHO strategy to reduce the burden of tuberculosis com- prises the so-called ‘three Is’: intensified case-finding, isoniazid pre- ventive therapy, and infection control. As part of intensified case finding, HIV-positive people should be screened for tuberculosis at every clinical encounter, based on reporting any of cough, weight loss, night sweats, or fever. Screening is particularly important for people newly diagnosed HIV positive, among whom the prevalence of active tuberculosis is particularly high. The four-symptom screen has high negative predictive value for active tuberculosis. Those without symptoms might benefit from isoniazid preventive therapy for six months, or potentially lifelong if a test for latent tuberculosis infection is positive. ART reduces the risk of a new tuberculosis epi- sode, although the risk remains high, particularly among those with low CD4 counts. All people with newly diagnosed tuberculosis should know their HIV status, because in some settings more than 70% will be HIV-positive, and should receive ART and co-trimoxazole prophy- laxis. For patients whose HIV-positive status is diagnosed at the time of a tuberculosis episode, WHO guidelines recommend that tuber- culosis treatment should be started first, followed by ART as soon as possible afterwards, regardless of the CD4 count. Randomized controlled trials suggest that people with newly diagnosed HIV- associated tuberculosis and CD4 less than 50 cells/μl are most likely to benefit from early initiation of ART, within two weeks of initiation of tuberculosis treatment. Among individuals with tuberculous meningitis, data from one trial showed no survival benefit from im- mediate vs. deferred ART, and further data are needed to determine the optimum timing of ART initiation for these patients. Interaction between HIV infection and ‘tropical’ diseases Malaria (Chapter 8.8.2) In areas of year-round (stable or holoendemic) malarial transmis- sion, studies from Uganda and Malawi suggest that HIV infection impairs acquired immunity to falciparum malaria, resulting in in- creased frequency of malarial parasitaemia and clinical malaria among adults and older children proportional to the degree of im-munosuppression, but no increase in severe or complicated malaria. However, HIV-positive infants in a holoendemic area of Kenya were at increased risk of severe anaemia and hospitalization for malaria. In studies from South Africa of nonimmune adults and older children resident in areas of intermittent (low or unstable) malaria transmis- sion, HIV-positivity was associated with an increased risk of severe and fatal falciparum malaria, inversely proportional to their CD4 counts. In HIV-positive pregnant women, the beneficial effects of parity on severity of malaria are attenuated, and their peripheral and placental parasitaemia, and risk of suffering an episode of malaria or anaemia during pregnancy, are increased. Among HIV-positive pregnant women, malaria is associated with an increased risk of low birth weight, preterm birth, intrauterine growth retardation, and postnatal infant mortality. ART and co-trimoxazole reduce the risk of febrile malarial episodes. HIV-positive people in malaria- endemic areas should sleep under insecticide-

treated bed nets, and nonimmune people travelling to malarial areas should use bednets and take antimalarial chemoprophylaxis. In malaria-endemic areas, HIV-positive pregnant women should take either continuous co- trimoxazole or intermittent preventive therapy to prevent adverse malaria outcomes in infants. In malaria-endemic areas, HIV-positive people who develop fever should be investigated for other causes in addition to malaria; those taking co-trimoxazole prophylaxis should not be given pyrimethamine with sulfadoxine as malaria treatment or seasonal malaria chemoprophylaxis. ART might interact with antimalarial drugs (see http://www.hiv-druginteractions.org). In particular, artesunate plus amodiaquine is more likely to cause se- vere neutropaenia in HIV-positive people, particularly if they are taking zidovudine or co-trimoxazole, and these combinations should be avoided if possible. Amodiaquine should also be avoided among people taking efavirenz because of increased risk of hepatotoxicity. Leishmaniasis (Chapter 8.8.13) The HIV epidemic led to localized increases in visceral leishmaniasis, predominantly in people with CD4 counts below 200 cells/µl, particu- larly among injecting drug users around the Mediterranean; in the

 northeast of Africa (Ethiopia and Sudan); Brazil; and India. Wider use of ART has resulted in declining numbers of coinfected cases in some areas. In HIV-positive people, visceral leishmaniasis most often pre- sents classically with fever, hepatosplenomegaly, and pancytopenia, although presentations range from asymptomatic to multiorgan in- volvement. The treatment of choice is liposomal amphotericin B, but treatment outcomes are less good for HIV-positive compared to HIV-negative people. Amphotericin B deoxycholate or sodium stibogluconate are much less satisfactory. Observational studies sug- gest that combination treatment, such as with liposomal amphotericin B and miltefosine, might be effective; a trial comparing this combin- ation to liposomal amphotericin B alone is in progress among HIV- positive people in Ethiopia. ART is important to reduce mortality and risk of relapse, and expert opinion supports early ART initiation. Relapse remains common, and secondary prophylaxis is needed, al- though there is no trial-based evidence to support choice of regimen. Cutaneous leishmaniasis can present with atypical skin lesions, which might be disseminated and can recur after treatment. Trypanosomiasis (Chapters 8.8.11, 8.8.12) Asymptomatic infection with Trypanosoma cruzi can reactivate to cause Chagas disease in the context of advanced HIV disease, most often resulting in meningoencephalitis or cerebral mass lesions. Myocarditis is common at autopsy, although rarely apparent clin- ically. Screening of HIV-positive individuals from endemic areas is recommended: early ART is important to prevent reactivation of chronic disease. There is no evidence of an interaction between human African trypanosomiasis and HIV infection, although re- ports suggest high mortality among HIV-positive patients treated for central nervous system disease. Helminths There is little evidence of interaction between intestinal nematodes and HIV infection; the expected association with Strongyloides ster- coralis hyperinfection has not been observed, although it is common with another retroviral infection, human T-lymphotropic virus (HTLV-1) (Chapter 8.5.25). HIV infection does not affect the man- agement of onchocerciasis, although skin disease may be more se- vere. Data concerning an association between Wuchereria bancrofti infection and HIV infection are inconsistent. There is no consistent association between Schistosoma mansoni infection and HIV; how- ever female genital schistosomiasis is reported to be associated with HIV infection and could facilitate HIV transmission. Atypical forms of neurocysticercosis, such as giant brain cyst and spinal epidural lesions, are reported. Fungi People with advanced HIV disease are at risk of systemic fungal in- fections. Cryptococcal disease and histoplasmosis (which, based on clinical features, might be mistaken for tuberculosis) are found

worldwide. Others have restricted geographical distribution, such as talaromycosis in Southeast Asia and China. Paracoccidioidomycosis (Paracoccidioides brasiliensis infection—Chapter 8.7.4), is the most common invasive fungal infection in South America, but reports of coinfection with HIV are less common. There is no evidence of important interactions between HIV in- fection and typhoid fever, melioidosis, amoebiasis, or giardiasis. Leprosy might be unmasked by ART as an immune reconstitution phenomenon. Clinical staging of HIV disease Given limited laboratory facilities in some settings, HIV viral load es- timation and CD4 counts are not always available. A system designed to estimate HIV disease stage based on clinical symptoms, modified by CD4 count if available, was published by WHO in 1990 and re- vised in 2006 (Table 8.5.24.1). This has been widely used in resource- constrained settings to guide when to start ART. As countries move towards 'test and start', clinical staging will be less important, but re- mains a guide to prognosis where CD4 counts are not available. The 'cascade of care' The cascade of care concept has gained popularity as a way to illustrate, at population level, the proportion of HIV-positive people at different stages of accessing care and treatment (Fig. 8.5.24.1). This concept is Table 8.5.24.1 WHO clinical staging system for adults and adolescents with confirmed HIV infection WHO clinical stage Defining conditions 1 Asymptomatic Persistent generalized lymphadenopathy 2 Unexplained moderate weight loss (<10%) Recurrent respiratory tract infections Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruption Seborrhoeic dermatitis Fungal nail infections 3 Unexplained severe (>10%) weight loss Unexplained chronic diarrhoea (>1 month) Unexplained persistent fever (>1 month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 109/l) or thrombocytopaenia (<50 × 109/l) 4 HIV wasting syndrome Pneumocystis pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (>1-month duration) Oesophageal candidiasis Extrapulmonary tuberculosis Kaposi's sarcoma Cytomegalovirus infection Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis Disseminated nontuberculosis mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (extrapulmonary histoplasmosis or coccidioidomycosis) Recurrent septicaemia Lymphoma (cerebral or B-cell non-Hodgkin) Invasive cervical carcinoma Atypical disseminated leishmaniasis Symptomatic HIV-associated nephropathy or
cardiomyopathy

 not new, and similar ideas have been described previously for other diseases such as tuberculosis. Nonetheless, cascade of care diagrams are valuable to illustrate how the ultimate goal of maximizing the pro- portion of HIV-positive people whose viral load is suppressed on ART is dependent on preceding steps in the care pathway. Cascade analyses can highlight where, for a given population, where there are bottle-necks, and thus where efforts are most needed. UNAIDS' target of '90:90:90' by 2020, considered in the context of the cascade of care, would result in 73% of HIV-positive people having an undetectable viral load. Mathematical modelling has sug- gested this would result in substantial epidemic impact at a popula- tion level, but more ambitious targets will be needed subsequently. HIV testing HIV testing is the point of entry to prevention, care, and support services. Healthcare workers should recommend HIV testing; spe- cific recommendations for provider-initiated testing and counsel- ling in different epidemiological settings are listed in Table 8.5.24.2. Rapid diagnostic tests for HIV, allowing point-of-care testing with same-day results, have made it much easier for

people to gain knowledge of their HIV status in healthcare facilities at all levels, in community-based sites, or at home. HIV self-testing, whereby an individual performs their own test on a suitable specimen, is be- coming more widely available; people with reactive results on self- testing always need retesting using a recommended algorithm. Testing strategies should be guided by local HIV prevalence; WHO provides comprehensive guidance on testing systems and ap- propriate algorithms. Quality management systems are essential to ensure that correct results are delivered. People who test positive for the first time should always have a second test, based on a different specimen, before initiating HIV treatment, to minimize the risk that a false positive test result leads to inappropriate treatment. People with previously-confirmed HIV infection who are taking ART should not be retested for HIV antibodies; they might have false- negative results, particularly with tests based on oral fluid specimens. People with confirmed HIV-positive test results need to be linked to treatment and care services, to promote timely initiation of ART and avoid the morbidity and mortality associated with advanced disease. In some studies promoting HIV testing in community set- tings, subsequent linkage to care has been limited. Reasons include structural barriers such as distance to clinic and social barriers such as stigma; further work is needed to find effective ways to overcome context-specific barriers and optimize linkage, especially for men, who access care at routine health services less often than do women. Antiretroviral treatment The roll-out of ART has been an extraordinary public health success. By 2017, 21.7 million people were estimated to have started ART, representing more than half of those estimated to be living with HIV worldwide. Guidelines have evolved to recommend immediate ART initiation, reflecting increasing evidence supporting the clin- ical benefits of treatment at earlier stages of HIV disease, along with the development of treatment regimens which are far more tolerable and less demanding, generally allowing once-daily dosing. WHO now recommends ART for all HIV-positive people, regard- less of their clinical stage or CD4 count, with particular priority for those in WHO clinical stage 3 and 4, and those with a CD4 count of 350 cells/μl or less. The approach to ART delivery in low- and middle-income coun- tries has taken a public health rather than an individualized ap-proach. The aim is to maximize the survival of all HIV-positive people in the population by using ART regimens which are stand- ardized, rather than tailored to the individual; by simplifying man-agement so that HIV care can be undertaken by other healthcare 2015 2016 2017 50M 40M 30M 20M 10M People living with HIV People living with HIV who know their status People receiving antiretroviral therapy People living with HIV who have suppressed viral loads 0 Number
Fig. 8.5.24.1 Global HIV treatment cascade, 2015-2017. The pale section at the top of the bar shows the gap between the number reached and the number needed to achieve the 90:90:90 target. Courtesy of UNAIDS (http://aidsinfo.unaids.org/).

940 section 8 Infectious diseases workers where there are few doctors; and using clinical and basic laboratory monitoring so that ART can be delivered even if CD4 counts and HIV viral load measurements cannot be done. However, without viral load measurements, it is much harder to know if treat- ment is effective or not, and scale-up of viral load monitoring is a priority. Dried blood spots can be used to transport specimens for viral load measurements from remote clinics. Antiretroviral agents are described in detail in Chapter 8.5.23. The recommended first-line regimen for treatment of adults (including pregnant or breastfeeding women) or adolescents with HIV-1 in-fection comprises two nucleoside reverse transcriptase inhibitors (NRTIs) and one nonnucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor (Table 8.5.24.3). For HIV-2 in-fections, NNRTIs are ineffective, and a boosted protease inhibitor- based regimen would be the preferred first-line regimen. Second-line therapy is based on a boosted protease inhibitor in combination with two previously unused NRTIs. The increasing number of people taking ART

includes people with a diverse range of care needs. This has led to the concept of ‘differ- entiated care’, meaning there may be particular priorities for certain categories of patient. Specific categories identified include people starting ART when they are well, who may need extra support with adherence and retention; people presenting with advanced disease (CD4 count below 200 cells/µl and/or WHO stage 3 or 4) who are at high risk of morbidity and mortality and may need a more intensive package of care; and among people taking ART, distinguishing be- tween those who are stable, whose care could potentially be decen- tralized to community-based models, and those who are ‘unstable’, needing additional support, closer monitoring, or a change in treat- ment regimen. Conventionally, ART initiation has been considered to be non- urgent in most circumstances, and much emphasis was placed on counselling around adherence and treatment preparedness prior to ART initiation. While treatment literacy is important, it is also im- portant that ART initiation is not unduly delayed, particularly for people with advanced disease. The package of care for people with advanced disease should also include screening for tuberculosis and cryptococcal disease, and treatment if necessary; and co-trimoxazole and isoniazid preventive therapies, as indicated. Immune reconstitution inflammatory syndrome (IRIS) (see also Chapter 8.5.23), either ‘paradoxical’, that is, worsening of an existing HIV-associated disease, or ‘unmasking’ of a previously undiagnosed disease after the start of ART, occurs in about 16% patients, and is associated with a low baseline CD4 count, and (for paradoxical IRIS) with earlier ART initiation. Case fatality for patients with IRIS is rela- tively low (4.5% overall) but appears higher (around 21%) in patients with cryptococcal meningitis; in these patients ART initiation should be deferred until there is evidence of a response to antifungal therapy (usually 2–6 weeks, depending on the antifungal regimen used). Supporting adherence to treatment and retention in care is critical to assuring that individuals and populations gain maximum benefit from ART. Interventions may include adherence clubs supporting community-based care; medication adherence training, peer coun- sellor interventions, mobile-phone based text messaging, and re- minder devices. Prevention of HIV-related disease In addition to the provision of ART, other interventions are effective in preventing illness among HIV-positive people. Co-trimoxazole prophylaxis reduces morbidity and mortality among HIV-posi- tive children and adults. WHO guidelines recommend starting co- trimoxazole for adults in WHO stage 3 or 4, or with tuberculosis, irrespective of CD4 count; or if the CD4 count is below 350 cells/ µl, irrespective of WHO stage. Co-trimoxazole can be discontinued among adults who are clinically stable on ART with immune re- covery and/or virological suppression. Where malaria and / or se- vere bacterial infections are common, WHO recommends provision of co-trimoxazole to all, continued indefinitely. The benefits of long- term co-trimoxazole use, particularly among people stable on ART with virological suppression, might need to be balanced against the potential for promoting antibiotic resistance. HIV-positive people should be screened for symptoms of active tuberculosis (cough, Table 8.5.24.2 WHO recommendations for provider-initiated counselling and testing Type of HIV epidemic Provider-initiated testing and counselling should be recommended for: All All clients attending services for malnutrition, sexually transmitted infections, viral hepatitis, and tuberculosis (confirmed or under investigation), and services for key populations Generalized All clients in all services, including those listed above; also children under 5 years; immunization and antenatal care services Concentrated All clients (adults, adolescents, and children) in clinical settings who present with symptoms or medical conditions that could indicate HIV infection, including tuberculosis, whether confirmed or under investigation Table 8.5.24.3 First-line antiretroviral therapy recommendations for adults: WHO recommendations Preferred regimen Tenofovir plus lamivudine (or emtricitabine) plus efavirenz Alternative regimens Zidovudine plus lamivudine plus efavirenz (or nevirapine) Tenofovir plus lamivudine (or emtricitabine) plus dolutegravira Tenofovir

plus lamivudine (or emtricitabine) plus efavirenz 400 mga Tenofovir plus lamivudine (or emtricitabine) plus nevirapine Special circumstances Regimens containing abacavir and boosted protease inhibitors a Efficacy (and, for dolutegravir, safety) data for pregnant/breastfeeding women and people receiving treatment for tuberculosis are pending.

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