CLINICAL GUIDELINES: MANAGING COMMON COINFECTIONS AND COMORBIDITIES

5

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5.1 Introduction

Various coinfections, comorbidities and other concomitant health conditions are common among people living with HIV and have implications for their treatment and care, including the timing and choice of ARV drugs. This section provides a brief overview of the most common and important conditions. It summarizes selected key recommendations from existing WHO guidelines and related materials, focusing on the screening, prophylaxis and timing of ART for these conditions; it does not cover their management in detail. Sources are provided for relevant, previously published recommendations. These recommendations were not reviewed during the 2015 guideline development process.

Evidence reviews were undertaken in 2015 with regard to presumptive treatment for tuberculosis (TB), depression and cardiovascular disease in people living with HIV. Although no formal recommendation on presumptive TB treatment is made, guidance is provided. New recommendations are presented for the screening and management of cardiovascular disease and depression in people living with HIV.

5.2 Prevention, screening and management of common coinfections

5.2.1 Co-trimoxazole prophylaxis

Background and rationale

Co-trimoxazole (CTX) is a fixed-dose combination of two antimicrobial agents (sulfamethoxazole and trimethoprim) used to treat a variety of bacterial, fungal and protozoan infections. CTX prophylaxis is a feasible, well-tolerated and inexpensive intervention to reduce HIV-related morbidity and mortality in people living with HIV. CTX is an off-patent drug and is widely available in resource-limited settings.

In 2006, the first WHO guidelines on CTX prophylaxis in resource-limited settings recommended CTX prophylaxis as an integral component of HIV care *(1)*. These guidelines were reviewed in 2014 and updated in the context of expanded access to and earlier initiation of ART *(2)*. In recent years, new evidence has emerged showing that with expanded access to ART, there is a broader benefit of CTX prophylaxis beyond the prevention of some AIDS-associated opportunistic diseases (*Pneumocystis jirovecii* pneumonia [PCP] and toxoplasmosis) and the reduction of HIV-associated mortality in people with low CD4 cell counts. These benefits relate to prevention of malaria and severe bacterial infections (SBIs) in adults and children with HIV.

Recommendations

Co-trimoxazole prophylaxis for adults

Co-trimoxazole (CTX) prophylaxis is recommended for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with a CD4 count ≤350 cells/mm^3 (strong recommendation, moderate-quality evidence).

In settings where malaria and/or severe bacterial infections (SBIs) are highly prevalent, co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage (conditional recommendation, moderate-quality evidence).

Co-trimoxazole prophylaxis may be discontinued in adults (including pregnant women) with HIV who are clinically stable on ART, with evidence of immune recovery and viral suppression (conditional recommendation, low-quality evidence).

In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage (conditional recommendation, moderate-quality evidence).

Routine co-trimoxazole prophylaxis should be given to all HIV-infected patients with active TB disease regardless of CD4 cell count (strong recommendation, high-quality evidence).

Co-trimoxazole prophylaxis for HIV-infected infants, children and adolescents

Co-trimoxazole prophylaxis is recommended for infants, children and adolescents with HIV, irrespective of clinical and immune conditions. Priority should be given to all children younger than 5 years old regardless of CD4 cell count or clinical stage, and children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with a CD4 count ≤350 cells/mm^3 (strong recommendation, high-quality evidence).

In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued until adulthood, irrespective of whether ART is provided (conditional recommendation, moderate-quality evidence).

In settings with low prevalence for both malaria and bacterial infections, co-trimoxazole prophylaxis may be discontinued for children five years of age and older who are clinically stable and/or virally suppressed on ART for at least six months and with a CD4 count > 350 cells/mm^3 (strong recommendation, very low-quality evidence).

Co-trimoxazole prophylaxis is recommended for HIV-exposed infants 4 to 6 weeks of age and should be continued until HIV infection has been excluded by an age-appropriate HIV test to establish final diagnosis after complete cessation of breastfeeding (strong recommendation, very low-quality evidence).

Source: Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for a public health approach – December 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_dec2014/en).

The effectiveness of CTX prophylaxis in reducing death among people starting ART with a CD4 cell count at or below 350 cells/mm^3 and/or WHO clinical stage 3 or 4 disease is supported by moderate-quality evidence from nine observational studies *(3–11)*. In addition, a new expanded recommendation for use of CTX prophylaxis is based on a recent systematic review showing the effectiveness of CTX prophylaxis in reducing mortality, SBIs, malaria and hospitalization in adults and adolescents with HIV, regardless of clinical and immunological parameters *(12)*. One randomized clinical trial in children with HIV showed survival benefits regardless of age and CD4 cell count and also supports the expansion of CTX prophylaxis in paediatric populations, particularly in settings with a high prevalence of malaria and/or SBIs *(13,14)*.

Continuation of CTX prophylaxis regardless of ART status, age, CD4 cell count or WHO clinical stage in settings with a high prevalence of malaria and/or SBIs is also recommended based on data from randomized controlled trials, which show significant reduction in the risk of hospitalization, malaria and diarrhoea among adults and children with HIV in settings with a high prevalence of malaria and/or SBIs *(15–17)*. In addition, the recommendation to continue CTX prophylaxis in settings with a high prevalence of malaria and/or SBIs may simplify HIV management, forecasting and supply management issues.

The risks and benefits of continuing versus stopping CTX prophylaxis after viral suppression induced by ART were also evaluated in settings with a low burden of malaria and SBIs. Two studies found that the rates of PCP and death were similar in people on ART who achieved viral suppression and had CD4 cell counts above 100 cells/mm^3 in study arms *(18,19)*. In these settings, discontinuation of CTX prophylaxis in adults based on clinical, immunological and virological parameters indicative of ART immune recovery can be considered, although the quality of the evidence is low to very low *(2)*. However, in settings with a low prevalence of malaria and/or SBI, and limited or no access to CD4 testing, CTX prophylaxis should not be discontinued.

The recommendation on the use of CTX prophylaxis during pregnancy in women and adolescents living with HIV to prevent malaria complications and avoid simultaneous intermittent preventive treatment is maintained, based on a systematic review showing that CTX prophylaxis is not inferior to intermittent preventive treatment of malaria in pregnancy with respect to mortality, low birth weight, placental malaria, maternal deaths and severe adverse events *(20)*. The recommendation to discontinue CTX prophylaxis at the end of the risk period for transmission in HIV-exposed uninfected infants is also maintained, as there is insufficient evidence available to establish the clinical benefit of CTX prophylaxis in HIV-exposed uninfected infants.

Table 5.1 summarizes the criteria for initiation and discontinuation of CTX prophylaxis in adults, adolescents, pregnant women and children with HIV.

Table 5.1. Criteria for initiation and discontinuation of co-trimoxazole prophylaxis

Population	Recommendation	
	Criteria for initiation of co-trimoxazole prophylaxis	**Criteria for discontinuation of co-trimoxazole prophylaxis**
Adults (including pregnant women) with HIV	• Initiate in all with severe /advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤350 cells/mm^3[a] • **In settings with a high prevalence of malaria and/or severe bacterial infections**[b]**:** initiate in all regardless of WHO clinical stage or CD4 cell count	• May be discontinued in those who are clinically stable,[c] with evidence of immune recovery and/or viral suppression on ART[d,e] • In settings with a high prevalence of malaria and/or severe bacterial infections: should be continued
Children and adolescents with HIV	• Initiate in all regardless of WHO clinical stage or CD4 cell count • **As a priority:** (1) initiate in all less than 5 years of age, regardless of WHO clinical stage or CD4 cell count; (2) initiate in all older than 5 years of age and with severe /advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤350 cells/mm^3	• **In settings with a high prevalence of malaria and/or severe bacterial infections:** should be continued until adulthood • **In settings with a low prevalence of both malaria and severe bacterial infections:** may be discontinued for those older than 5 years of age who are clinically stable, with evidence of immune recovery[f] and/or viral suppression on ART
HIV-exposed uninfected infants	• Initiate in all starting at 4–6 weeks after birth	• Until the risk of HIV transmission ends or HIV infection is excluded[g]
People living with HIV and TB[h]	• Initiate in all with active TB regardless of CD4 cell count	• Until criteria for discontinuation in adults or children are met

[a] This group is also prioritized for ART initiation (as recommended for ART in the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection).

[b] Settings where malaria and/or SBIs are highly prevalent includes low- and middle-income countries with high rates of mortality among children less than 5 years old (http://www.who.int/gho/child_health/mortality/mortality_under_five/en).

[c] Clinically stable adults are defined as those individuals on ART for at least one year without any new WHO clinical stage 2, 3 or 4 events.

[d] CD4 count >350 cells/mm^3, with viral load suppression, is considered indicative of immune recovery (some countries may adopt a threshold of CD4 count >500 cells/mm^3).

[e] WHO recognizes that in settings with a low prevalence of malaria and SBIs where CTX is used primarily as prophylaxis for some AIDS-associated opportunistic infections (PCP and toxoplasmosis), guidelines exist for discontinuing CTX in adults with HIV infection when there is evidence of viral suppression and immune recovery at CD4 cell counts >200 cells/mm^3 and being on ART for at least 1 year.

[f] Parameter for immune recovery in children when >5 years old: CD4 cell count >350 cells/mm^3, with viral load suppression.

[g] In settings with a high malaria transmission, consideration may be given to extend CTX prophylaxis in HIV-exposed uninfected infants up to 2 years of age.

[h] Recommendation maintained from: WHO policy on collaborative TB/HIV policy activities: guidelines for national programmes and other stakeholders. Geneva: WHO; 2012.

Implementation considerations

Some of the major barriers to CTX implementation include supply chain and management issues leading to stock-outs; imposing costs on patients for medication and/or monitoring; inadequate training, supervision, and/or mentoring of health-care workers; low coverage of HIV testing and counselling; and lack of coordination across programmes. National programmes can implement CTX prophylaxis policy and guidelines more effectively through the approaches shown in Box 5.1.

Box 5.1. Steps to improve the implementation of co-trimoxazole prophylaxis policy and guidelines at the national level

- Adapt WHO guidelines to national context.
- Strengthen national and local drug supply management systems to ensure sustained availability of CTX at health-care facilities.
- Secure financing for providing CTX prophylaxis to ensure that no charges for CTX are imposed on patients.
- Coordinate with malaria programmes at a country level with regard to recommendations related to intermittent preventive treatment of malaria in pregnancy and seasonal malaria chemoprophylaxis in children less than 5 years.
- Provide CTX prophylaxis to eligible people at TB, maternal, newborn and child health (MNCH) and opioid substitution therapy (OST) services.
- Scale up training and sensitization of health-care workers.
- Increase knowledge of CTX prophylaxis at the community level.
- Ensure that a human rights framework is used (e.g. people with HIV should always consent to the use of CTX prophylaxis).
- Ensure that high-quality CTX formulations are provided.
- Toxicity monitoring should be done for adverse reactions, particularly in the context of chronic CTX prophylaxis use.
- Assess adherence to policies and impact of CTX prophylaxis on population health.

5.2.2 Tuberculosis

Background

TB is the most common cause of death in hospitalized adults and children living with HIV, accounting for about a third of all mortality *(21)*. A systematic review of autopsy studies among adults who had had HIV showed a pooled prevalence of almost 40% in the cadavers, with just under half of the cases previously undetected *(22)*.

Routine TB symptom screening for people with HIV, using an algorithm containing fever, cough of any duration, weight loss and night sweats, will help to identify people who should either be expedited for TB diagnosis or given preventive TB therapy. The combined use of isoniazid preventive therapy (IPT) and ART has been shown to have both TB prevention and mortality benefits, including in people with a higher CD4 count *(23,24)*. The timely initiation of ART and implementation of the "Three I's" for HIV/TB (increased TB case-finding, IPT and infection control) are critical to prevent TB and mortality from HIV-associated TB.

Diagnosis of HIV-associated TB using smear microscopy, a widely available method, is very challenging in people with HIV, resulting in delayed diagnoses and misdiagnoses. WHO-approved nucleic acid-based molecular tests (e.g. Xpert MTB/RIF) improve the yield and speed of diagnosis, and need to be scaled up in all HIV clinical settings. This section presents the review of evidence and relevant recommendations on the use of urine lipoarabinomannan (LAM) antigen test for diagnosis and presumptive TB treatment for people living with HIV who are severely immunocompromised. A recent review of evidence on the timing of ART for TB patients is described in section 4.3.5.

TB diagnosis and treatment

Recommendations

- Xpert MTB/RIF should be used rather than conventional microscopy, culture and drug susceptibility testing (DST) as the initial diagnostic test in adults and children suspected of having multidrug-resistant TB (MDR-TB) or HIV-associated TB (strong recommendation, adults: high-quality evidence; children: very low-quality evidence).
- Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test for cerebrospinal fluid specimens from patients suspected of having TB meningitis (strong recommendation, very low-quality evidence).
- Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture or histopathology) for testing specific non-respiratory specimens (lymph nodes and other tissues) from patients suspected of having extrapulmonary TB (conditional recommendation, very low-quality evidence).

Source: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children: WHO policy update. Geneva: World Health Organization; 2013 (http://www.who.int/tb/laboratory/xpert_policyupdate/en).

- Except as specifically described below for people with HIV infection with low CD4 counts or who are seriously ill,[a] urine lateral flow (LF)-LAM should not be used for the diagnosis of TB (strong recommendation, low-quality evidence).
- LF-LAM may be used to assist in the diagnosis of active TB in adult inpatients living with HIV, with signs and symptoms of TB (pulmonary and/or extrapulmonary), who have a CD4 count less than or equal to 100 cells/mm^3, or people living with HIV who are seriously ill,[a] regardless of CD4 cell count or with unknown CD4 cell count (conditional recommendation, low-quality evidence).[b]
- LF-LAM should not be used as a screening test for active TB (strong recommendation, low-quality evidence).

Source: The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV: Policy guidance. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/193633/1/9789241509633_eng.pdf).

- TB patients with known positive HIV status and TB patients living in HIV-prevalent settings should receive at least six months of a rifampicin-containing treatment regimen. The optimal dosing frequency is daily during the intensive and continuation phases (strong recommendation, high-quality evidence).

[a] "Seriously ill" is defined as four danger signs: respiratory rate >30/min, temperature >39°C, heart rate >120/min and unable to walk unaided.

[b] This recommendation also applies to adults living with HIV who are outpatients with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/mm^3 or who are seriously ill[a] regardless of CD4 count or with unknown CD4 count, based on the generalization of data from inpatients. This recommendation also applies to children living with HIV, with signs and symptoms of TB (pulmonary and/or extrapulmonary) based on the generalization of data from adults, while acknowledging that data are very limited and that there are concerns regarding low specificity of the LF-LAM assay in children.

Source: WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. Geneva: World Health Organization; 2012 (http://www.who.int/tb/publications/2012/tb_hiv_policy_9789241503006/en).

Early identification of TB among people with HIV through careful assessment of symptoms and signs, diagnosis using proper investigation (i.e. Xpert MTB/RIF) and prompt initiation of anti-TB treatment is important to improve survival and quality of life as well as reduce transmission of TB in the clinic and the community.

All people living with HIV should be regularly screened for TB using a clinical symptom-based algorithm. Those who report any one of the symptoms may have active TB and should be evaluated for TB and other diseases. Xpert MTB/RIF should be used as the initial diagnostic test in adults and children suspected of having HIV-associated TB. Xpert MTB/RIF should also be used as a preferred initial diagnostic test for cerebrospinal fluid investigation in people with HIV presumed to have TB meningitis.

Diagnosis of TB in people with HIV should always be expedited and anti-TB treatment initiated as soon as possible. In peripheral settings where TB investigations are not available, clinical assessment and judgement should be used to provide presumptive TB treatment for select individuals who are seriously ill. Diagnostic algorithms for individuals living with HIV who are suspected of having TB are in Annexes 14 and 15.

Tests based on the detection of mycobacterial LAM antigen in urine have emerged as potential point-of-care tests for TB. LAM antigen is a lipopolysaccharide present in mycobacterial cell walls, which is released from metabolically active or degenerating bacterial cells and appears to be present only in people with active TB disease. The LF-LAM assay (Alere Determine™ TB LAM Ag) is a commercially available strip test for active TB.

In 2015, evidence was reviewed regarding the accuracy of LF-LAM and its use as a screening or diagnostic tool for TB in people with HIV. Sixteen unique studies were identified that assessed the diagnostic accuracy of LF-LAM for TB in people with HIV with signs or symptoms of TB (TB diagnostic tool) or in people with HIV regardless of signs or symptoms of TB (TB screening tool) *(25)*. The review suggested that, in general, LF-LAM should not be used for either the diagnosis or the screening of active TB in adults with HIV. However, because the sensitivity and specificity of the test were highest in adults with CD4 counts at or below 100 cells/mm^3 in inpatient settings, LF-LAM may be used to assist in the diagnosis of active TB in adult inpatients with HIV who are

presumed to have TB and who have a CD4 cell count at or below 100 cells/mm^3. LF-LAM could be performed for seriously ill HIV-positive adult patients with danger signs, regardless of CD4 count, in both in-hospital and outpatient settings. This recommendation also applies to children based on the generalization of data from adults but recognizing that data are limited and that there are concerns regarding the low specificity of LF-LAM in children.

TB patients with known HIV-positive status and TB patients living in HIV-prevalent settings should receive daily isoniazid, rifampicin, pyrazinamide and ethambutol for two months, followed by rifampicin and isoniazid alone for four months. Pulmonary and extrapulmonary disease should be treated with the same regimens. However, it is noted that some experts recommend 9–12 months of treatment for TB meningitis, given the serious risk of disability and mortality, and 9 months of treatment for TB of bones or joints, because of the difficulties in assessing treatment response. Unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for TB meningitis and pericarditis. In TB meningitis, ethambutol should be replaced by streptomycin.

Presumptive treatment of TB for people living with HIV

The rationale for presumptive TB treatment is to prevent the death of people with HIV in situations where expedited diagnosis of TB is not possible or feasible due to the clinical condition of the patient or limited access to TB diagnostic services. While there is no case definition of presumptive TB, WHO algorithms include initiation of TB treatment for people with HIV in peripheral facilities based exclusively on clinical suspicion (without TB investigations) for seriously sick patients (with respiratory distress) based on the judgement of the clinician *(26)*. This approach is based on expert opinion and emphasizes that every effort should be made to confirm the diagnosis of TB after initiation of presumptive treatment and that treatment should be stopped only if there is bacteriological, histological or strong clinical evidence of an alternative diagnosis.

In 2015, a systematic review was performed to assess the role of presumptive treatment for people living with HIV, with a particular focus on its efficacy in reducing mortality as well as the risk of severe adverse events following treatment. A total of 2563 citations were identified, together with three ongoing randomized controlled trials *(27–29)* and one cluster randomized trial of presumptive anti-TB treatment. The REMEMBER trial is a multicountry study that compares the provision of ART and TB treatment with ART and IPT in people with HIV with a CD4 count below 50 cells/mm^3 and presumed not to have active TB. The trial showed no evidence of reduced mortality, reduced incidence of AIDS-associated illnesses or increased viral suppression as a result of presumptive therapy in individuals in whom TB was not suspected and in whom it had been ruled out by extensive investigations.

Based on the available evidence, WHO makes no new recommendation on presumptive TB treatment for people with HIV and notes the importance of further research on this issue, including research on the clinical predictors for selecting people with HIV for presumptive treatment and whether nurses or clinical officers can initiate it. Nevertheless, expert opinion continues to support presumptive TB treatment in peripheral health facilities in HIV-prevalent settings for people with HIV who are seriously ill due to suspected TB. The algorithm in Annex 15 may help to facilitate presumptive TB treatment.

Extrapulmonary TB in people living with HIV

The risk of extrapulmonary TB is higher in people living with HIV, especially in those with lower CD4 cell counts *(30)*. People living with HIV with extrapulmonary TB often have disseminated disease and are at high risk of rapid clinical deterioration and death. The commonest forms include lymph node (especially in the neck or under the arms), pleural (usually one-sided pleural effusion) and disseminated TB (disease that is not limited to one site in the body). Pericardial and meningeal TB are less frequent forms of extrapulmonary TB but are more likely to result in fatal outcomes *(31)*.

The diagnosis of extrapulmonary TB is challenging. In people living with HIV with advanced immunosuppression, lack of pulmonary findings is not uncommon and disseminated TB can manifest as non-specific febrile illness. Extrapulmonary TB can be suspected in all HIV-positive individuals presenting with TB symptoms. Furthermore, symptoms suggesting a specific organ involvement, such as breathlessness (pleural effusion/pericarditis), enlarged glands in the neck or armpit (lymphadenitis) and chronic headache or altered mental status (meningitis) should prompt further investigation for extrapulmonary TB *(31)*.

Bacterial confirmation is often difficult due to a low sensitivity of smear microscopy and difficulty in obtaining samples from extrapulmonary sites. If possible, extrapulmonary specimens should be obtained. For patients with suspected TB meningitis, Xpert MTB/RIF is the preferred initial diagnostic test for cerebrospinal fluid *(32)*. If lymphadenitis is suspected, Xpert MTB/RIF may be used to test for samples obtained from lymph node biopsies or fine-needle aspiration *(33)*. LF-LAM may also assist in the diagnosis because these people living with HIV are likely to have low CD4 cell counts *(25)*. The accurate diagnosis of extrapulmonary tuberculosis is complex and difficult, particularly in peripheral health facilities with limited support and diagnostic infrastructure. Therefore, presumptive TB treatment should be initiated for patients with danger signs according to the latest clinical algorithms (Annexes 14 and 15).

Timing of ART for adults and children with TB

Early initiation of ART in TB patients living with HIV is critical for reducing mortality. Section 4.3.5 provides more detailed information and recommendations on the co-treatment of TB and HIV.

Isoniazid preventive therapy (IPT)

Recommendations

- Adults and adolescents living with HIV should be screened with a clinical algorithm; those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT (strong recommendation, moderate-quality evidence).
- Adults and adolescents living with HIV who have an unknown or positive tuberculin skin test (TST) status and are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals regardless of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women (strong recommendation, high-quality evidence).
- Adults and adolescents living with HIV who have an unknown or positive tuberculin skin test status and among whom active TB disease has been safely ruled out should receive at least 36 months of IPT. IPT should be given to such individuals regardless of whether or not they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy (conditional recommendation, moderate-quality evidence).
- Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB. Children living with HIV who have poor weight gain, fever or current cough or contact history with a TB case may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, they should be offered IPT regardless of their age (strong recommendation, low-quality evidence).
- Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening and have no contact with a TB case should receive six months of IPT (10 mg/kg/day) as part of a comprehensive package of HIV prevention and care (strong recommendation, moderate-quality evidence).
- In children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months of IPT if the evaluation shows no TB disease (strong recommendation, low-quality evidence).
- All children living with HIV, after successful completion of treatment for TB, should receive IPT for an additional six months (conditional recommendation, low-quality evidence).

Source: Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization; 2011 (http://apps.who.int/iris/bitstream/10665/44472/1/9789241500708_eng.pdf).

Isoniazid 300 mg given daily prevents the progression of latent TB infection to active clinical disease. The combined use of IPT and ART has also been shown to have both TB prevention and mortality benefits, including in people with higher CD4 counts *(23,24)*.

TST should not be a requirement for initiating IPT for people with HIV. People with HIV whose TST status is unknown should be started on IPT after symptom-based screening for TB. However, given those TST-positive patients who are not receiving ART benefit more from IPT than those who are TST negative, the test is encouraged where feasible.

Infection control

Recommendations

Administrative (facility-level infection control committee and protocols)

- A triage system should be in place to identify people suspected of having TB and minimize diagnostic delays with rapid diagnostics, e.g. Xpert MTB/RIF.
- Separate people with suspected or confirmed TB.
- Ensure cough etiquette and respiratory hygiene.
- Minimize the time spent in health-care facilities (e.g. through community-based approaches).

(all administrative recommendations: strong recommendation, low-quality evidence).

Health workers and caregivers

- Inform and encourage health workers with TB symptoms to undergo TB diagnostic investigation as well as HIV testing and counselling.
- Provide a package of care for HIV-positive workers (ART and IPT) and relocation for health-care workers living with HIV to a lower-risk area.

(all health worker recommendations: strong recommendation in settings with a high prevalence of HIV and conditional with a low prevalence, high-quality evidence).

Use of particulate respirators

- Protective equipment (particulate respirator masks that meet or exceed N95 standards set by the CDC/NIOSH or the FFP2 standards that are CE certified) should be provided for health-care workers caring for patients with infectious TB (suspected or confirmed) (strong recommendation, low-quality evidence).

Environmental

- Ventilation (i.e. natural and/or mechanical) (strong recommendation, low-quality evidence).
- Upper-room ultraviolet germicidal irradiation (conditional recommendation, low-quality evidence).

Source: WHO policy on TB infection control in health-care facilities, congregate settings and households. Geneva: World Health Organization; 2009 (http://www.who.int/tb/publications/2009/9789241598323/en).

Health-care facilities and congregate settings can present a high risk for acquiring TB (including MDR-TB) for people living with HIV as well as for health-care workers. National TB programmes and national HIV programmes should provide managerial direction for implementing TB infection control. Each health-care facility should have a TB infection control plan that includes administrative, environmental and personal protection measures as well as measures for health workers and caregivers to reduce TB transmission within the facility. Periodic evaluation of infection control practices is essential for ensuring that appropriate measures are in place. Facility-level assessment of TB infection control should be incorporated into the routine supervisory activities of all health facilities providing care for people living with HIV. A standardized essential checklist for periodic evaluation of infection control practices can serve as a tool for such an assessment and can help measure progress over time. An example of such a checklist that can be adapted by countries to suit the context can be found in Annex 16.

To reduce the transmission of TB to the family and the community, key information should also be provided to the patient and family members. This should include advice on cough etiquette, sleeping alone, avoiding congregate settings and public transport while smear-positive and spending as much time as possible outdoors where feasible.

Multidrug-resistant TB and HIV

Recommendation

- Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line antituberculosis drugs irrespective of CD4 cell count, as early as possible (within the first eight weeks) following initiation of antituberculosis treatment (strong recommendation, very low-quality evidence).

Source: Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva: World Health Organization; 2011 (http://apps.who.int/iris/bitstream/10665/44597/1/9789241501583_eng.pdf).

MDR-TB is TB that does not respond to at least isoniazid and rifampicin. Patients with both HIV and MDR-TB face complicated clinical management, fewer treatment options and poorer treatment outcomes *(34)*. Systematic reviews have shown a worrying association between HIV and primary MDR-TB *(35,36)*. Outbreaks of MDR-TB among people with HIV have been documented in hospital and other settings, especially in eastern Europe and in southern African countries with a high HIV prevalence *(37)*. Factors contributing to the occurrence of drug-resistant TB include failure to recognize drug resistance allowing further transmission, inadequate isolation procedures in health-care facilities and congregate settings and inadequate treatment.

Extensively drug-resistant TB (XDR-TB) is a form of TB that is resistant to any fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance. Although the association between HIV and XDR-TB remains unclear, the rapid and deadly spread of XDR-TB among people living with HIV has been observed *(38,39)*. As with MDR-TB, nosocomial outbreaks involving people with HIV have been reported, suggesting a need for intensified efforts to ensure infection control in health-care settings *(40–42)*.

Because unrecognized drug-resistant TB is associated with very high mortality in people with HIV, Xpert MTB/RIF is recommended as the initial diagnostic test in adults and children suspected of having HIV-associated TB. Those found to have MDR-TB or rifampicin resistance should be further tested for second-line anti-TB drug resistance. People with HIV who have MDR-/XDR-TB should start ART as soon as possible, within eight weeks of starting TB treatment.

WHO recently issued recommendations on the use of the novel anti-TB drugs delamanid and bedaquiline, which may also be used by people living with HIV, although bedaquiline should be used with caution and proper clinical judgement in people aged over 65 years, people with diabetes, HIV, hepatic or severe renal impairment or people who use alcohol or other substances, given that data on efficacy and safety under such conditions are very limited or unavailable *(43)*. In general, there is limited evidence on the frequency and severity of toxicities and adverse events from ART and second-line anti-TB drugs. However, people with HIV tend to have a higher rate of adverse drug reactions to both TB and non-TB medications, and the risk of adverse drug reactions increases with the degree of immunosuppression. The complexity of ARV regimens and second-line TB treatment, each with its own toxicity profiles and some of which may be potentiated by concomitant therapy, demands rigorous clinical monitoring. Detailed information on the use of second-line anti-TB drugs, including delamanid and bedaquiline, are available in the Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (http://www.who.int/tb/publications/pmdt_companionhandbook/en).

Appropriate TB infection control measures in all facilities caring for people with HIV and efforts to optimize adherence and completion of TB treatment are important to help reduce the incidence of MDR-TB. MDR-TB can also be minimized by strengthening HIV prevention, improving collaboration between HIV and TB programmes and focusing attention on the groups at the highest risk of MDR-TB and HIV, such as people who inject drugs and people exposed in prison and other congregate settings.

Additional relevant guidance

- Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization; 2011 (www.who.int/tb/challenges/hiv/ICF_IPTguidelines/en/index.html).
- Treatment of tuberculosis: guidelines for national programmes, fourth edition. Geneva: World Health Organization; 2010 (http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf).
- Improving the diagnosis of and treatment of smear-negative pulmonary and extra-pulmonary tuberculosis among adults and adolescents: recommendations for HIV-prevalent and resource-constrained settings. Geneva: World Health Organization; 2007 (www.who.int/hiv/pub/tb/pulmonary/en).
- Xpert MTB/RIF implementation manual – technical and operational "how-to". Practical considerations. Geneva: World Health Organization; 2014 (http://www.who.int/tb/publications/xpert_implem_manual/en).
- Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/77741/1/9789241504492_eng.pdf).

5.2.3 Cryptococcal disease

Cryptococcal meningitis is a common opportunistic infection and a leading cause of death in people with HIV before and after ART is initiated, especially in sub-Saharan Africa and South-East Asia *(44–48)*. The main reasons for this high death rate include delayed presentation, together with poor availability and high cost of treatment *(49–52)*. Furthermore, there are no standardized guidelines applicable to resource-limited settings for the diagnosis and management of cryptococcal disease.

A rapid advice on diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children was published by WHO in 2011. The advice covers diagnosis, screening and prevention of cryptococcal infection; induction, consolidation and maintenance regimens; monitoring and managing toxicities; timing of ART; and discontinuation of maintenance regimens *(53)*. These recommendations encourage earlier diagnosis and early treatment with amphotericin B–based regimens as part of a minimum package of toxicity prevention, monitoring and management, prompt management of raised intracranial pressure and systematic evaluation of a clinically deteriorating patient. They also provide guidance on timing of ART initiation and discontinuation of maintenance treatment.

Infection control

Recommendations

Diagnosis of cryptococcal disease

Prompt lumbar puncture with measurement of CSF opening pressure and rapid CSF cryptococcal antigen (CrAg) assay or rapid serum CrAg (either LA or LFA) is the preferred diagnostic approach (strong recommendation, moderate-quality evidence).

Prevention of cryptococcal disease

The routine use of antifungal primary prophylaxis for cryptococcal disease in HIV-infected adults, adolescents and children with a CD4 count less than 100 cells/mm^3 and who are CrAg negative or where CrAg status is unknown is not recommended prior to ART initiation, unless a prolonged delay in ART initiation is likely (strong recommendation, high-quality evidence).

The use of routine serum or plasma CrAg screening in ART-naive adults , followed by pre-emptive antifungal therapy if CrAg positive to reduce the development of cryptococcal disease, may be considered prior to ART initiation in:

a. patients with a CD4 count less than 100 cells/mm^3; and
b. where this population also has a high prevalence (>3%)[a] of cryptococcal antigenaemia.

(conditional recommendation, low-quality evidence).

Induction, consolidation and maintenance antifungal treatment regimens

For the induction phase of treatment in HIV-infected adults, adolescents and children with cryptococcal disease (meningeal and disseminated non-meningeal), the following two-week antifungal regimens are recommended in order of preference.

a. Amphotericin B + flucytosine (strong recommendation, high-quality evidence).

b. Amphotericin B + fluconazole (strong recommendation, moderate-quality evidence).

c. Amphotericin B short course (5–7 days) + high-dose fluconazole (to complete 2 weeks of induction) when a minimum package of pre-emptive hydration and electrolyte replacement and toxicity monitoring and management cannot be provided for the full two-week induction period (conditional recommendation, low-quality evidence).

d. Fluconazole high dose + flucytosine, when amphotericin B is not available (conditional recommendation, low-quality evidence).

e. Fluconazole high dose alone, when amphotericin B is not available (conditional recommendation, low-quality evidence).

For the consolidation phase treatment of HIV-infected adults, adolescents and children with cryptococcal meningitis or disseminated non-meningeal disease, the following eight-week antifungal regimen is recommended:

Fluconazole 400–800mg/day after a two-week induction with amphotericin B regimen (6–12 mg/kg/day up to 400–800 mg/day if below 19 years).

Fluconazole 800 mg/day after induction treatment with short-course amphotericin B or fluconazole-based induction regimen (fluconazole 12 mg/kg/day up to 800 mg/day if below 19 years).

(strong recommendation, low-quality evidence).

For maintenance treatment of cryptococcal disease in HIV-infected adults, adolescents and children, oral fluconazole 200 mg daily (6 mg/kg/day up to 200 mg/day if below 19 years) is recommended (strong recommendation, high-quality evidence).

For localized non-meningeal disease, or in patients with isolated serum CrAg positivity (where active cryptococcal meningitis has been excluded). Fluconazole 800 mg/day (or 12 mg/kg/day if below 19 years) for two weeks, then 400 mg/day (or 6 mg/kg/day up to 400–800 mg/day if below 19 years) for eight weeks, and continued maintenance with fluconazole 200 mg/day is recommended. The optimal antifungal regimen in this population remains to be determined (conditional recommendation, low-quality evidence).

Prevention, monitoring and management of amphotericin B toxicity

In HIV-infected adults receiving amphotericin B–containing regimens for treatment of cryptococcal disease, a minimum package of toxicity prevention, monitoring and management is recommended to minimize the serious amphotericin B–related toxicities of hypokalaemia and nephrotoxicity (strong recommendation, moderate-quality evidence).

Timing of ART initiation

Immediate ART initiation is not recommended in HIV-infected patients with cryptococcal meningitis due to the high risk of IRIS that may be life threatening. (conditional recommendation, low-quality evidence).

In HIV-infected adults, adolescents and children with a recent diagnosis of cryptococcal meningitis, ART initiation should be deferred until there is evidence of a sustained clinical response to antifungal therapy, and after 4 weeks of induction and consolidation treatment with amphotericin B–containing regimens combined with flucytosine or fluconazole, or after 4–6 weeks of treatment with a high-dose oral fluconazole induction and consolidation regimen (conditional recommendation, low-quality evidence).

Discontinuation of azole maintenance treatment (secondary prophylaxis)

In HIV-infected adults and adolescents with successfully treated cryptococcal disease (meningeal and non-meningeal), discontinuation of antifungal maintenance treatment is recommended based on the following criteria:

a. If HIV viral load monitoring is not available
   When patients are stable and adherent to ART and antifungal maintenance therapy for at least one year and
b. If HIV viral load monitoring is available
   Patient stable and adherent to ART and antifungal maintenance treatment for at least one year and with CD4 count greater than or equal to 100 cells/mm^3 (two measurements six months apart) and a suppressed viral load. (conditional recommendation, low-quality evidence).

In HIV-infected children aged between 2 and 5 years with successfully treated cryptococcal disease (meningeal and non-meningeal), discontinuation of antifungal treatment maintenance is recommended if the child is stable and adherent to ART and antifungal maintenance treatment for at least one year and with a CD4 cell count percentage greater than 25% or absolute count greater than 750 cells/mm^3 (two measurements six months apart) (strong recommendation, low-quality evidence).

Maintenance therapy for cryptococcal disease should NOT be discontinued in children less than two years (strong recommendation, low-quality evidence).

[a] The prevalence threshold above which screening is cost-effective was 1% using LFA in a recent study (Meya D, Rajasingham R, Rolfes M, Birkenkamp K, Boulware D. Cost benefit of integrating cryptococcal antigen screening and preemptive treatment into routine HIV care. In: International AIDS Conference, Washington DC, 22–27 July 2012 [Abstract MOAB0102]). The prevalence cost-effectiveness threshold is likely to vary depending on the cost of the antigen assay used (latex agglutination [LA] vs. LFA) and cost of drug treatment.

Maintenance treatment for cryptococcal disease should be restarted if CD4 count drops to 100 cells/mm^3 or below in HIV-infected adults and adolescents (or CD4 cell count less than or equal to 25% or 750 cells/mm^3 in children aged between two and five years), or if a WHO stage 4 clinical event occurs, irrespective of patient age (strong recommendation, low-quality evidence).

Source: Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Geneva: World Health Organization; 2011 (www.who.int/hiv/pub/cryptococcal_disease2011/en).

5.2.4 Hepatitis B and C

Chronic hepatitis B virus (HBV) infection affects 5–20% of the 36 million people living with HIV worldwide, and hepatitis C virus (HCV) affects 5-15%, rising to 90% among people who inject drugs. The burden of coinfection is highest in low- and middle-income countries, particularly in South-East Asia and sub-Saharan Africa for hepatitis B *(54–56)*.

Viral hepatitis is an increasing cause of morbidity and mortality among people living with HIV in some regions, including among people on ART. A comprehensive approach includes prevention, HBV and HCV testing, hepatitis B vaccination and treatment and care for people with HIV who are coinfected with hepatitis B and/or hepatitis C.

Management of HIV and hepatitis B coinfection

HIV coinfection has a profound impact on the course of HBV infection, including more rapid progression to cirrhosis and hepatocellular carcinoma, higher liver-related mortality and decreased treatment response compared with people who do not have HIV *(57–62)*.

The 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs* recommended providing ART to all people coinfected with HIV and HBV regardless of CD4 count for those with evidence of severe chronic liver disease.[1] This recommendation has now been superseded by the new recommendation in 2015 to treat all people with HIV regardless of CD4 cell count. Nevertheless, in settings where prioritization is required, people coinfected with HIV and HBV and evidence of severe chronic liver disease should be considered a priority for ART. WHO recommends that adults, adolescents and children with chronic hepatitis B and clinical evidence of cirrhosis (or cirrhosis based on the non-invasive APRI test score >2 in adults) should be treated regardless of alanine aminotransferase (ALT) levels, hepatitis B e antigen (HBeAg) status or HBV DNA levels. WHO guidelines for the prevention, care and treatment of people with chronic hepatitis B infection *(63)* provide recommendations on who should receive HBV treatment and recommend the use of NRTIs or entecavir for this treatment.

[1] Severe chronic liver disease includes cirrhosis and end-stage liver disease and is categorized into compensated and decompensated stages. Decompensated cirrhosis is defined by the development of clinically evident complications of portal hypertension (ascites, spontaneous bacterial peritonitis, variceal haemorrhage and hepatic encephalopathy), sepsis or liver insufficiency (jaundice).

The recommended NRTI drugs for ART – TDF with 3TC or FTC – are active against HBV *(64)*. However, of these, only TDF is recommended in the WHO HBV guidelines for patients with HBV monoinfection. Furthermore, treatment of HIV-HBV coinfection without the use of TDF in the regimen may lead to flares of hepatitis B due to ART-associated immune reconstitution. Similarly, treatment discontinuation, especially of 3TC, has been associated with HBV reactivation, ALT flares and, in rare cases, hepatic decompensation. If ARV drugs need to be changed because of HIV drug resistance or toxicity, then TDF with 3TC or FTC should be continued together with the new ARV drugs.

The risk of HBV infection may be higher in HIV-infected adults. All people newly diagnosed with HIV should therefore be screened for hepatitis B surface antigen (HBsAg) and vaccinated if non-immune.

Management of HIV and hepatitis C coinfection

Hepatitis C virus (HCV)-related liver disease progresses more rapidly in people coinfected with HIV. Treatment of HCV is therefore a priority for people with HIV/HCV coinfection.

The decision to initiate treatment for HCV is more complex than in those with HCV monoinfection, because response rates are lower, the risk of potential toxicities is higher and treatment is complicated by a high pill burden, overlapping toxicities and interactions between drugs used for treating HCV and HIV. In general, clinical stabilization of HIV disease with ART is advisable prior to starting treatment for HCV, especially in people with advanced immunosuppression (CD4 count below 200 cells/mm^3). The newer, all-oral direct-acting antiviral HCV regimens (DAAs) produce similar rates of sustained virological response regardless of HIV status.

Careful consideration of drug–drug interactions is important to avoid toxicity and to ensure the efficacy of regimens used to treat both HIV and HCV. Further information regarding choice of anti-HCV regimen, including potential drug–drug interactions with ARV drugs, is provided in the 2014 WHO Global guidelines for the screening, care and treatment of persons living with hepatitis C infection *(65)*, HCV treatment using older regimens (pegylated interferon and ribavirin) generally yielded low rates of success among HCV/HIV coinfected patients, but outcomes for HCV therapy with DAAs in people with HIV coinfection are comparable to those with HCV monoinfection. Updated WHO guidelines for the treatment of people with HCV infection, including management of HCV in HIV-coinfected patients, will be released in 2016. The newer all-oral DAAs also have fewer drug–drug interactions than earlier interferon-based regimens (*see* Annex 13).

The decision to start ART among people coinfected with HCV should follow the same principles as in HIV monoinfection. Potential harmful effects of ARV drugs include their hepatotoxic effects. However, the highest rates of hepatotoxicity have been observed with ARV drugs that are no longer commonly used or recommended, including stavudine, didanosine, nevirapine or full-dose ritonavir (600 mg twice a day) *(66)*. For most HIV/HCV coinfected people, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury.

Additional guidance

- Guidelines for the screening, care and treatment of persons with hepatitis C infection. Updated version, April 2016. Geneva: World Health Organization; 2016 (http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en).
- Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/hepatitis/hepatitis-b-guidelines/en).
- Guidance on prevention of viral hepatitis B and C among people who inject drugs. Geneva: World Health Organization; 2012 (www.who.int/hiv/pub/guidelines/hepatitis/en/index.html).

5.2.5 Malaria

There is significant geographical overlap between HIV and malaria. People living with HIV have increased risk of more frequent and higher-density infection, severe malaria and malaria-related death, depending on the malaria transmission intensity of the area.

Key interventions to control malaria include early diagnosis, prompt and effective treatment with artemisinin-based combination therapies and use of insecticide-treated nets and indoor residual insecticide spraying to control the vector mosquitoes. In areas of stable malaria transmission, people with HIV (as for the general population) should routinely use insecticide-treated bed-nets or have access to indoor residual spraying to reduce their exposure to malaria. Intermittent preventive treatment during pregnancy and seasonal malaria chemoprophylaxis are also recommended in areas of high transmission. Treatment or intermittent preventive treatment with sulfadoxine-pyrimethamine should not be given to patients with HIV or HIV-exposed infants who are taking CTX prophylaxis.

People with HIV who develop malaria should receive prompt, effective antimalarial treatment. Parasitological confirmation should be undertaken for all suspected malaria cases using either microscopy or a rapid diagnostic test. However, absence or delay of parasitological diagnosis should not delay the immediate start of antimalarial treatment.

Some drugs used to treat malaria and ARV drugs may share toxicities (particularly sulfa-based drugs) and may have important pharmacokinetic interactions (especially artemesinins, lumefantrine, NNRTIs and PIs). For this reason, people receiving treatment for both HIV and malaria should be monitored closely for adverse drug reactions, and people with HIV receiving AZT or EFV should, if possible, avoid amodiaquine-containing artemisinin-based combination regimens because of the increased risk of neutropaenia in combination with AZT and hepatotoxicity in combination with EFV.

Recommendation

In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage (conditional recommendation, moderate-quality evidence).

Source: Guideline on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children. Recommendations for a public health approach. December 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_dec2014/en).

Good practice statement

In people who have HIV and uncomplicated *P. falciparum* malaria, avoid artesunate + sulfadoxine-pyrimethamine if they are being treated with co-trimoxazole and avoid artesunate + amodiaquine if they are being treated with efavirenz or zidovudine.

Intermittent preventive treatment for malaria in pregnancy should not be provided in addition to CTX prophylaxis.

Source: Guidelines for the treatment of malaria, third edition. Geneva: World Health Organization; 2015 (http://www.who.int/malaria/publications/atoz/9789241549127/en).

Additional guidance

- Guidelines for the treatment of malaria, third edition. Geneva: World Health Organization; 2015 (http://www.who.int/malaria/publications/atoz/9789241549127/en).
- WHO policy recommendation: seasonal malaria chemoprevention (SMC) for *Plasmodium falciparum* malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa. Geneva: World Health Organization; 2012 (www.who.int/malaria/publications/atoz/who_smc_policy_recommendation/en/index.html).
- Intermittent preventive treatment for infants using sulfadoxine–pyrimethamine (SP-IPTi) for malaria control in Africa: implementation field guide. Geneva: World Health Organization; 2011 (www.who.int/malaria/publications/atoz/whoivb11_07/en/index.html).
- WHO website: www.who.int/topics/malaria/en

5.2.6 Sexually transmitted infections and cervical cancer

The epidemiological synergy between HIV and sexually transmitted infections (STIs) is well established, and they frequently coexist *(67)*. Most of these infections are asymptomatic, especially among women. However, even asymptomatic STIs can cause complications, be transmitted to sexual partners and enhance HIV transmission. It has been shown that infection with *N. gonorrhoeae* substantially increases shedding of HIV-1 from the male genital tract in seminal fluid *(68)*. It has also been shown that herpes simplex virus (HSV) is associated with increased acquisition and transmission of HIV *(69–72)*. HIV infection may also alter the natural history of STIs. HIV infection has been found to change the natural history of HSV infection, resulting in more frequent recurrences in coinfected individuals, many of which are subclinical *(73)*. In addition, serious clinical manifestations of HSV, human papillomavirus (HPV), syphilis and other STIs are observed among people with advanced HIV disease.

A systematic review showed that the prevalence of STI among people with HIV on ART was as high as people not on ART, suggesting that STI coinfection could undermine efforts to use ART for prevention unless STIs are appropriately treated *(74)*. It is necessary to appropriately screen, diagnose and treat STIs, especially among the most vulnerable populations and people living with HIV. STI services should be an important part of comprehensive HIV care among adults and adolescents.

WHO guidelines on treatment of specific STIs (gonorrhoea, chlamydial infection, syphilis and HSV) are in the process of being updated. Existing recommendations on STI case management and screening for sex workers and men who have sex with men are given in the resource list below.

Cervical cancer is a preventable disease and is curable if diagnosed and treated early. Women living with HIV have a higher risk of pre-cancer and invasive cervical cancer *(75–77)*. The risk and persistence of HPV infection increases with low CD4 count and high HIV viral load. Women living with HIV should be followed closely for evidence of precancerous changes in the cervix, regardless of whether they are taking ART or their CD4 count or viral load. Cervical cancer screening leads to early detection of precancerous and cancerous cervical lesions that will prevent serious morbidity and mortality. All women with HIV should therefore be screened for cervical cancer regardless of age. Immediate management for precancerous and cancerous lesions should be provided. WHO guidance covers HPV vaccination and prevention, screening and treatment and palliative care of cervical cancer *(78)*. To date, concerns about the safety or reduced efficacy among women who may be infected with HIV should not defer the initiation of large-scale HPV immunization. HIV testing should not be a prerequisite before routine HPV immunization.

Additional resources

WHO guidance on STIs

- Sexually transmitted and other reproductive tract infections: a guide to essential practice. Geneva: World Health Organization; 2005 (http://www.who.int/reproductivehealth/publications/rtis/9241592656/en).
- STI treatment for specific STIs. Geneva; World Health Organization. Guideline revision in process.

- Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/keypopulations/en).
- Essential prevention and care interventions for adults and adolescents living with HIV in resource-limited settings. Geneva: World Health Organization; 2008 (www.who.int/hiv/pub/prev_care/OMS_EPP_AFF_en.pdf).
- Global strategy for the prevention and control of sexually transmitted infections: 2006–2015. Breaking the chain of transmission. Geneva: World Health Organization; 2007 (www.who.int/reproductivehealth/publications/rtis/9789241563475/en/index.html).
- Prevention and treatment of HIV and other sexually transmitted infections for sex workers in low- and middle-income countries. Geneva: World Health Organization; 2012 (www.who.int/hiv/pub/guidelines/sex_worker/en).
- Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people: recommendations for a public health approach. Geneva: World Health Organization; 2011 (www.who.int/hiv/pub/guidelines/msm_guidelines2011/en).
- Management of sexually transmitted infections – regional guidelines. New Delhi: WHO Regional Office for South-East Asia; 2011 (http://www.searo.who.int/entity/hiv/documents/9789290224105/en).

Other STI guidelines

- 2015 Sexually transmitted diseases treatment guidelines. Atlanta: Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention; 2015 (http://www.cdc.gov/std/tg2015).
- British Association for Sexual Health and HIV. UK guidelines on STIs: BASHH Clinical Effectiveness Group guidelines [webpage] (http://www.bashh.org/BASHH/Guidelines/Guidelines/BASHH/Guidelines/Guidelines.aspx?hkey=072c83ed-0e9b-44b2-a989-7c84e4fbd9de).
- International Union against Sexually Transmitted Infections. European STI guidelines [webpage] (http://www.iusti.org/regions/Europe/euroguidelines.htm).
- Australian Sexual Health Alliance (ASHA). Australian STI management guidelines for use in primary care [webpage] (http://www.sti.guidelines.org.au).

Cervical cancer

- Comprehensive cervical cancer control: a guide to essential practice, second edition. Geneva: World Health Organization; 2014 (http://www.who.int/reproductivehealth/publications/cancers/cervical-cancer-guide/en).
- Treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ: cryotherapy, large loop excision of the transformation zone, and cold knife conization: WHO guidelines. Geneva: World Health Organization; 2014 (http://www.who.int/reproductivehealth/publications/cancers/treatment_CIN_2-3/en).
- Human papillomavirus vaccines: WHO position paper. Wkly Epidemiol Rec. 2009;84:118–31 (www.who.int/wer/2009/wer8415.pdf).

- Comprehensive cervical cancer prevention and control: a healthier future for girls and women. Geneva: World Health Organization; 2013 (www.who.int/reproductivehealth/topics/cancers/en/index.html).
- Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Geneva: World Health Organization; 2013 (http://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en).
- Use of cryotherapy for cervical intraepithelial neoplasia. Geneva: World Health Organization; 2011 (http://whqlibdoc.who.int/publications/2011/9789241502856_eng.pdf).

5.2.7 Vaccines for people living with HIV

Immunizations are an important component of the HIV care package in many international guidelines, and people living with HIV should be assessed for eligibility for vaccination at all stages of care *(79–81)*.

Vaccines usually have better safety and efficacy among people with HIV who are receiving ART and those without significant immunosuppression, notably when the CD4 count is above 200 cells/mm^3. People with more severe immunosuppression may be at higher risk of complications from some live attenuated vaccines. Inactivated vaccines, although safe, can be less effective in this group and may require supplemental doses or revaccination after ART-induced immune reconstitution. Transient increases in plasma HIV-RNA load have also been reported after the administration of several vaccines. Available evidence indicates that these transient increases do not have clinical significance *(82,83)*.

In general, HIV-exposed infants, children and adolescents with HIV should receive all vaccines under routine vaccination according to recommended national immunization schedules *(84,85)*. In adults living with HIV, immunization against some diseases such as influenza, hepatitis B, pneumococcal disease and tetanus are frequently indicated. Other immunizations may be recommended based on age, risk factors or travel plans.

For currently recommended vaccination schedules and detailed guidance on immunization for all age groups, see WHO recommendations for routine immunization – summary tables at www.who.int/immunization/policy/immunization_tables/en/index.html.

For position papers on each vaccine, and statements about their use in people with HIV, see (www.who.int/immunization/documents/positionpapers/en/index.html).

5.2.8 HIV-related skin and oral conditions

HIV infection increases the prevalence and severity of skin and oral diseases, especially when the person's CD4 count declines below 200 cells/mm^3. As a result, skin and oral conditions affect up to 90% of adults and children with HIV in resource-limited settings. Adverse drug reactions of the skin are also 100 times more common in people living with HIV compared to the general population, and their prevalence increases as immunodeficiency worsens. Skin and oral manifestations of HIV infection can aggravate stigma in some societies, as physical signs in the form of skin diseases, such as papular pruritic eruptions, which suggest the possibility of HIV infection, could make the affected person more vulnerable to discrimination.

Certain systemic diseases, such as Kaposi sarcoma, may initially be noted on the skin and may require urgent ART to reduce mortality. Others, while not always a major cause of mortality, can be a source of severe morbidity through, for example, itching that provokes scratching, secondary infections, disfigurement, sleep disturbance and psychological stress. In the case of candidiasis, it can cause pain on swallowing, limiting a person's ability to take ARV drugs.

Due to a lack of services to promptly diagnose and manage skin and oral conditions, many people attempt to conceal the skin disease or avoid social contact. These could affect their health-seeking behaviour, leading to a negative impact on their self-esteem and quality of life. Skin and oral conditions are among the most common management problems faced by health-care workers caring for patients with HIV infection.

In 2014, WHO released guidelines for the treatment of common HIV-associated skin and oral conditions in low- and middle-income countries. These guidelines are applicable for all adults, pregnant women, adolescents and children living with HIV and recommend HIV testing for all those with unknown HIV status presenting with the discussed skin conditions. If the HIV status is known, they should be evaluated for initiation of ART.

ART is the initial treatment of choice for a number of these conditions (e.g. Kaposi sarcoma, papular pruritic eruption, eosinophilic folliculitis, molluscum contagiosum).

Additional resources

- Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults. Geneva: World Health Organization; 2014 (http://apps.who.int/iris/bitstream/10665/136863/1/9789241548915_eng.pdf?ua=1&ua=1).

5.3 Prevention, screening and management of other comorbidities and chronic care for people living with HIV

5.3.1 Assessment and management of noncommunicable diseases

General

Several studies have demonstrated that, compared to the general population, people living with HIV are at increased risk of developing a range of chronic noncommunicable diseases (NCDs), including cardiovascular disease (CVD), hypertension, diabetes, chronic obstructive pulmonary disease (COPD), kidney disease and cancers *(86–91)*.

The intersection of HIV and NCDs is strongly influenced by increasing survival due to effective ART, lifestyle factors, long-term complications of ART and other disease conditions associated with ageing *(92,93)*. Both HIV and NCDs require health systems that can deliver effective acute and chronic care and support adherence to treatment. Chronic HIV care provides the opportunity for assessment, monitoring and managing NCDs, especially through primary care. Integrating interventions, such as nutrition assessment, dietary counselling and support, smoking cessation, exercise promotion, blood pressure monitoring and – where available – cholesterol management as part of HIV care can help to reduce the risks of NCDs among people with HIV and improve HIV treatment outcomes *(94,95)*.

WHO has defined a package of essential NCD interventions (WHO PEN) and published recommendations on assessment and management of the major NCDs from the primary care level to the district hospital level. The interventions are mainly focused on assessment and management of CVD risk, including high blood pressure, type 2 diabetes, chronic respiratory diseases (asthma and COPD) and early identification of breast and cervical cancer. More information and additional guidance on WHO PEN and management of NCDs are available in the following resources:

- Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings. Geneva: World Health Organization; 2010 (www.who.int/cardiovascular_diseases/publications/pen2010/en).
- Prevention and control of noncommunicable diseases: guidelines for primary health care in low-resource settings. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/76173/1/9789241548397_eng.pdf).

Assessment and management of cardiovascular diseases

NEW

Recommendation

Assessment and management of cardiovascular risk should be provided for all individuals living with HIV according to standard protocols recommended for the general population[a] (conditional recommendation, very low-quality evidence).

[a] The WHO PEN protocol targets the following populations for CVD screening: age >40 years, smokers, people with known hypertension or diabetes mellitus, waist circumference >90 cm in women and >110 cm in men and family history of diabetes mellitus or premature CVD. See more about PEN at www.who.int/cardiovascular_diseases/ publications/ pen2010/en.

NEW

Good practice statement

Strategies for the prevention and risk reduction of cardiovascular diseases by addressing modifiable factors such as high blood pressure, smoking, obesity, unhealthy diet and lack of physical activity should be applied to all people living with HIV.

Background and rationale

Several studies have demonstrated that people with HIV have an increased risk of CVD compared to HIV-negative people in the same age ranges and that CVD accounts for an increasing proportion of mortality observed in this population *(96,97)*. Large cohort studies have confirmed that the risk of both myocardial infarction and cerebrovascular disease is 40–70% higher among people with HIV than among age- and gender-matched HIV-uninfected controls *(98–103)*. This association has been reported both in people on ART and in those who are treatment naive. Similar findings have also been reported in children and adolescents with HIV *(104)*. The mechanisms underlying the association between HIV and CVD are multifactorial and include HIV-related chronic immune

activation and inflammation, immunodeficiency and higher burdens of traditional CVD risk factors among people living with HIV *(105–109)*.

Findings from cohort data have shown that the role of ART in CVD risk and exposure to some classes of ARV drugs (PIs) causes lipid abnormalities and may increase the risk of premature CVD *(110–113)*. Associations between NRTIs and CVD risk remain the subject of debate. Although recent and cumulative exposure to some NRTIs such as ddI and ABC has been associated with increased relative risk for CVD *(114–117)*, other reviews have not found such an association *(118,119)*. However, regardless of the class of ARV drug used, it is clear that treatment with ART is beneficial compared with no treatment. Several studies have demonstrated an increased risk of CVD events among people discontinuing ART *(120)* and in people with detectable viral load *(96)*. It has been hypothesized that the increased attributable risk among people with HIV is due to increased immune activation and chronic inflammation, which remain abnormally high among people with HIV even after viral suppression *(121,122)*; both are associated with preclinical and clinical atherosclerosis. The overall beneficial role of ART on HIV morbidity and mortality has therefore been demonstrated to outweigh potential CVD risks in people with HIV.

CVD screening for people with HIV has been recommended in several HIV clinical guidelines, and several risk tools for calculating CVD probability have been used *(123–127)*. Several studies have demonstrated that incorporation of routine CVD screening for people with HIV could improve health outcomes and be cost-effective *(128–130)*. A systematic review on the use of validated tools to identify people at highest CVD risk for primary prevention shows that there is potential to lower CVD mortality and the incidence of cardiovascular events; this was particularly evident in studies with high-intensity interventions *(131)*. However, despite the overall consensus that the current CVD screening tools designed for the general population have a moderate discriminatory power to identify people with HIV at high risk for CVD events or eligibility for therapeutic interventions, these tools frequently underestimate the CVD risk in people with HIV and need to be adjusted or validated in HIV-infected populations *(132–139)*. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study group has described a CVD risk algorithm that incorporates some HIV-specific factors such as CD4 cell count and ARV drug use, which has reported better accuracy in predicting serious CVD events *(140–142)*. While this is an important step towards improving CVD risk prediction in people, it still has limitations because the study populations – all in high-income settings – have different genetic and behavioural CVD risk profiles from the majority of people living with HIV in the world. In addition, as in the case of studies reporting less direct risk predictions, the D:A:D: instrument can also significantly overestimate and underestimate CVD risk *(135–137)*.

Implementation considerations

No specific WHO recommendation for the management of CVD in people with HIV has been made in previous guidelines. However, since 2010, WHO has defined a package of essential NCD interventions (WHO PEN), along with recommendations on screening for and treating NCDs in the general population. The WHO PEN *(143)* has several programmatic advantages in the context of resource-limited settings, as it integrates other major NCDs in addition to CVD, can be implemented at the primary health-care level, can be managed by non-physicians, consists of a minimal package and has good discrimination to identify those with high CVD risk. However, the systematic review did

not identify any studies assessing the impact or use of WHO PEN interventions in people with HIV with any outcomes relevant to low- and middle-income countries. Studies on WHO PEN-based interventions in the general population from low- and middle-income countries were found, showing that the PEN protocol and universal risk assessment are cost-effective *(144–146)*. Furthermore, an evaluation of the short-term outcomes of PEN in pilot districts indicated a significant reduction in CVD risk and a healthy lifestyle in the target population *(139)*.

Disparities in CVD care among people with HIV have been reported. In two studies, people with HIV were significantly less likely to receive aspirin for CVD prevention than those without HIV *(147,148)*. Other data on medical management and outcomes following acute myocardial infarction showed that people with HIV received significantly fewer cardiovascular procedures and/or therapeutics than people without HIV *(149)*. Regular assessment and management of CVD risk among people with HIV is expected to result in better and more equitable care.

One major remaining barrier to equitable access to CVD prevention and care for people with HIV is the lack of quality data assessing proven CVD therapies in this population. For example, prospective trials on the use of statins for people with HIV have generally been small in size and have not assessed hard clinical end-points *(150)*.

Integrated multiple disease campaigns conducted in Lesotho and Uganda (SEARCH consortium), which included CVD screening and HIV testing, demonstrated the feasibility of integrated screening for communicable diseases and NCDs in community-based HIV programmes *(151,152)*. Improved diagnosis and linkage to care for CVD conditions have been shown to also improve linkage to HIV care and ART *(153)*. CVD/HIV integrated pilot services have been implemented in Kenya, Nigeria and Zambia since 2012 and shown to be feasible and acceptable, with CVD service integration implemented within the context of an HIV chronic care model *(154)*.

Research gaps

Further research is needed to unravel the complex pathophysiology of atherogenesis in people with HIV, to elucidate the relationships between traditional and HIV-associated CVD risk factors and to investigate how ART alters these interactions. Studies on the impact of early ART on CVD development, particularly in adolescents and children with HIV, are also needed. Clinical studies to assess methods of risk prediction and risk-reduction strategies for CVD applicable to people with HIV would be of great use. There is a need to validate simplified CVD screening protocols and risk-assessment algorithms that include HIV-specific risk factors to improve accuracy. Use of co-therapies for CVD such as statins, aspirin, antihypertensive drugs and metformin and measurement of their impact on HIV mortality are also important. Assessments of the unique pathophysiology, related risk factors and optimal management of downstream CVD complications associated with HIV, such as heart failure and malignant arrhythmia, are also needed. Such studies should be conducted in both high-income and resource-limited countries.

5.3.2 Assessment and management of depression in people living with HIV

NEW

Recommendation

Assessment and management of depression should be included in the package of HIV care services for all individuals living with HIV (conditional recommendation, very low-quality evidence).

People living with HIV are at high risk of mental, neurological and substance-use disorders *(155)*. Systematic reviews from both from low- and high-income countries showed that depression is one of the most prevalent mental health comorbidities in people with HIV *(156,157)*. A systematic review conducted in 2015 reported depression prevalence rates as high as 80% among people with HIV, but with wide variation across studies, which is attributed to the screening and diagnostic criteria used *(158)*. Depressive symptoms have been reported as common in many studies in sub-Saharan Africa, where the HIV burden is also high *(159,160)*.

People living with HIV who have depression are less likely to achieve optimal treatment adherence. Although chronic HIV care settings provide an opportunity to detect and manage depression among people living with HIV, it is often overlooked and unrecognized by health-care providers. Treatment or lack of it for mental health disorders can affect general health, adherence to ARV drugs and retention in care and may lead to potential side-effects and drug interactions being overlooked *(160–164)*.

The WHO Mental Health Gap Action Programme (mhGAP), first published in 2008 and updated in 2015, provides evidence-based comprehensive guidelines on the diagnosis and management of a range of mental, neurological and substance use disorders, including developmental and behavioural disorders in children and adolescents. It focuses on nine priority mental health conditions, including the diagnosis and management of depression *(165)*. Implementation of mhGAP through primary care would improve the detection and management of depression in adults when compared to standard-of-care approaches *(166)*.

A systematic review conducted to support the guideline update in 2015 *(167)* aimed to determine whether routine screening and management of depression (specifically with mhGAP criteria) improve ART adherence and treatment outcomes in people with HIV. No studies were identified explicitly reporting on mhGAP for this specific population.

Indirect evidence from a systematic review on the accuracy of using screening tools to identify depression in people living with HIV in all settings identified 18 studies, using 25 different screening instruments, compared to criterion standards for diagnosing depression *(168)*. Studies included a total of 5209 unique participants, and criterion-diagnosed depression prevalence ranged very widely by region and population. Multiple index test and criterion standards were assessed and the review evaluated each test's area under the curve (AUC) as a summary measure of accuracy (AUC above 0.9 is

considered to be highly accurate; 0.7–0.9 to be moderately accurate; 0.51–0.69 to be of low accuracy) *(168)*). Although several instruments showed very good or even excellent performance in diagnosing depression in people with HIV, the overall quality of evidence is very low. The Guideline Development Group, citing acceptability and feasibility from end-users and lack of harm, made a conditional recommendation.

Though depression is more common among people with HIV compared to the general population, there is less consistent and limited evidence to show that management of depression improves HIV treatment outcomes. However, management of depression improves mental health and general well-being in people with HIV.

The limited data on HIV and mental health service delivery models indicate that integration supports efficiency and does not increase costs of care. A narrative review from South Africa and sub-Saharan Africa suggests that integration of mental health care into existing health systems is an effective and cost-efficient approach to expanding access to mental health services for people with HIV in resource-limited settings *(169)*. There is also an ongoing study on the cost-effectiveness of screening and treatment of depression among people with HIV in sub-Saharan Africa *(170)*. However, more evidence is needed on effective models of HIV–mental health service integration in various settings *(171)*.

A survey of national HIV programme managers *(172)* found that 38% of respondents reported that mental health screening is performed in some HIV care settings, with referral for treatment when indicated. Forty-three per cent did not have mental health screening and treatment available for people with HIV. None of the countries reported countrywide implementation of mental health screening and treatment services in all HIV care settings. The top three challenges identified by programme managers for integration of mental health services in HIV care settings are shortage of human resources, skills and capacity of health-care providers and lack of funding. WHO estimates that up to 85% of people with severe mental disorders and 56% of people with depression in low- and middle-income countries do not have access to treatment *(173)*.

Implementation considerations

Screening for depression may support adherence to ART, retention in care and viral load suppression and improve the quality of life. If implemented, depression should be managed according to national standards or mhGAP. Integration or linkage to mental health services should be implemented in settings where health-care infrastructure and trained human resources are available. Implementation of treatment for depression among people with HIV may require task-shifting, building health worker capacity, national adaptation of screening tools and simplification of tools for use by non-specialized primary care providers.

Research gaps

There are several research gaps related to screening and treatment for mental health disorders and depression among people living with HIV:

- Current estimates of HIV and depression are inaccurate due to the wide variability in reports.

- Packages of care for common mental disorders are likely to be most effective among people living with HIV in low- and middle-income countries.
- The long-term impact of depression interventions in relation to HIV outcomes needs to be studied.
- The optimal time-points for mental health interventions need to be identified.

5.3.3 Drug use and drug use disorders

People living with HIV who use drugs may experience a range of disorders related to drug use, including drug dependence, intoxication, withdrawal and overdose. Injecting drug use is associated with a range of diseases and infections, including viral hepatitis, TB, septicaemia and bacterial endocarditis, in addition to HIV.

WHO, the United Nations Office on Drugs and Crime (UNODC) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommend a comprehensive package of nine interventions for HIV prevention, treatment and care for people who inject drugs; these are needle and syringe programmes, OST, HIV testing and counselling, ART, preventing and treating STIs, condom programmes, targeted behaviour change communication, preventing and treating viral hepatitis and preventing, diagnosing and treating TB.

Additional guidance

- WHO, UNODC, UNAIDS. Technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users – 2012 revision. Geneva: World Health Organization; 2012 (www.who.int/hiv/pub/idu/targets_universal_access/en/index.html).
- Community management of opioid overdose. Geneva: World Health Organization; 2014 (http://www.who.int/substance_abuse/publications/management_opioid_overdose/en).
- Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Geneva: World Health Organization; 2009 (http://whqlibdoc.who.int/publications/2009/9789241547543_eng.pdf).
- Guidance on prevention of viral hepatitis B and C among people who inject drugs. Geneva: World Health Organization; 2012 (www.who.int/hiv/pub/guidelines/hepatitis/en/index.html).
- Policy guidelines for integrating collaborative TB and HIV activities within the comprehensive package of harm reduction for people who inject drugs. Geneva: World Health Organization; 2016 (In press).

5.3.4 Nutritional care and support

Nutrition for adults and adolescents living with HIV

Low energy intake combined with increased energy demands due to HIV infection *(174–176)* and related infections may lead to HIV-related weight loss and wasting. In addition, altered metabolism, reduced appetite and higher incidence of diarrhoea may

lower nutrient intake and absorption and lead to nutrient losses. These effects may all be compounded in low-income and food-insecure contexts. Low body mass in adults (body mass index less than 18.5 kg/m^2) and weight loss and wasting in children are all independent risk factors for HIV disease progression and mortality *(177,178)*. Nutritional assessment (anthropometry, clinical and dietary assessment), counselling and support should be an integral component of HIV care and conducted at enrolment in care and monitored across the care continuum. Malnourished HIV-infected patients, especially in food-insecure contexts, may require food supplements in addition to ART to support nutritional recovery. Weight loss or failure to regain or maintain a healthy weight at any stage of HIV infection and/or while on ART should trigger further assessment and appropriate interventions.

WHO is revising recommendations for nutritional care and support of adolescents and adults living with HIV, including pregnant and lactating women.

Nutrition for children living with HIV

Nutritional assessment is essential to identify malnutrition and growth faltering early. Infants and children should undergo initial nutritional assessment (evaluation of nutritional status, diet and symptoms) and then be weighed and have height measured at each visit, and monitored with reference to WHO or national growth curves. Growth monitoring should also be integrated into the assessment of ART response *(179)*. If poor growth is identified, then further assessment should be performed to determine the cause, and plan an appropriate response. The 2009 guidelines for an integrated approach to the nutritional care of children living with HIV provide details of nutritional interventions.

Additional guidance

- Nutrition assessment, education, counselling and support for adolescents and adults living with HIV: A programming guide. Food and nutrition in the context of HIV and TB. Geneva: World Food Programme, PEPFAR, USAID, UNAIDS 2014. (http://reliefweb.int/sites/reliefweb.int/files/resources/wfp271543.pdf).
- Guidelines on HIV and infant feeding 2010: principles and recommendations for infant feeding in the context of HIV and a summary of evidence. Geneva: World Health Organization; 2010 (http://whqlibdoc.who.int/publications/2010/9789241599535_eng.pdf).
- Guidelines for an integrated approach to the nutritional care of HIV-infected children (6 months–14 years): handbook. Preliminary version for country introduction. Geneva: World Health Organization; 2009 (http://whqlibdoc.who.int/publications/2009/9789241597524_eng_Handbook.pdf).
- WHO, FAO. Nutritional care and support for people living with HIV/AIDS: a training course. Geneva: World Health Organization; 2009 (www.who.int/nutrition/publications/hivaids/9789241591898/en/index.html).

5.3.5 Palliative care: symptom management and end-of-life care

Through all stages of HIV disease, and when receiving treatment, people living with HIV may experience various forms of pain and other discomfort. Care providers should identify and treat the underlying cause where possible, while also controlling the pain. Further, effectively managing the side-effects of ART is important to support adherence. WHO is currently in the process of developing guidelines for palliative care.

Additional guidance

- IMAI district clinician manual: hospital care for adolescents and adults. Guidelines for the management of common illnesses with limited resources. Geneva: World Health Organization; 2011 (www.who.int/hiv/pub/imai/imai2011/en).

5.3.6 General care for people living with HIV

Countries should establish a package of general HIV care interventions, in addition to ART, for people living with HIV to reduce HIV transmission, prevent illness and improve their quality of life. General care includes basic HIV prevention, promoting the health of people living with HIV, and screening, prophylaxis and management of HIV-related coinfections and comorbidities. WHO has produced summary guidance on general care and prevention interventions *(180–182)*, and recommends a package of 13 prevention interventions for adults and adolescents living with HIV in resource-limited settings *(1)*. These are (1) psychosocial counselling and support; (2) disclosure and partner notification; (3) CTX prophylaxis; (4) TB counselling, screening and preventive therapy; (5) preventing common fungal infections; (6) treatment of STIs and supporting reproductive health needs, including prevention of and screening for cervical cancer; (7) preventing malaria (CTX, bed-nets and particularly preventing malaria among pregnant women); (8) the use of vaccines for the prevention of pneumococcal disease, influenza, hepatitis B and yellow fever; (9) provision of adequate nutrition; (10) family planning services; (11) prevention of mother-to-child HIV transmission; (12) needle and syringe programmes for people who inject drugs; and (13) water, sanitation and hygiene.

A general care package will vary according to the epidemic type, populations affected and prevalence of coinfections, other comorbidities and health conditions. Table 5.2 provides an overview of the elements of a general care package for people living with HIV. In the era of universal treatment for all people with HIV, the time between HIV diagnosis, enrolment into care and initiation of ART may be addressed in one visit or in an expedient manner to reduce loss to follow-up and provide life-saving ART as soon as possible. WHO no longer recommends the need for preparation visits prior to ART initiation; many of the care aspects outlined in Table 5.2 can be accomplished once ART has started.

Table 5.2. Overview of key elements of general care over the continuum of HIV care for people living with HIV

Service	At HIV diagnosis	At enrolment into care	At initiation of ART	Stable while receiving ART	At treatment failure and switching of ART regimen
General care					
WHO clinical staging Past and current HIV- related conditions	✔	✔	✔		
Preparing people for ART	✔	✔	✔		
Preparing, assessing and supporting adherence	✔	✔	✔	✔	✔
Current medications		✔	✔	✔	✔
Pregnancy status Family planning and contraception	✔	✔	✔	✔	✔
Support for disclosure and partner notification	✔	✔	✔	✔	✔
Risk reduction counselling and combination HIV prevention approaches	✔	✔	✔	✔	✔
Assessing, preventing and managing noncommunicable diseases	✔	✔	✔	✔	✔
Screening for and managing mental health problems and substance use **Psychosocial counselling and support**	✔	✔	✔	✔	✔
Managing pain and symptoms	✔	✔	✔	✔	✔
Nutritional assessment and counselling	✔	✔	✔	✔	✔
Nutritional, growth and development assessment in children and adolescents Infant and child feeding	✔	✔	✔	✔	✔

Table 5.2. (continued)

Service	At HIV diagnosis	At enrolment into care	At initiation of ART	Stable while receiving ART	At treatment failure and switching of ART regimen
Preventing and treating coinfections					
Co-trimoxazole preventive therapy	✔	✔	✔	✔	✔
Intensified TB case-finding	✔	✔	✔		✔
Isoniazid preventive therapy		✔	✔		
Screening for cryptococcal infection and fungal prophylaxis		✔	✔		
Screening for hepatitis B and C		✔	✔		✔
Malaria prevention (insecticide-treated bed-nets and prophylaxis)	✔	✔	✔	✔	✔
Screening for sexually transmitted infections	✔	✔	✔	✔	✔
Prevention of and screening for cervical cancer		✔	✔	✔	✔
Assessing for vaccine-preventable diseases	✔	✔	✔	✔	✔

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