



World Health
Organization

GUIDELINES



GUIDELINES FOR
**MANAGING ADVANCED
HIV DISEASE AND
RAPID INITIATION
OF ANTIRETROVIRAL
THERAPY**

JULY 2017

HIV TREATMENT



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Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy,
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ABBREVIATIONS AND ACRONYMS

ARV	antiretroviral
ART	antiretroviral therapy
BCG	Bacille Calmette-Guérin
CI	confidence interval
CrAg	cryptococcal antigen
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIV	human immunodeficiency virus
LF-LAM	lateral flow lipoarabinomannan
NNRTI	non-nucleoside reverse-transcriptase inhibitor
PICO	population, intervention, comparator and outcome
RR	relative risk
TB	tuberculosis
UNICEF	United Nations Children's Fund

DEFINITION OF KEY TERMS

Age groups and populations

The following definitions for adults, adolescents, children and infants are used to ensure consistency within these guidelines. Other agencies may use different definitions.

- An adult is a person older than 19 years.
- An adolescent is a person 10–19 years old inclusive.
- A child is a person younger than 10 years old.
- An infant is a child younger than one year of age.

Advanced HIV disease

- For adults, adolescents, and children \geq five years, advanced HIV disease is defined as a CD4 cell count <200 cells/mm³ or a WHO clinical stage 3 or 4 event at presentation for care.
- All children with HIV younger than five years old should be considered as having advanced disease at presentation (for rationale, see section 2.2).
- A seriously ill adult or adolescent is defined as having any of the following danger signs: respiratory rate ≥ 30 breaths per minute; heart rate ≥ 120 beats per minute; or unable to walk unaided. Other clinical conditions, such as body temperature $\geq 39^\circ\text{C}$ can also be considered based on local epidemiology and clinical judgement.
- A seriously ill child is defined as having any of the following danger signs: lethargy or unconsciousness; convulsions; unable to drink or breastfeed; and repeated vomiting. Other clinical conditions such as body temperature $\geq 39^\circ\text{C}$ and age-defined tachycardia and/or tachypnoea can be considered based on clinical judgement.
- A severely immunosuppressed adult is defined as having a CD4 cell count <50 cells/mm³.
- WHO Clinical Staging is a way to categorize HIV disease severity based on new or recurrent clinical events. There are 4 WHO clinical stages which range from mild symptoms (WHO clinical stage 1) to severe symptoms (WHO clinical stage 4).

Antiretroviral therapy

ARV (antiretroviral) drugs refer to the medicines used to treat and prevent HIV infection.

ART (antiretroviral therapy) refers to the use of a combination of three or more ARV drugs for treating HIV infection. ART involves lifelong treatment.

Clinically well refers to a person who has no active WHO clinical stage 3 or 4 disease and a CD4 cell count ≥ 200 cells/mm³.

Stable on ART refers to the following criteria: receiving ART for at least 12 months; no adverse drug reactions requiring regular monitoring; no current illnesses; and good understanding of adherence and evidence of treatment success: two consecutive undetectable viral load measures or, in the absence of viral load monitoring, rising CD4 cell counts or CD4 cell counts exceeding 200 cells/mm³ and an objective adherence measure.

Treatment failure refers to the current WHO virological criteria for treatment failure, which is two consecutive viral load tests ≥ 1000 HIV RNA copies/ml.

Viral suppression refers to a viral load below the detection threshold using viral assays (< 1000 HIV RNA copies/ml).

Prophylaxis and treatment

Prophylaxis aims to avoid either the first occurrence of infections (primary prophylaxis) or their recurrence (secondary prophylaxis or maintenance).

Pre-emptive therapy is an alternative strategy to prophylaxis that aims to prevent progression to disease after infection has occurred. For example, the term pre-emptive therapy is used to describe treating people who are positive for cryptococcal antigen since, by the time cryptococcal antigen is positive in the blood, disease and dissemination are considered significant even if they are not clinically apparent.

Presumptive treatment (also referred to as empirical treatment) refers to treatment that is initiated based exclusively on clinical suspicion and relying on clinical judgement. Presumptive treatment is generally reserved for severely ill people in settings where laboratory investigations are not available. There are two broad approaches: (1) treatment without laboratory diagnosis based on the opinion of an experienced clinician after considering all the available information and (2) treatment based on a prespecified clinical rule that aims to identify individuals at higher risk and does not require clinical judgement.

Service delivery

Continuum of HIV services refers to a comprehensive package of HIV prevention, diagnostic, treatment, care and support services provided for people at risk of HIV infection or living with HIV and their families. Examples of these services include pre-exposure prophylaxis; HIV testing and linkage to care; TB screening, prevention, diagnosis and care; management of opportunistic infections and other comorbid conditions; initiating, maintaining and monitoring ART response; adherence support; switching to second-line and third-line ART; and palliative care.

Continuum of HIV care refers to a comprehensive package of HIV services for people living with HIV.

Differentiated service delivery is an approach that simplifies and adapts HIV services to better serve the needs of people living with HIV and reduce unnecessary burdens on the health system. For example, under a differentiated service delivery approach, people who are stable on treatment would have a reduced frequency of clinical visits and medication prescribing (3-6 months), allowing health service resources to focus on care for patients who are ill and need intensive clinical follow up.

A public health approach aims to ensure the widest possible access to high-quality services at the population level, based on simplified and standardized approaches, and to strike a balance between implementing the best-proven standard of care and what is feasible on a large scale in resource-limited settings. For HIV, key elements of a public health approach include: simplified drug formularies; large-scale use of fixed-dose combinations for first-line treatment for adults, adolescents and children; care and drugs provided free of user charges at the point of service delivery; decentralization and integration of services, including task sharing and simplified approaches to clinical monitoring.

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Diana Gibb and **Sayoki Mfinanga** were principal investigators on trials considered for the formulation of the recommendation for the package of care for people presenting with advanced disease and were excluded from the decision-making process for these recommendations. There were no other conflicts of interest. Annex 3 describes the full process for managing declarations of interests.

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EXECUTIVE SUMMARY

In 2016, WHO published its consolidated guidelines on the use of antiretroviral (ARV) drugs for treating and preventing HIV infection. As part of this revision, WHO recognized that, as antiretroviral therapy (ART) is scaled up and countries adopt the “treat all” policy, ART services will need to be differentiated to provide adapted packages of care to people living with HIV with varied clinical needs. The four groups of people defined are (1) individuals presenting or returning to care with advanced HIV disease, (2) individuals presenting or returning to care when clinically well (3), individuals who are clinically stable on ART and (4) individuals receiving an ART regimen that is failing.

The objectives of these guidelines are to provide recommendations outlining a public health approach to managing people presenting with advanced HIV disease, and to provide guidance on the timing of initiation of antiretroviral therapy (ART) for all people living with HIV. To develop these recommendations, WHO convened a Guideline Development Group in March 2017. Using the evidence generated through two systematic reviews, the GRADE process was used to determine the strength of the recommendation and quality of the evidence.

The first set of recommendations addresses the specific needs of people with advanced HIV disease and defines a package of interventions aimed at reducing HIV-associated morbidity and mortality. WHO recommends that a package of screening, prophylaxis, rapid ART initiation and intensified adherence interventions be offered to everyone living with HIV presenting with advanced disease. This is a strong recommendation that applies to all populations and age groups. The specific components of the advanced HIV disease package are detailed in Table 1, page 9 of the guidelines. The guidelines also include an algorithm to support decision making for providing care for people with advanced HIV disease.

The second set of recommendations defines how rapidly ART should be initiated within the context of the “treat all” policy, especially when coinfections are present. WHO strongly recommends that rapid ART initiation should be offered to people living with HIV following confirmed diagnosis and clinical assessment. Rapid initiation of ART is defined as within seven days of HIV diagnosis. WHO further strongly recommends ART initiation on the same day as HIV diagnosis based on the person’s willingness and readiness to start ART immediately, unless there are clinical reasons to delay treatment. Both of these recommendations apply to all populations and age groups. People with advanced HIV disease should be given priority for clinical assessment and treatment initiation.

The target audience for these guidelines is primarily national HIV programme managers, who are responsible for adapting these new recommendations at the country level. The guidelines are also relevant to clinicians and to other stakeholders, including people living with HIV, national civil society organizations, implementing partners, nongovernmental organizations and domestic and international funders of HIV programmes.

Recommendations

Management of advanced HIV disease

A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease.

(Strong recommendation, moderate-quality evidence)

Rapid initiation of antiretroviral therapy

Rapid ART initiation^a should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment.

(Strong recommendation: high-quality evidence for adults and adolescents; low-quality evidence for children)

^aRapid initiation is defined as within seven days from the day of HIV diagnosis; people with advanced HIV disease should be given priority for assessment and initiation.

ART initiation should be offered on the same day to people who are ready to start.

(Strong recommendation: high-quality evidence for adults and adolescents; low-quality evidence for children)

Good practice statement

ART initiation should follow the overarching principles of providing people-centred care. People-centred care should be focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity and respect, especially for vulnerable populations, and should promote engaging and supporting people and families to play an active role in their own care by informed decision-making.

The introduction of the “treat all” recommendation (ART for all people living with HIV regardless of CD4 cell count) supports the rapid initiation of ART, including the offer of same-day initiation where there is no clinical contraindication. People with no contraindication to rapid ART initiation should be fully informed of the benefits of ART and offered rapid ART initiation, including the option of same-day initiation. Rapid ART start is especially important for people with very low CD4 cell count, for whom the risk of death is high. People should not be coerced to start immediately and should be supported in making an informed choice regarding when to start ART.

1. INTRODUCTION

1.1 Objectives

The objectives of these guidelines are:

- to provide updated, evidence-informed clinical recommendations outlining a public health approach to managing people presenting with advanced HIV disease, focusing on settings with limited health system capacity and resources; and
- to provide guidance on the rapid initiation of antiretroviral therapy (ART) for all people living with HIV, including starting ART on the same day as HIV diagnosis.

1.2 Target audience

These guidelines are primarily intended for use by national HIV programme managers. They are also of value to the following audiences:

- people living with HIV and community-based organizations;
- national HIV treatment and prevention advisory boards;
- national TB programme managers;
- clinicians and other health workers;
- managers of national laboratory services; and
- international and bilateral agencies and organizations that provide financial and technical support to HIV programmes in low- and middle-income countries.

1.3 Guiding principles

The following principles have informed the development of these guidelines and should guide the implementation of the recommendations.

- The guidelines should contribute to realizing the Sustainable Development Goals through achieving key global and national HIV goals.
- The guidelines are based on a public health approach to scaling up the use of antiretroviral (ARV) drugs along the continuum of HIV prevention, care and treatment.
- Implementation of the guidelines need to be accompanied by efforts to promote and protect the human rights of people who need HIV services, including ensuring informed consent, preventing stigma and discrimination in the provision of services and promoting gender equity.
- Implementation of the recommendations in these guidelines should be informed by local context, including HIV epidemiology and prevalence of other comorbidities, availability of resources, the organization and capacity of the health system and anticipated cost-effectiveness.

Methods for the development of these guidelines are provided in Annex 2.

2. RECOMMENDATIONS TO REDUCE MORTALITY AND MORBIDITY AMONG PEOPLE PRESENTING WITH ADVANCED HIV DISEASE

2.1 Background

The burden of morbidity and mortality associated with HIV infection has decreased over the past decade as access to ART has increased. Since 2003, the annual number of people dying from AIDS-related causes has declined by 43%, with 1.1 million AIDS-related deaths reported in 2015 (1). This decline is largely the result of expanded access to ART and an evolution towards treating people earlier in the course of HIV infection (2); however, the decline in AIDS-related deaths appears to have plateaued during the past three years (1).

In 2015, WHO recommended that all people living with HIV start ART irrespective of clinical or immune status, and most national guidelines have adopted this recommendation (3). This shift towards earlier initiation of ART, together with improved access to HIV testing and treatment, has led to an overall improvement in health status at the start of ART (4), as reflected by a gradual increase in the median CD4 cell count at the start of ART in most settings (5).

Despite this progress, up to half of people living with HIV continue to present to care with advanced HIV disease – defined by WHO as having a CD4 cell count <200 cells/mm³ or a WHO clinical stage 3 or 4 disease (6). People presenting with advanced HIV disease are at high risk of death, even after starting ART, with the risk increasing with decreasing CD4 cell count, especially with CD4 cell count <100 cells/mm³ (7–9). Advanced HIV disease is also associated with increased health-care costs (10).

The scaling up of ART has benefited from a public health approach that has emphasized standardized, simplified treatment protocols along with decentralization, integration and task sharing to support service delivery (11). To date, service delivery within a public health approach in resource-limited settings has provided little differentiation of how ART is provided to people with differing clinical needs. The 2016 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (hereinafter referred to as the 2016 WHO consolidated ARV guidelines) identifies four groups of people with specific needs:

- individuals presenting or returning to care with advanced HIV disease (WHO stage 3 or 4 disease and/or CD4 < 200 cells/mm³); such individuals may be ART naive or have interrupted treatment;
- individuals presenting or returning to care when clinically well (absence of WHO clinical stage 3 or 4 disease and/or CD4 cell count ≥ 200 cells/mm³); such individuals may be ART naive or have interrupted treatment;
- individuals who are clinically stable on ART;¹ and
- individuals receiving an ART regimen that is failing.

For each of these categories, services may be differentiated to ensure that a people-centred approach to ART delivery is provided within a public health approach. People who are stable on ART with a suppressed viral load may be seen less frequently and receive longer supplies

¹ Defined by WHO as: receiving ART for at least 12 months, no adverse drug reactions requiring regular monitoring, no current illnesses, good understanding of adherence and evidence of treatment success (two consecutive undetectable viral load measures or, in the absence of viral load monitoring, rising CD4 cell counts or CD4 cell counts exceeding 200 cells/mm³) and an objective adherence measure.

of ART. For those with advanced HIV disease, more intensive follow-up and a package of interventions could reduce morbidity and mortality in this vulnerable group.

These guidelines focus on individuals presenting with advanced HIV disease. This category includes people presenting to care for the first time following an HIV diagnosis and people who had previously started ART and are re-engaging with care after a period of ART interruption.

The 2016 WHO consolidated ARV guidelines contain several recommendations to support disease prevention, diagnosis and treatment among people presenting with advanced HIV disease. However, the uptake of these recommendations is variable. The objective of these guidelines is to provide evidence-informed clinical recommendations outlining a public health approach to managing people presenting with advanced HIV disease, focusing on settings with limited health system capacity and resources.

2.2 Definition of advanced HIV disease

The following consensus definition of advanced HIV disease (see panel below) was defined through a Delphi process during the development of the 2016 WHO consolidated ARV guidelines (6). This definition has been used throughout the development of the recommendations for advanced HIV disease for adults. For children, the Guideline Development Group put forward an expanded definition that all children younger than five years should be considered to have advanced HIV disease at presentation. This recognizes the fact that most children younger than five years present for care with advanced immunosuppression (12), and they have a heightened risk of disease progression and mortality regardless of their clinical and immune condition (13). Moreover, varying age-dependent CD4 cell count definitions for advanced immunosuppression among children younger than five years make definitions based on CD4 cell count difficult to implement in programmatic settings.

Definition of advanced HIV disease

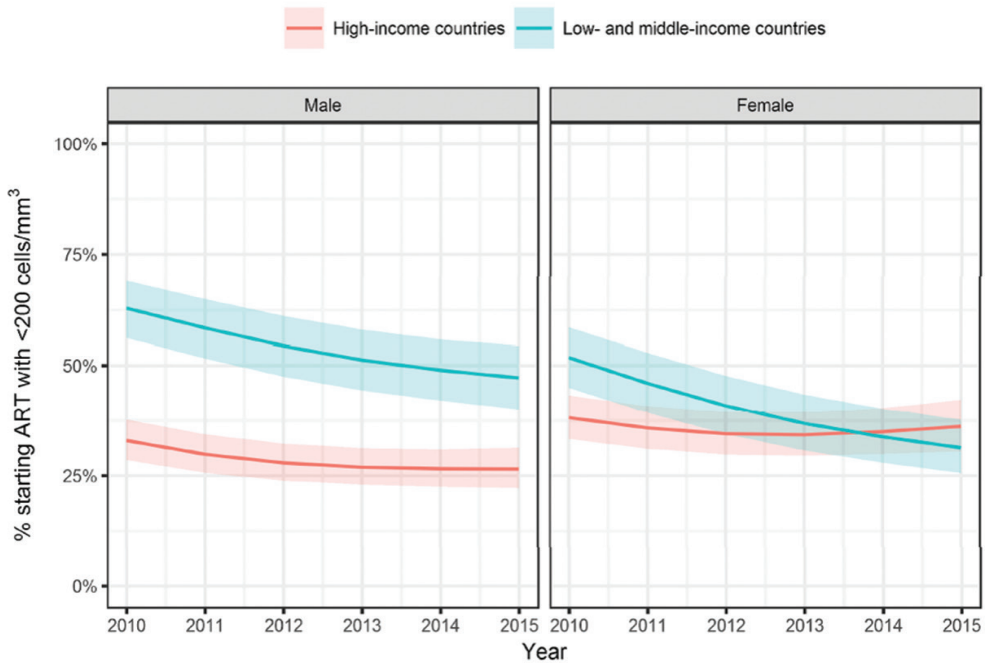
For adults and adolescents, and children older than five years, advanced HIV disease is defined as CD4 cell count $<200\text{cells/mm}^3$ or WHO stage 3 or 4 event.

All children younger than five years old with HIV are considered as having advanced HIV disease.

2.3 Burden of advanced HIV disease

The proportion of people presenting with advanced HIV disease has remained largely unchanged during the past five years although the number of people receiving ART in low- and middle-income settings more than doubled over this period (1). Recent estimates suggest that about 30–40% of people living with HIV starting ART in low- and middle-income settings have a CD4 cell count of less than 200 cells/mm^3 , and 20% have a CD4 cell count of less than 100 cells/mm^3 (14,15); in some settings, up to half of people present to care with advanced HIV disease (Figure. 1) (16). An additional number of people with advanced HIV disease have temporarily interrupted ART and return to care after a period of time off treatment when their CD4 cell count has dropped and they may have developed clinical symptoms. Studies suggest that about 25% of people interrupt treatment at some point after starting ART, with durations of treatment interruption ranging from a few days to longer than six months (17,18). One study, from South Africa, found that 19% of the people admitted to hospital with advanced HIV disease had previously initiated and interrupted their ART, and a further 21% of admissions were receiving ART with an unsuppressed viral load (19).

Figure 1 Proportion of people with advanced HIV disease starting ART by sex and country income group, 2010–2015



The results are based on 951 855 adults from 55 countries after imputation of missing data. The shaded areas represent 95% confidence intervals. Source: IeDEA/COHERE–WHO Collaboration (20)

Leading causes of mortality among adults with advanced HIV disease globally include tuberculosis (TB), severe bacterial infections, cryptococcal meningitis, toxoplasmosis and *Pneumocystis jirovecii* pneumonia. Among children, TB, severe bacterial infections, *Pneumocystis jirovecii* pneumonia, diarrhoeal diseases, malnutrition and wasting are the leading causes of death (9 21,23).

Tuberculosis

TB is the leading cause of morbidity and mortality among people living with HIV (24), accounting for one third of the estimated 1.1 million people dying from AIDS-related causes globally in 2015, with most of these TB-associated deaths (200 000 cases) occurring among men (25). TB also remains a leading cause of HIV-associated hospitalization among adults and children living with HIV worldwide (26). Young children living with HIV have an especially high risk of progressing to TB disease following initial infection (27,28). The 2016 WHO consolidated ARV guidelines summarize the WHO recommendations for the prevention, diagnosis and treatment of TB among people living with HIV (29).

Severe bacterial infections

People with advanced HIV disease frequently have severe bacterial infections, including bloodstream, respiratory, central nervous system and gastrointestinal infections (30). The burden of mortality and morbidity attributable to severe bacterial infections is poorly characterized largely because appropriate diagnostic facilities are lacking. Severe bacterial infections are estimated to cause more than one third of the hospitalizations among adults and children living with HIV worldwide (21). Co-trimoxazole (trimethoprim-sulfamethoxazole) prophylaxis provides protection against some but not all severe bacterial infections, and WHO guidelines recommend providing lifelong co-trimoxazole prophylaxis to everyone living with

HIV regardless of CD4 cell count in settings where severe bacterial infections or malaria are highly prevalent. Increasing resistance to antimicrobial drugs can complicate the treatment of people with severe bacterial infections.

Cryptococcal meningitis

The incidence of cryptococcal meningitis remains substantial despite scale-up of ART (31). A recent review (32) estimated that there were 223 100 incident cryptococcal meningitis cases globally in 2014, with 73% of the cases occurring in sub-Saharan Africa; the annual global deaths from cryptococcal meningitis were estimated to be 181 100. Cryptococcal meningitis is a leading cause of mortality among hospitalized adults living with HIV, accounting for 15–20% of adult deaths (21,33), but is less common among children living with HIV (34). The 2016 WHO consolidated ARV guidelines summarize the WHO recommendations for the prevention, diagnosis and treatment of cryptococcal meningitis. Pre-emptive therapy for cryptococcal antigen-positive asymptomatic people is a key strategy to prevent cryptococcal meningitis (29).

***Pneumocystis jirovecii* pneumonia**

Pneumocystis jirovecii pneumonia is a leading cause of mortality among hospitalized adults (13%) and children (29%) living with HIV (21). However, the global burden of morbidity and mortality attributable to *Pneumocystis jirovecii* pneumonia is poorly characterized because appropriate diagnostic facilities are lacking in most settings. This highlights the need for more accurate and feasible diagnostic approaches and improved access to co-trimoxazole and ART.

Toxoplasmosis

Cerebral toxoplasmosis is the most frequent cause of expansive brain lesions among adults living with HIV not receiving co-trimoxazole. Toxoplasmosis is a common protozoan infection among people with HIV, with the prevalence of coinfection especially high in sub-Saharan Africa (45%), Latin America and the Caribbean (49%) and North Africa and the Middle East (61%) (35). People with latent toxoplasmosis infection are at risk of developing cerebral toxoplasmosis when their CD4 count falls below 200 cells/mm³. The diagnosis of cerebral toxoplasmosis requires imaging techniques, such as computed tomography scans, which are rarely available in most sub-Saharan African settings, and thus, the knowledge of disease burden is limited. About 15% of the hospitalized adults living with HIV dying from AIDS-related illnesses die from cerebral toxoplasmosis (21). Ocular and pulmonary disease can also occur with or without concomitant encephalitis (36). Treatment options include high-dose co-trimoxazole or pyrimethamine-based regimens (plus sulfadiazine or clindamycin plus folinic acid), which appear to be equivalent in terms of safety and efficacy; however, co-trimoxazole is readily available in resource-limited settings (37).

Cytomegalovirus

Cytomegalovirus infection is a systemic viral infection that usually manifests as cytomegalovirus retinitis among severely immunocompromised people; the reported prevalence of cytomegalovirus retinitis is highest in Asia and appears to be low in Africa (38). Among children, cytomegalovirus is responsible for cytomegalovirus pneumonitis, and HIV-exposed infants have a higher incidence of congenital cytomegalovirus (39). Since cytomegalovirus is a systemic infection, improving access to early diagnosis and affordable, oral systemic treatment with valganciclovir is a priority.

Other causes

Other fungal infections, notably histoplasmosis and talaromycosis, are associated with advanced HIV disease in specific geographical areas.

Histoplasmosis is a systemic fungal infection with an especially high prevalence in Central and South America, where it can be a leading cause of AIDS-related deaths (40). Lack of simple diagnostic tests limits knowledge of the disease burden.

Talaromycosis (formerly known as penicilliosis) is a systemic mycosis that is endemic to many countries in South-East Asia, including parts of China and India, and is a leading cause of HIV-associated mortality, especially among individuals with a CD4 cell count <100 cells/mm³ (41,42). Untreated disseminated infection is usually fatal, and even when appropriate therapy is provided, the mortality rates among hospitalized people are up to 30% (41,42). The results from a recent randomized trial conducted in Viet Nam (43) found that mortality among people treated with amphotericin B was half that among people treated with itraconazole (11.3% versus 21.0%); amphotericin B was also associated with better clinical response, fungicidal activity and fewer disease complications, suggesting that amphotericin B should be made available to people living with HIV who have *Talaromyces* infection.

Other causes of mortality among people with advanced disease that are less common and not addressed by these guidelines include Kaposi sarcoma, gastrointestinal infections and renal failure.

2.4 Role of CD4 cell count testing in identifying and managing people with advanced HIV disease

The 2016 WHO consolidated ARV guidelines recommend starting ART regardless of CD4 cell count and that the use of CD4 cell count for ART response monitoring can be stopped in settings where routine viral load monitoring is available and people are stable on ART (29). However, CD4 cell count testing at baseline for all people living with HIV remains important (44). Relying on clinical staging alone risks missing substantial numbers of people living with HIV with severe immune suppression. In a study from Kenya, Malawi, Uganda and Zimbabwe, almost half the people with CD4 count <100 cells/mm³ were classified as having WHO clinical stage 1 or 2 disease (45). Hence, identifying people with advanced HIV disease who are eligible for elements of a package of care requires CD4 cell count testing. In addition, determining the immune status of people whose treatment is failing by virological criteria can help in guiding clinical management decisions.

2.5 Providing a package of care to reduce mortality and morbidity among people with advanced HIV disease

Recommendation

A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease.

(Strong recommendation, moderate-quality evidence)

Rationale and supporting evidence

To address the leading causes of morbidity and mortality among people with advanced HIV disease, notably TB, severe bacterial infections, cryptococcal meningitis and cerebral toxoplasmosis (9,21), the 2016 WHO consolidated ARV guidelines recommend several individual interventions aimed at reducing morbidity and mortality among people with advanced HIV disease (29). Summarized in Table 1 below, these include the use of co-trimoxazole prophylaxis, TB preventive treatment, using Xpert® MTB/RIF (a nucleic acid based molecular test) for TB diagnosis among symptomatic people, using the lateral flow lipoarabinomannan (LF-LAM) antigen test for people with symptoms suggesting TB and who have a CD4 count ≤ 100 cells/mm³ or who are seriously ill, and cryptococcal antigen screening in those with CD4 cell count ≤ 100 and pre-emptive antifungal treatment for those with positive blood cryptococcal antigen.

A systematic review identified two randomized trials of packaged interventions aimed at people presenting with advanced HIV disease (45,46).

The first trial (REMSTART), conducted in the United Republic of Tanzania and Zambia, randomized 1999 ART-naïve adults living with HIV with CD4 cell count < 200 cells/mm³ to receive enhanced clinic-based care with serum cryptococcal antigen screening and pre-emptive antifungal treatment for those who tested cryptococcal antigen-positive and additional community support compared with standard care (46). ART was initiated within an average of two weeks for all trial participants (delayed by two weeks among people diagnosed with TB). The additional community support comprised a weekly home or community visit provided by trained and paid lay workers who delivered ART in the community, provided adherence support, and monitored participants for signs and symptoms of drug toxicity or new symptoms. Both groups received enhanced TB screening with Xpert® MTB/RIF regardless of symptoms at baseline (in the United Republic of Tanzania, people were rescreened for TB 6–8 weeks after ART initiation using Xpert® MTB/RIF regardless of symptoms). In this trial, the combination of four short home or community visits by lay workers combined with cryptococcal antigen screening followed by treatment for cryptococcal antigenaemia led to a 28% reduction in mortality among people presenting with advanced HIV disease (mortality was 13% in the intervention group versus 18% in the group receiving standard care). A tendency towards improved ART adherence in the intervention group compared with the standard-of-care group was reported at six months in the intervention arm (relative risk (RR) 1.05, 95% CI 1.00–1.10), but no difference was noted by 12 months on ART.

The second trial (REALITY) enrolled 1805 mainly adults living with HIV with CD4 cell counts < 100 cells/mm³ (median CD4 cell count was 36 cells/mm³ and half were classified as WHO clinical stage 1 or 2) from Kenya, Malawi, Uganda and Zimbabwe (45). All underwent screening for active TB at enrolment using a symptom checklist with sputum examination and chest X-ray if symptoms were present. Trial participants were randomized to the standard of care (co-trimoxazole) according to national guidelines or an enhanced prophylaxis package (12 weeks of fluconazole (100 mg once daily), 12 weeks of a fixed-dose combination of co-trimoxazole (800 + 160 mg) + isoniazid (300 mg) + pyridoxine (25 mg) as a scored once-daily tablet, five days of 500 mg of azithromycin once daily and a single dose of 400 mg of albendazole). The doses were halved for children 5–12 years old (except for albendazole). All drugs were started simultaneously, and ART was offered on the same day as the prophylaxis package. Cryptococcal antigen screening was not performed prospectively. After 12 weeks, fluconazole was stopped and either co-trimoxazole (Malawi) or the fixed-dose combination (other countries) was continued in the enhanced-prophylaxis group; co-trimoxazole was continued or switched to the fixed-dose combination in the standard-prophylaxis group. Isoniazid + pyridoxine use beyond 12 weeks followed national isoniazid preventive therapy guidelines. Participants already receiving or needing antimicrobial treatment or prophylaxis pragmatically received it outside the randomized design and received other prophylaxis according to randomization.

In this study, the enhanced prophylaxis package at the time of ART initiation reduced mortality by 27% (from 12.2% to 8.9%) over 24 weeks. Mortality from *Cryptococcus* was significantly reduced from 1.5% to 0.4%, and mortality from unascertained causes (most people died at home) from 6.0% to 3.8%. TB incidence was reduced by 28%, cryptococcal disease by 62% and hospitalization by 17% in the enhanced prophylaxis group compared with the standard-of-care group. The additional pill burden (three pills on day 1, two pills on days 2–5 and one pill thereafter) did not adversely affect viral load suppression which was the same in both groups. No difference in serious adverse events was observed. Most of the deaths in this study occurred within the first three weeks, highlighting the value of early prophylaxis for people with advanced disease. Economic analysis suggested that enhanced prophylaxis would be cost-effective for nearly all resource-limited countries.

Overall, the Guideline Development Group considered that these two randomized trials together provide moderate-quality evidence for the general approach to providing a package of targeted interventions to reduce mortality and morbidity among people presenting with advanced HIV disease in sub-Saharan Africa. Nevertheless, the Guideline Development Group was concerned about the available evidence to support the specific interventions assessed in the trials. Although severe bacterial infections are recognized as a common and frequently overlooked cause of HIV-associated morbidity and mortality, the Guideline Development Group did not consider that there is currently enough evidence to recommend including an additional broad-spectrum antibiotic (500 mg of azithromycin once a day for five days) within the package and that the unclear benefits of this specific component of the REALITY package (mortality reduction could not clearly be attributed to a decline in bacterial infections) do not outweigh concerns about the potential for antimicrobial resistance development. Nevertheless, the Guideline Development Group recognized the importance of further assessing the role of antibiotics in preventing mortality from severe bacterial infections among people presenting with advanced HIV disease.

Routine use of primary fluconazole prophylaxis for cryptococcal disease among adults, adolescents and children with advanced HIV disease has also not been included for routine administration as part of the package. Concerns with this approach include cost, development of fluconazole resistance and the need to avoid use because of fetal safety concerns among women of childbearing age who may not be taking adequate contraception. Nevertheless, in settings where cryptococcal screening tests are not available or results will be delayed, fluconazole prophylaxis may offer programmatic benefits after ruling out pregnancy, with a proven reduction in mortality and the incidence of cryptococcal disease (47). The updated WHO cryptococcal disease management guidelines to be issued later in 2017 will further review this recommendation.

The Guideline Development Group recommended that a package of opportunistic infection screening, opportunistic infection prophylaxis, fluconazole pre-emptive therapy for those who are CrAg positive and without evidence of meningitis, and intensified adherence interventions be offered to everyone presenting with advanced HIV disease, in addition to rapid ART initiation according to the new recommendation outlined in Chapter 3. The package should comprise key diagnostic, screening, prophylaxis and adherence interventions defined in the recommendations developed as part of the 2016 WHO consolidated ARV guidelines (29). Intensified adherence support is recognized as benefiting people with advanced HIV disease; such support may be provided at the time of diagnosis and initiation of ART and during episodes of acute illness both while hospitalized and during the immediate discharge period (46). WHO already strongly recommends adherence support interventions for people receiving ART (29). People with advanced HIV disease are likely to have an increased pill burden during the treatment of an acute opportunistic infection and during ongoing maintenance prophylaxis but may also have significant physical challenges in attending clinic appointments; for these people, opportunistic infections affecting the central nervous system and HIV encephalopathy

may pose a further challenge to comprehending and remembering adherence messages. Hence, an adapted approach to providing treatment support, including an option for home- or community-based follow-up, should be considered. Early tracing of anyone who misses an appointment should also be implemented. The use of fixed-dose combinations is recommended as one way to improve adherence, and the fixed-dose combination tablet of co-trimoxazole, pyridoxine and isoniazid, as used in the REALITY trial, has recently been added to the WHO List of Essential Medicines.

Components of the package for people with advanced HIV disease

Table 1 summarizes the package of interventions from the 2016 WHO consolidated ARV guidelines that should be offered to everyone presenting with advanced HIV disease. Annex 1 provides full details of the recommendations.

Table 1 Components of the package of care for people with advanced HIV disease

	Intervention	CD4 cell count	Adults	Adolescents	Children
Diagnosis	Sputum Xpert® MTB/RIF as the first test for TB diagnosis among symptomatic people	Any	Yes	Yes	Yes
	LF-LAM for TB diagnosis among people with symptoms and signs of TB	≤100 cells/mm ³ Or at any CD4 count if seriously ill	Yes	Yes	Yes ^a
	Cryptococcal antigen screening	≤100 cells/mm ³	Yes	Yes	No
Prophylaxis and pre-emptive treatment	Co-trimoxazole prophylaxis ^b	≤350 cells/mm ³ or clinical stage 3 or 4 Any CD4 count in settings with high prevalence of malaria or severe bacterial infections	Yes	Yes	Yes For criteria, see Annex 1
	TB preventive treatment ^b	Any	Yes	Yes	Yes ^c
	Fluconazole pre-emptive therapy for cryptococcal antigen-positive people without evidence of meningitis	<100 cells/mm ³	Yes	Yes	Not applicable (screening not advised)
ART initiation	Rapid ART initiation (as recommended in Chapter 3)	Any	Yes	Yes	Yes
	Defer initiation if clinical symptoms suggest TB or cryptococcal meningitis (see Chapter 3)	Any	Yes	Yes	Yes
Adapted adherence support	Tailored counselling to ensure optimal adherence to the advanced disease package, including home visits if feasible	<200 cells/mm ³	Yes	Yes	Yes

^aLimited data available for children. ^bCo-trimoxazole, isoniazid and pyridoxine are available as a fixed-dose combination tablet.

^cFor children younger than 12 months, only those with a history of TB contact should receive TB preventive treatment if the evaluation shows no TB disease.

The role of presumptive treatment in managing TB, *Pneumocystis jirovecii* pneumonia, bacterial infections and cryptococcal disease should be considered in settings in which access to diagnostic tests is limited and people present with typical signs and symptoms (especially when accompanied by clinical signs indicating severe illness²). To reflect this, the WHO algorithm for managing people with HIV who are suspected of having TB and are seriously ill incorporates presumptive treatment of TB, bacterial infections and *Pneumocystis jirovecii* pneumonia into the care pathway (48).

Co-trimoxazole, TB preventive treatment and fluconazole pre-emptive therapy for those with cryptococcal antigenaemia should be started as soon as they meet the criteria for the intervention. All medications may be started together. For people with advanced HIV disease who are eligible to start ART on the same day as HIV diagnosis (see the recommendation on ART initiation, Chapter 3), prophylaxis medications may be started at the same time (45). ART initiation should be deferred when clinical symptoms suggest TB or cryptococcal meningitis to avoid paradoxical worsening of the existing infection that can be life-threatening (see Chapter 3) (49); however, cryptococcal antigen screening is not a pre-condition for ART initiation.

Comparing benefits and harm

Providing a package of essential interventions will focus attention on diagnosing, preventing and treating the most common causes of morbidity and mortality among people with advanced HIV disease. However, attention should also be paid to other important causes of severe illness not covered by the package, in particular in regions where specific comorbidities and coinfections are prevalent. Increased pill burden and side effects may affect treatment adherence; however, in the trial setting, co-trimoxazole, isoniazid and pyridoxine were provided as a fixed-dose combination, and most participants found the enhanced prophylaxis package of medications to be easy or very easy to take (45).

Cost and cost-effectiveness

The package of screening and diagnostic tests and prophylactic and pre-emptive medications requires an initial investment in settings where these are not currently available. However, these costs are likely to be offset by savings incurred by reducing the costs associated with treating incident infections, hospitalization and death. Both randomized trials assessed for these guidelines included a formal cost analysis. In the REMSTART trial, the main costs were associated with ARV drugs (50%), clinic visits (19%) and hospitalization (19%). The incremental cost of the intervention to the health service over the first three months was US\$ 59 and over a one-year period US\$ 67, equivalent to a 25% increased cost over one year of follow-up. The investigators concluded that the package was an affordable approach to improving HIV care in resource-limited settings (50). In the REALITY trial, cost-effectiveness was assessed as being US\$ 201 per quality-adjusted life-year and US\$ 162 per life-year saved; this is likely to fall within the cost-effectiveness thresholds for most resource-limited settings (45).

Equity and acceptability

People with advanced HIV disease still account for a substantial proportion of the people starting ART (15). Recent attention has focused on adapting service delivery models to provide people-centred services for the people who are stable on ART (51), with less attention on the specific package required for those with advanced HIV disease. Providing a package of care for people with advanced HIV disease focuses attention on this vulnerable group of people.

² A seriously ill adult is defined as having any of the following danger signs: respiratory rate ≥ 30 breaths per minute; heart rate ≥ 120 beats per minute; or unable to walk unaided. Other clinical conditions, such as body temperature $\geq 39^{\circ}\text{C}$ can also be considered based on local epidemiology and clinical judgement. A seriously ill child is defined as having any of the following danger signs: lethargy or unconsciousness; convulsions; unable to drink or breastfeed; and repeated vomiting. Other clinical conditions such as body temperature $\geq 39^{\circ}\text{C}$ and age-defined tachycardia and/or tachypnoea can be considered based on clinical judgement.

Providing less frequent clinical visits for people who are stable on ART is expected to more equitably direct clinical resources to those in greatest need of clinical care.

A community consultation conducted for these guidelines found support for providing a package of interventions to reduce mortality and morbidity in advanced HIV disease. People living with HIV also perceived increased adherence support as acceptable. However, the ability to provide home visits may depend on resources, and in settings where this may increase stigma people should be given options for where this support is received.

With respect to gender equity, the package of care is anticipated to have the greatest impact for men, who are more likely to present to care with advanced HIV disease and have higher HIV-associated mortality and lower life expectancy compared to women.

Feasibility

Both health-care workers and programme managers perceived delivering a package of interventions for advanced HIV disease as being feasible. Challenges to feasibility included the additional cost of such a package and the training of health-care workers required to implement the package of care. The ability to employ sufficient human resources to provide the increased intensity of adherence support such as that demonstrated in the REMSTART study (46) may also be a challenge where resources are limited.

The cost and programmatic challenges of performing baseline CD4 cell count testing, and the increased costs associated with the additional medication, may also challenge the feasibility of delivering such a package in resource-limited settings.

Implementation considerations

Providing a package of care for people with advanced HIV disease will require adapting the current service delivery models in resource-limited settings. The algorithm on the following page summarizes the steps to be considered in managing a person with advanced HIV disease.

In addition to CD4 cell count testing or WHO clinical staging the following additional assessments should be carried out:

- Does the person have signs of being seriously ill? Should this person be admitted to an inpatient facility?
- Is the person receiving an ART regimen that is failing (or has the person interrupted ART)?
- Does the person have signs or symptoms of TB (current cough, fever, weight loss, night sweats or other signs suggesting extrapulmonary TB such as enlarged lymph nodes)? Is the person currently receiving TB therapy?
- Taking a history and examining for major causes of morbidity and mortality among people with advanced HIV disease, such as cryptococcal meningitis, severe bacterial infections, cerebral toxoplasmosis, *Pneumocystis jirovecii* pneumonia, other fungal infections, and cytomegalovirus disease.
- Diagnostic tests: viral load if ART failure is suspected, sputum Xpert® MTB/RIF, urine LF-LAM if TB symptoms and CD4 cell count ≤ 100 cell/mm³ or if the person is seriously ill at any CD4 cell count, lumbar puncture for those with symptoms or signs of meningitis and, where feasible, for those with cryptococcal antigenaemia; and X-ray and blood culture if health system capacity allows.
- Screening tests (cryptococcal antigen test if the CD4 cell count is ≤ 100 cells/mm³). To expedite and increase the uptake of cryptococcal antigen screening, laboratory-based reflex testing on any CD4 cell count sample ≤ 100 cells/mm³ should be considered. Point-of-care CD4 cell count testing should be accompanied by point-of-care cryptococcal antigen testing if the CD4 cell count is less than 100 cells/mm³.

- Treatment of confirmed diagnoses.
- If referral to a facility with diagnostic testing is not feasible, presumptive treatment of TB, *Pneumocystis jirovecii* pneumonia, cryptococcal meningitis, toxoplasmosis, and severe bacterial infections should be considered if the person is seriously ill.

Importantly, if access to investigations is limited or there are significant delays in receiving results, presumptive treatment should be initiated and ART initiation should not be delayed.

Developing appropriate treatment literacy strategies is important to support people to identify signs and symptoms of advanced HIV disease and support adherence to medication. Empowering civil society organizations should also be considered within any differentiated service delivery model for people with advanced HIV disease.

Particular attention should be paid to people with advanced HIV disease who miss a clinic visit after initiating treatment for an opportunistic infection or during the first months after starting or restarting ART, since they are at high risk of mortality. Programmes should ensure capacity for actively tracing such people. Ideally, such people should consent to and be linked with a community-based health worker who may visit them at home.

Where can the package of care for advanced HIV disease be offered?

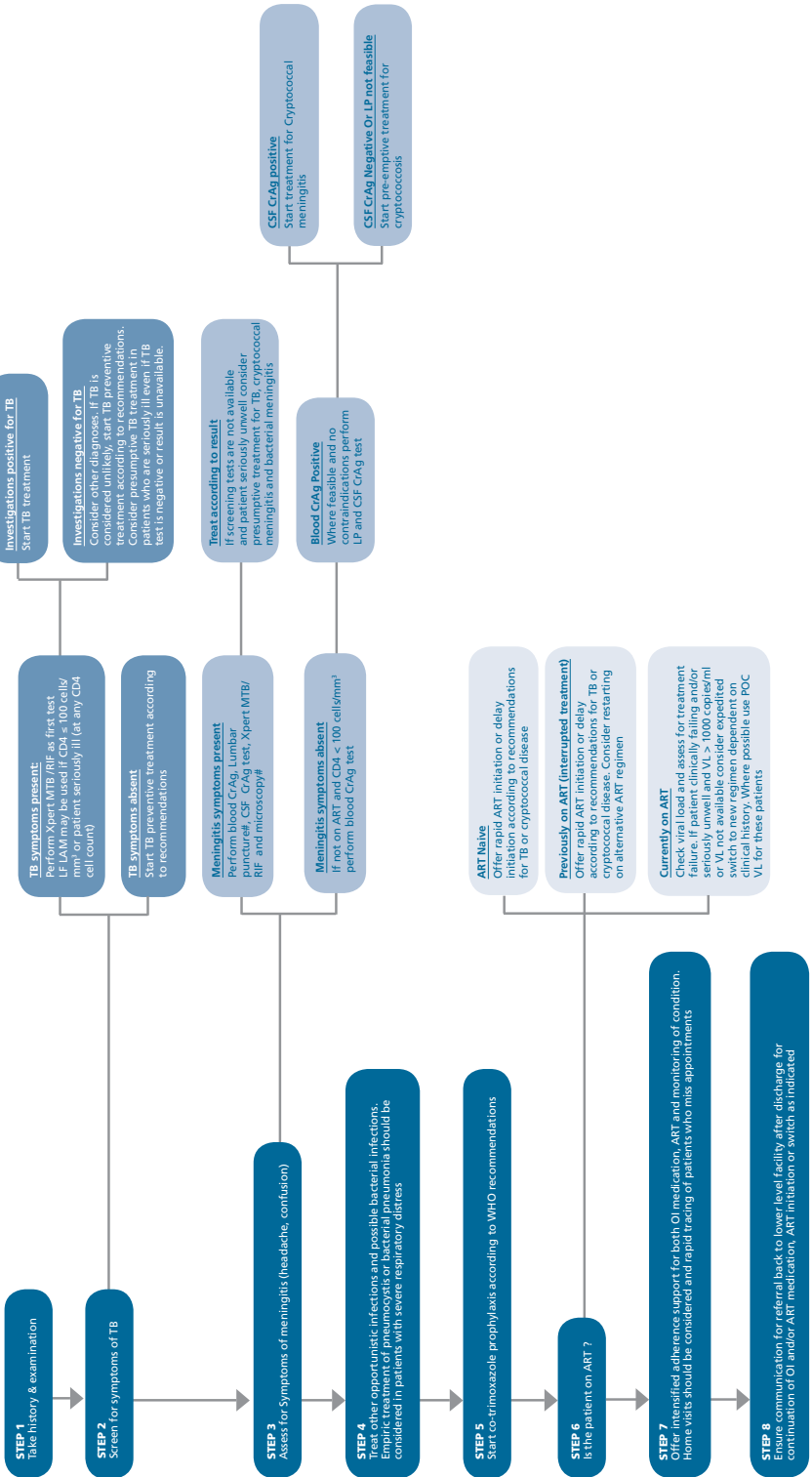
The package of care for people with advanced HIV disease should be offered at both hospitals and decentralized primary care clinics according to the clinical status of the person living with HIV (ambulatory or requiring hospital admission), the clinical skills of the health-care workers and access to diagnostics. However, to increase access to the package, improving access at peripheral sites through mobile outreach or decentralization should be encouraged. This may be enabled by providing point-of-care diagnostic tests at the peripheral level where feasible (CD4 cell count, cryptococcal antigen testing, LF-LAM testing and Xpert® MTB/RIF) or through sample transport systems.

Where care has been decentralized, clear referral criteria should be established to ensure that people requiring further investigation or specialist management receive services in a timely manner. Likewise, referral mechanisms and optimal communication following discharge back to the peripheral clinic must be implemented to ensure appropriate follow-up (such as continuation of fluconazole, TB treatment or the timing of the switch to second-line ART for those receiving an ART regimen that is failing). Where referrals are not feasible because of cost or distance constraints, advice should be sought from an experienced clinician and, where indicated, presumptive treatment started at the peripheral site. Referral and assessment should not result in unwarranted delays in starting ART and prophylaxis.

Algorithm for providing a package of care for people with advanced HIV disease

- Any person who has signs of being seriously ill should be referred to the appropriate higher-level facility for management.
- A seriously ill adult is defined as having any of the following danger signs: respiratory rate ≥ 30 breaths per minute; heart rate ≥ 20 beats per minute; or unable to walk unaided. Other clinical condition, such as temperature $\geq 39^{\circ}\text{C}$ combined with other signs such as headache, can also be considered based on local epidemiology and clinical judgement. A seriously ill child is defined as having any of the following danger signs: lethargy or unconsciousness; convulsions; unable to drink or breastfeed; repeated vomiting. Other clinical conditions such as temperature ≥ 39 and age-defined tachycardia and/or tachypnea can be considered based on clinical judgement.
- Clear criteria for referral should be available. If the person is not seriously ill, the decision as to what interventions may be decentralized will be programmatic.
- In those admitted, mortality is highest in the first 48 hours after admission. Steps 1-4 should be completed as soon as possible on the same day as presentation. Based on clinical assessment, start TB and opportunistic infection therapies as soon as possible among those who are seriously ill. The availability of point of care diagnostics (CD4, cryptococcal antigen, LP-LAM, viral load) will support rapid diagnosis including at decentralized sites.

ART, antiretroviral therapy; CSF, cerebrospinal fluid; LP, lumbar puncture; TB, tuberculosis
 Blood CrAg = serum, plasma, or whole blood
 # = test that should have a lumbar puncture if CrAg+
 ## in settings where best results are available quickly, it would be more cost effective to test for cryptococcal infection prior to TB infection



STEP 1
Take history & examination

STEP 2
Screen for symptoms of TB

STEP 3
Assess for symptoms of meningitis (headache, confusion)

STEP 4
Treat other opportunistic infections and possible bacterial infections. Empiric treatment of pneumocystis or bacterial pneumonia should be considered in patients with severe respiratory distress

STEP 5
Start co-trimoxazole prophylaxis according to WHO recommendations

STEP 6
Is the patient on ART?

STEP 7
Offer intensified adherence support for both OI medication, ART and monitoring of condition. Home visits should be considered and rapid tracing of patients who miss appointments

STEP 8
Ensure communication for referral back to lower level facility after discharge for continuation of OI and/or ART medication, ART initiation or switch as indicated

Investigations positive for TB
Start TB treatment

Investigations negative for TB
Consider other diagnoses. If TB is considered unlikely, start TB preventive therapy. Consider other diagnoses. Consider presumptive TB treatment if TB test is negative or result is unavailable.

Treat according to result
If training tests are not available, consider other diagnoses and presumptive treatment for TB, cryptococcal meningitis and bacterial meningitis

CSF CrAg positive
Start treatment for cryptococcal meningitis

CSF CrAg Negative or LP not feasible
Start preemptive treatment for cryptococcosis

Blood CrAg positive
Where feasible and no contraindications perform LP and CSF CrAg test

TB symptoms present:
Perform Xpert MTB/RIF as first test. LP-LAM may be used if CD4 ≤ 100 cells/mm³ or patient seriously ill (at any CD4 cell count)

TB symptoms absent
Start TB preventive treatment according to recommendations

Meningitis symptoms present
Perform blood CrAg, Lumbar puncture[#], CSF CrAg test, Xpert-MTB/RIF, and microscopy^{##}

Meningitis symptoms absent
If not on ART and CD4 < 100 cells/mm³ perform blood CrAg test

ART Naive
Offer rapid ART initiation or delay according to recommendations for TB or cryptococcal disease

Previously on ART (interrupted treatment)
Offer rapid ART initiation or delay according to recommendations for TB or cryptococcal disease. Consider restarting on alternative ART regimen

Currently on ART
Check adherence and assess for treatment failure. If unable to adhere, clinically failing and/or seriously unwell and VL > 1000 copies/ml or VL not available consider expedited switch to new regimen dependent on clinical history. Where possible use POC VL for these patients

Who can offer the package of care for advanced HIV disease?

Task sharing may be considered both for performing the point-of-care diagnostics within the package and for clinical management. A good practice statement within the 2016 WHO consolidated ARV guidelines states that trained and supervised non-laboratory staff, including laypeople, can undertake blood finger prick for testing and sample collection (29). This may enable lay health workers to perform point-of-care CD4 cell count, cryptococcal antigen testing and urine LF-LAM testing at peripheral sites (52). Task sharing to nurses and other mid-level health workers for the clinical management of people with advanced HIV should also be supported with training and mentorship. Initial screening procedures, treatment of TB and some opportunistic infections and prophylaxis may all be provided within a well-supported nurse-led programme. However, clear referral criteria and care pathways must be in place to ensure appropriate investigation and higher-level clinical management when required. Where referral is not feasible, lower-level health workers should consider presumptive treatment based on the clinical presentation, ideally after consulting with an experienced clinician.

Intensity of follow-up for people with advanced HIV disease

People with advanced HIV disease require closer follow-up during the initial period of receiving ART to monitor the response to ART and to identify signs and symptoms of possible immune reconstitution inflammatory syndrome. During the REMSTART study, weekly home visits were provided during the first month on ART (46). Even with close initial follow-up in the REALITY trial, many people died at home, with most deaths occurring very soon after ART initiation. People discharged after hospitalization for advanced HIV disease may also require more intensive follow-up. The feasibility of the frequency of visits is context specific and may also depend on the person's ability to travel to the clinical site. People missing appointments should also be rapidly traced by phone or through home visits. Where face-to-face contact is not feasible, distance contact through telephone consultation, mHealth, text messaging or other mobile interventions, or visits through a community health worker or home-based caregiver should be considered, with consent of the client.

For hospitalized patients, programmes should provide measures to improve linkage and follow-up after discharge such as outpatient primary care clinic visits and home visits by community health workers to reduce the risks of loss to follow-up and of mortality after discharge.

Considerations for specific populations

The package of care should be provided to all patients presenting with advanced HIV disease, unless specifically contra-indicated (Table 1 and Annex 1). The following section provides some additional considerations for specific populations.

Children

The same definition of advanced HIV disease used for adults is applied to children older than five years. Based on data showing that more than 80% of children younger than five years starting ART are WHO clinical stage 3 or 4 and/or have severe immunosuppression, the Guideline Development Group considered all children younger than five years to be eligible for the package for advanced HIV disease (12). The major causes of mortality and morbidity among children with advanced HIV disease remain TB, severe bacterial infections and *Pneumocystis jirovecii* pneumonia but, in contrast with adults, cryptococcal disease is relatively rare. A laboratory-based survey performed in South Africa estimated the incidence of cryptococcal disease to be 47 per 100 000 children living with HIV (34) and within two trial cohorts of children, no cases of cryptococcal disease were reported in children younger than five years (53).

Data on the use of a package of interventions in children older than five years are limited, and no data are available for children younger than five years. In the REALITY study, 4% (72/1805)

of the participants were 5–17 years old and received the same package of prophylactic interventions as the adults. No child had cryptococcal disease, one child had candidiasis at enrolment and no new cases were detected during the trial. One death was reported from probable bacterial pneumonia (45).

Based on previous recommendations included in the 2016 WHO consolidated ARV guidelines (29), Table 1 outlines the package of screening and prophylaxis interventions for children and adolescents, and Annex 1 provides the detailed recommendations. Increased pill or syrup burden is of particular concern for children, and fixed-dose combinations should be used if possible, including the new fixed-dose combination of co-trimoxazole, isoniazid and pyridoxine. Whether the current package is sufficiently adapted to the specific pathogens causing mortality among children is also of concern, especially to address the high rates of bacteraemia in those younger than three months (54). Further research is needed to determine the components of the package of care for young children and optimal administration and delivery in this age group.

Finally, the routine interventions recommended by WHO for children in general such as deworming, malaria prophylaxis, iron and vitamin A supplementation and growth monitoring should all be provided.

Adolescents

Adolescents generally face challenges in adhering to medication, and enhanced adherence counselling may be especially valuable.

Pregnant and breastfeeding women

For pregnant and breastfeeding women, WHO guidelines on antenatal care provide recommendations regarding nutrition support, disease prevention, managing common physiological symptoms and infant feeding support for women who cannot breastfeed (55).

Region-specific comorbidities and coinfections

Consideration should be given to regional differences in comorbidities and coinfections that may require additional prophylactic, diagnostic and therapeutic options not covered by the package (see section 2.3).

2.6 Considerations for people with advanced HIV disease re-engaging with care after treatment interruption or treatment failure

People re-engaging with care after treatment interruption with advanced HIV disease should be offered a comprehensive clinical assessment. The evidence supporting the package of interventions for advanced disease is derived from studies among ART-naïve people. Nevertheless, the package should be given to people with advanced disease who are re-engaging with care after a period of ART interruption or when ART fails, since such people are likely to benefit from the same set of interventions as ART-naïve people with advanced HIV disease.

People interrupting treatment on a non-nucleoside reverse-transcriptase inhibitor (NNRTI)–containing regimen are at risk of drug resistance and may require more intensive virological monitoring, and consideration should be given to restarting ART using a non-NNRTI-containing regimen, with a goal of re-establishing viral suppression, according to the 2017 WHO guidelines on the public health response to pretreatment HIV drug resistance (56).

For people presenting with diagnoses consistent with treatment failure,³ WHO already

³ New or recurrent clinical event indicating severe immunodeficiency. Adults: WHO clinical stage 4 conditions; children: WHO stage 3 or 4 (excluding TB) after six months of effective treatment

recommends viral load testing; CD4 cell count testing is no longer recommended for ART monitoring for people stable on ART where viral load monitoring is available (29); however, CD4 cell count testing should be specifically prompted for people with a viral load exceeding 1000 copies/ml and for everyone whose clinical presentation suggests advanced HIV disease regardless of whether they have been exposed to ART or not. People presenting with advanced HIV disease as a result of treatment failure should also benefit from the advanced HIV disease package, and if severely ill, an expedited switch to a new regimen should be considered by reducing the time between the first and second viral load test (1–3 months) and by paying increased attention to ensuring rapid turnaround and action on the results. Where rapid viral load testing is not available the decision to switch should be assessed according to the individual clinical presentation of the patient. Further research is required to evaluate the optimal package of interventions to people presenting with treatment failure, for example before switching to second-line ART. A planned WHO review of the viral load algorithm for people receiving ART will also consider these monitoring considerations for managing people with advanced HIV disease.

2.7 Vaccination for people with advanced HIV disease

Providing vaccinations to people living with HIV does not appear to accelerate HIV disease progression and is recommended as an important part of the HIV care package. However, people with severe immunosuppression may be at higher risk of complications from some live attenuated vaccines, and the response to other inactivated vaccines may be less effective because of their degree of immunosuppression. Additional doses or revaccination after immune reconstitution on ART may therefore be required.

Nineteen of the 26 WHO vaccination position papers (57) provide general or specific guidance for people living with HIV. HIV-exposed infants, children and adolescents living with HIV should undergo the routine vaccination schedule according to local recommendations, with the following modifications.

Bacille Calmette-Guérin (BCG) vaccine

Children who are HIV positive or of unknown HIV status with symptoms consistent with HIV should not receive BCG vaccine. This policy is currently being reviewed by WHO and is potentially subject to change.

Human papillomavirus

A three-dose schedule (0, 1–2 and 6 months) should be used if human papillomavirus vaccination is initiated after 15 years of age and for those younger than 15 years known to be immunocompromised and/or living with HIV (regardless of whether they are receiving ART). It is not necessary to screen for human papillomavirus infection or HIV infection before human papillomavirus vaccination.

Measles

Vaccination should be routinely administered to potentially susceptible, asymptomatic children and adults living with HIV and should be considered for those with symptomatic HIV infection if they are not severely immunosuppressed according to WHO definitions (CD4 cell counts <50 cells/mm³).

In areas with a high incidence of both HIV infection and measles, the first dose of measles-containing vaccine may be offered as early as six months old followed by two additional doses according to the national immunization schedule up to two years.

An additional dose of measles-containing vaccine should be administered when immune reconstitution has been achieved, such as when the CD4 cell percentage reaches 20–25%; where CD4 cell count monitoring is not available, children should receive an additional dose of

measles-containing vaccine 6–12 months after initiation of ART. Current evidence is insufficient to recommend an additional dose for children who start ART before the first dose of measles-containing vaccine (58).

Meningococcal vaccination

Meningococcal vaccination should be offered to everyone with immunodeficiency, including those patients with advanced HIV infection.

Pneumococcal vaccine

Infants and preterm neonates living with HIV who have received their three primary vaccine doses before reaching 12 months of age may benefit from a booster dose in the second year of life. Interrupted schedules should be resumed without repeating the previous dose. The evidence supporting the use of pneumococcal vaccines for immunizing older populations (and the potential use of such vaccines for immunization in pregnancy to protect newborn babies) is currently not considered sufficient to support policy recommendations. Because of the low level of evidence for benefit, routine vaccination of adults living with HIV with 23-valent polysaccharide vaccine is not recommended in resource-limited settings.

Polio vaccine

Inactivated polio vaccine or bivalent oral polio vaccine may be administered safely to asymptomatic infants living with HIV. HIV testing is not a prerequisite for vaccination. Bivalent oral polio vaccine is contraindicated among severely immunocompromised people with known underlying conditions such as primary immunodeficiencies, disorders of the thymus, symptomatic HIV infection or low CD4 cell count; these populations can safely receive inactivated polio vaccine.

Rotavirus

Major contraindications for rotavirus vaccination include severe allergic reaction after a previous dose and severe immunodeficiency

Yellow fever

Yellow fever vaccine may be offered to asymptomatic people living with HIV with CD4 cell counts ≥ 200 cells/mm³; it is therefore contra-indicated in people with advanced HIV disease until they achieve a CD4 cell count ≥ 200 cells/mm³. Although the data on the safety and immunogenicity of yellow fever vaccine when used among children living with HIV are limited, yellow fever vaccine may be administered to all clinically well children. HIV testing is not a prerequisite for vaccination.

2.8 Research gaps

Research priorities related to diagnostics include the need for a simplified tool to perform CD4 cell count testing to ensure people with advanced immune disease are identified. Ongoing research is being undertaken, including using a semiquantitative CD4 cell count lateral flow assay for which operational research will be required to evaluate feasibility under field conditions. Further research is also needed to develop simplified point-of-care diagnostics for TB, severe bacterial infections, *Pneumocystis jirovecii* pneumonia, toxoplasmosis, cytomegalovirus disease and other opportunistic infections specific to geographical regions, such as histoplasmosis and talaromycosis. Enhanced TB screening with Xpert® MTB/RIF regardless of symptoms was provided in both groups in the REMSTART study (46) and its impact could therefore not be assessed. Further studies are needed on such strategies to improve TB screening.

Other research priorities include defining the optimal package of prophylactic interventions for people who have not yet started ART, additional prophylaxis for severe bacterial infections, the benefit of primary fluconazole prophylaxis among those with advanced HIV disease for whom cryptococcal antigen screening is not feasible, the optimal pre-emptive treatment strategy for

people identified as cryptococcal antigen–positive at screening and approaches to antibiotic therapy within a public health approach, and specifically, the independent effect of short-course azithromycin on mortality. Some concerns have also been raised regarding the impact of moving to a dolutegravir-containing first-line ART regimen on the incidence of immune reconstitution inflammatory syndrome among people with advanced HIV disease (59), and although there was no evidence of increased risk of immune reconstitution inflammatory syndrome in the REALITY trial in which one arm of people with advanced HIV disease started a drug from the same class, raltegravir (60), this may warrant further assessment when dolutegravir is scaled up in resource-limited settings. The Guideline Development Group also highlighted programmatic assessment of the intensity of follow-up required and adherence strategies for people with advanced HIV disease as important areas for future implementation research.

To date, trial evidence has only examined the benefits of an intervention package among those presenting for ART care without previous ART exposure. The optimal management approach for people re-presenting for care with advanced HIV disease after treatment interruption may warrant further investigation. Data to support the effectiveness and adverse events of intervention packages in routine care settings would also be of value. In addition, since these trials have not investigated the benefit of an intervention package for infants and children younger than five years, specific components and optimal delivery warrant further research. Finally, region-specific packages of care should be defined and their effectiveness assessed.



3. RECOMMENDATION FOR RAPID INITIATION OF ART

3.1 Background

Recent attention has focused on the question of how quickly ART should be started once HIV diagnosis is confirmed. In the early years of the HIV response, limited resources and concerns about suboptimal adherence led to a cautious approach in which people living with HIV underwent multiple counselling sessions that could last several weeks or months before starting ART (61). During this pre-ART period, substantial mortality and loss to follow-up were observed, especially among people with advanced HIV disease (62,63). This prompted research to focus on whether approaches to support rapid ART initiation, including initiating ART on the same day HIV infection is diagnosed or eligibility is determined, could reduce loss to care before ART starts and improve clinical outcomes.

The results of several recent randomized trials have indicated that rapid ART initiation, including same-day start, can improve programme outcomes, especially by reducing loss to care in the pre-ART period (64,65). Some evidence from programme settings, however, indicates that rapid initiation could lead to increased loss to follow-up after initiating ART because of insufficient time to accept and disclose HIV status and to prepare for lifelong treatment (66). This more rapid approach to ART initiation is particularly relevant to people with advanced HIV disease in consideration of the specific clinical benefits (reduced risk of mortality and morbidity) and potential harm (elevated risk of immune reconstitution inflammatory syndrome).

3.2 Recommendations for rapid ART initiation

Recommendations

Rapid ART initiation^a should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment.

(Strong recommendation: high-quality evidence for adults and adolescents; low-quality evidence for children)

a Rapid initiation is defined as within seven days from the day of HIV diagnosis; people with advanced HIV disease should be given priority for assessment and initiation.

ART initiation should be offered on the same day to people who are ready to start.

(Strong recommendation: high-quality evidence for adults and adolescents; low-quality evidence for children)

Good practice statement

ART initiation should follow the overarching principles of providing people-centred care. People-centred care should be focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity and respect, especially for vulnerable populations, and should promote engaging and supporting people and families to play an active role in their own care by informed decision-making.

The introduction of the “treat all” recommendation (ART for all people living with HIV regardless of CD4 cell count) supports the rapid initiation of ART, including the offer of same-day initiation where there is no clinical contraindication.

People with no contraindication to rapid ART initiation should be fully informed of the benefits of ART and offered rapid ART initiation, including the option of same-day initiation. Rapid ART start is especially important for people with very low CD4 cell count, for whom the risk of death is high. People should not be coerced to start immediately and should be supported in making an informed choice regarding when to start ART.

3.3 Clinical considerations when implementing rapid ART initiation or same-day initiation

People presenting for the first time or those returning to care should undergo history and clinical examination to evaluate for significant opportunistic infections (such as signs and symptoms of TB and signs and symptoms suggesting meningitis) before rapid ART initiation is offered. Although no longer a requirement for ART initiation, baseline CD4 cell count testing should be performed to determine whether the patient has advanced HIV disease.

People who have no clinical signs and symptoms of TB or other opportunistic infections and whose cryptococcal antigen test is negative may initiate ART the same day in combination with their package of prophylaxis outlined in Chapter 2. For people with CD4 cell count <100 cells/mm³ in settings where cryptococcal antigen testing result is not available on the same day, consideration could be given to starting fluconazole prophylaxis and discontinuing if a cryptococcal antigen screening result is subsequently found to be negative.

Previous WHO recommendations on the timing of ART initiation in the presence of TB and cryptococcal disease should be considered. These are as follows:

Timing of ART for people with TB

- 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 (if symptoms) or given preventive TB therapy (if no symptoms). Where feasible, suspected TB should be confirmed through laboratory testing (Xpert® MTB/RIF as the first test and LF-LAM in urine). ART should be briefly delayed while investigating for TB among people with TB symptoms.
- TB treatment should be initiated first, followed by ART as soon as possible within the first eight weeks of treatment (*strong recommendation, high-quality evidence*).
- TB patients⁴ living with HIV who have severe immunosuppression (such as CD4 cell counts <50 cells/mm³) should receive ART within the first two weeks of initiating TB treatment.
- Caution is needed for people living with HIV with TB meningitis, since immediate ART is associated with more severe adverse events than initiating ART two months after the start of TB treatment.
- Any child with active TB disease should start ART as soon as possible and within eight weeks after initiating TB treatment (other than TB meningitis⁵), regardless of CD4 cell count and clinical stage (*strong recommendation, low-quality evidence*).

⁴ A TB patient is defined as a person diagnosed with new or relapsed TB disease, starting treatment and reported to the national TB programme.

⁵ Caution is needed in people living with HIV with TB meningitis, as immediate ART is significantly associated with more severe adverse events when compared with initiation of ART 2 months after the start of TB treatment.

Timing of ART for people with cryptococcal meningitis

Immediate ART initiation is contraindicated among people living with HIV with cryptococcal meningitis because of the risk of life-threatening immune reconstitution inflammatory syndrome (*conditional recommendation, low-quality evidence*).⁶

- ART initiation should be deferred until there is evidence of a sustained clinical response to antifungal therapy and after four 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 fluconazole induction and consolidation regimen (*conditional recommendation, low-quality evidence*).
- For people with signs and symptoms of meningitis, ART should be delayed pending the results of lumbar puncture.
- There is no prospective evidence to support decisions about when to start ART among asymptomatic people with cryptococcal antigenaemia after initiation of pre-emptive antifungal therapy. Guidelines from the Southern African HIV Clinicians' Society (67) recommend starting ART two weeks after starting fluconazole, and consideration is being given to starting ART immediately if lumbar puncture excludes cryptococcal meningitis in people who test positive for blood cryptococcal antigen.

Rationale and supporting evidence

The widespread adoption of the recommendation to treat all people living with HIV with ART regardless of clinical stage or degree of immunosuppression has identified a need to re-examine how ART is initiated. To date, standard preparation for ART initiation has included several pre-ART counselling sessions that must be completed before initiation; this period of preparation may last several weeks or months, and although it enables screening for and treatment of opportunistic infections, it also places an additional burden on both people and providers, resulting in avoidable loss to care (68–70).

To assess the impact of a rapid initiation schedule, including the offer of same-day initiation, a systematic review was performed examining data from three randomized controlled trials (64,65,71), 11 observational studies (68,72–81) and five qualitative studies (66,82–85). Among the randomized controlled trials, two individual trials were carried out among non-pregnant adults; in the single cluster-randomized trial, about one quarter of the women were pregnant (64). Combined interventions including point-of-care CD4 cell count and a revised counselling intervention were provided as part of the intervention arm in two trials (64,65). Two of the trials offered ART initiation on the same day that HIV was diagnosed; the other trial offered ART initiation on the same day of the first HIV-related clinic visit following a positive HIV diagnosis. The observational studies provided additional data on pregnant women (72,73,77–79) and people with acute HIV infection (74–76).

Across the randomized trials with rapid initiation, the likelihood of starting ART within 90 days of eligibility (pooled RR 1.3, 95% CI 1.23–1.39) and within 12 months of eligibility (RR 1.09, 95% CI 1.05–1.13) was increased. Retention in care at 12 months (RR 1.12, 95% CI 0.99–1.28), viral suppression at 12 months (RR 1.18, 95% CI 1.08–1.29) and mortality (RR 0.47, 95% CI 0.24–0.93) were influenced positively. In the observational studies, offering rapid ART initiation resulted in a greater likelihood of having started ART within three months (RR 1.53, 95% CI 1.11–2.10). However, in the observational studies, there was no evidence that offering rapid ART resulted in a greater likelihood of remaining in care (RR 0.97, 95% CI 0.79–1.18), and the risk of being lost to follow-up after ART initiation tended to be increased (pooled RR: 1.85, 95% CI 0.96–3.55).

⁶ This issue will be reviewed in the next update to the WHO guidelines in late 2017

Comparing benefits and harm

Linking people testing positive for HIV to ART services is programmatically challenging (62,86). The offer of rapid initiation, including same-day ART, increases the number of people starting ART, reduces mortality, and may further reduce both mother-to-child transmission and transmission to HIV-negative partners. However, possible harm identified includes the potential for missing clinical conditions requiring management before ART, the risk of immune reconstitution inflammatory syndrome among severely immunosuppressed people and the potential for people to feel coerced to start when they are not ready psychologically. Where health-care workers feel pressured to meet targets for ART initiation, this may lead to undue pressure on people to start ART as soon as possible. Special consideration should also be given to women in some settings where they may not be in a position to take the decision to start lifelong therapy independently.

Cost and cost-effectiveness

Three studies within the systematic review reported the cost and cost-effectiveness of rapid ART initiation. In a study among pregnant women in South Africa, rapid initiation was found to be very cost-effective compared with standard services: US\$ 1160 per quality-adjusted life year saved (87). A second study, also from South Africa, found same-day treatment initiation to be both more effective and more expensive but noted that the use of the current point-of-care CD4 cell count technology predominantly drove the increased costs (88). In a low-prevalence study setting in China, the unit cost for an additional person receiving ART under the simplified testing and treatment approach was US\$ 83.80, declining to US\$ 9.69 in the second year; this was reported as an effective and sustainable intervention for the setting (81).

Equity and acceptability

Rapid initiation may improve the equity and accessibility of ART for people who may otherwise be lost to follow-up during ART preparation sessions (65). Nevertheless, in settings with limited ART access, setting priorities for initiating ART should still be based on clinical triage, ensuring that those with the most advanced HIV disease access care. Guiding principles highlighted within a community-led consultation on rapid initiation called for ensuring accurate information to be provided and the decision to start ART to be a collaborative process between the health-care worker and the person living with HIV (89).

Barriers and concerns regarding the acceptability of same-day ART initiation reported by people living with HIV included insufficient time to process information for pregnant women (82), limited time to disclose HIV status that could potentially result in stigma and conflict, including domestic violence (66), a need among pregnant women to seek approval from their partners before starting ART (83) and uncertainty about the HIV test result and the need for confirmatory testing (83). Assessment of these factors should be carefully monitored as the “treat all” policy is scaled up.

The acceptability of rapid ART initiation in specific populations must also be considered. To date, the evidence on rapid initiation has been derived only from adults. Preparing children and their caregivers to initiate ART, especially when syrups are prescribed, may require additional support. Adolescents and young adults should be included in the decision to start ART, since exclusion from this process may lead to adherence problems. Key populations should be offered rapid initiation but may have additional medical and psychosocial issues as well as adherence support issues before starting. For people who inject drugs, needle and syringe programmes and opioid substitution therapy should be given priority, but opioid substitution therapy should not be a prerequisite for initiating or maintaining ART for people who use opioids. Rapid initiation should also be offered to people returning to care. People should be assessed in a non-judgemental manner, discussing the reasons why they disengaged from care and stopped ART and giving the opportunity to restart ART rapidly, including on the same day if appropriate.

Feasibility

Health-care workers and programme managers reported rapid or same-day initiation as being feasible across all populations, despite some specific challenges in key populations. Adherence and time constraints within the clinic to perform all procedures required, including HIV re-testing before ART initiation, were the main issues raised regarding feasibility. One trial reported similar barriers such as the need for clinical confirmation of TB, having a WHO clinical stage 3 or 4 condition requiring treatment, insufficient time to complete all steps on the same day and individual preferences (65).

Access to baseline investigations may affect the feasibility of same-day ART initiation. Baseline CD4 cell count should be evaluated and the package of interventions for people with advanced HIV disease should be provided on the same day. However, the inability to perform such tests or the potential for results to be delayed should not delay the initiation of ART, except where this is clinically indicated (clinical suspicion of TB or cryptococcal meningitis, in which ART should be delayed to first investigate and decide on treating these conditions). TB preventive therapy, cotrimoxazole prophylaxis and, where indicated, fluconazole pre-emptive therapy and ART should be started at the same time.

Implementation considerations

WHO recommends that HIV positivity should be confirmed with a second specimen and, where circumstances allow, by a second operator using the same testing strategy and algorithm. This approach should be maintained in settings in which rapid ART initiation is being implemented to minimize the risk of misdiagnosis.

The 2016 WHO consolidated ARV guidelines (29) made recommendations on where and by whom ART initiation may be performed, including decentralizing ART initiation to peripheral health centres and task sharing to trained non-physician health-care providers, including midwives and nurses. For implementing rapid ART initiation, including same-day start, decentralization and task sharing should still be encouraged, ensuring adequate training in revised counselling schedules. ART initiation for people with advanced HIV disease may be feasible at decentralized sites and will be enabled through access to point-of-care diagnostics. Non-physician health-care providers with adequate training may initiate ART rapidly but should have clear referral criteria to ensure that people access appropriate investigation and specialist management.

Rather than giving HIV and ART education over several sessions before ART initiation, the timing of counselling should be adapted. Where initiation is to be performed on the same day, priority should be given to how to develop an immediate adherence plan and how to recognize side-effects. There is evidence that establishing good adherence in the initial period following ART initiation is important for long-term treatment success (90). Further counselling to support treatment literacy, including the need for lifelong optimal adherence, how ART is monitored, and options for future differentiation of care should be covered in subsequent counselling sessions during the first months on ART. For those clients who are not ready for same-day start, the content of the ART preparation should be given over the following seven days, while considering the ability of the person to travel to the clinic. Where community health workers or expert clients are trained in ART preparation counselling, this may also be performed at the community level (68). Flexibility in how these sessions are delivered requires adapting them for the people who need more preparation time to start ART. Checklists to support clinicians in assessing people's clinical and psychological readiness should be developed, and the impact on workload should be assessed further.

The availability of point-of-care diagnostics for CD4 cell count, TB diagnosis and cryptococcal antigen lateral flow assays (whole blood, plasma or serum) may also support the programmatic implementation of the package of care for people with advanced HIV disease, enabling such people to access appropriate prophylaxis or pre-emptive treatment when this is indicated and to allow rapid investigation for TB before ART initiation.

Finally, initiation processes need to be adapted to recognize the increasing number of people that will re-enter care after a period of treatment interruption. For example, to overcome stigma that may be associated with return to care, Welcome Back clinics have been established in South Africa to encourage those who have stopped ART to return and be provided with support to continue therapy.

3.4 Considerations for children living with HIV who are hospitalized or severely ill

Two recent trials have suggested that very rapid initiation of ART may not be appropriate for sick children. In the first study from South Africa, young children (median age 23 months) with severe acute malnutrition were randomized to receive ART within 14 days of admission or delay it until nutritional recovery. The results suggested that delayed ART improved immune recovery, viral suppression and anthropometric measures, but the treatment arms did not differ with respect to mortality (91). These results contrast with the results reported by a retrospective, non-randomized study in Malawi, which found that initiating ART within 21 days of outpatient therapeutic feeding was associated with improved outcomes among children living with HIV with uncomplicated malnutrition in Malawi (92). In the second study in Kenya, hospitalized children living with HIV (median age 23 months) were randomized to start ART within 48 hours versus 7–14 days. Although treatment arms did not differ with respect to mortality, the authors concluded that rapid treatment (whether immediate or within 14 days) is safe, and prompt initiation of ART is essential to reduce the very high mortality observed overall, with 21% of children dying during six-month follow-up (93). Overall, although ART initiation remains a priority, especially for children younger than five years and children who present with symptoms, timely provision of appropriate care for clinical conditions requiring acute management is the first priority.

3.5 Research gaps

Further implementation research is needed to assess the systems adaptations required to provide rapid or same-day ART initiation in programmatic settings. This should include analysing how clinical readiness is assessed, including the package of diagnostics, prophylaxis and screening for advanced HIV disease, and how psychosocial readiness is assessed in the context of busy operational settings, as well as approaches to support adherence. Important clinical questions related to situations in which ART is started prior to laboratory results (CD4, CrAg) being obtained, and what actions are then required once results are received that will require further investigation. Evidence on the impact of rapid initiation on long-term outcomes in programme settings is limited, and there is no evidence about adolescents and children who require specific counselling interventions to address both disclosure of HIV and to ensure correct administration and dosing of ART by caregivers. Finally, approaches to supporting rapid initiation in key populations and those reinitiating ART also warrant further research.

4. PLANS FOR UPDATING, DISSEMINATION AND EVALUATION

These guidelines will be launched as a web-based product for dissemination and will be supported by peer-reviewed publication of the systematic reviews and evidence on which these recommendations are based. The WHO HIV Department will work alongside WHO regional and country offices to ensure that further communication and country adaptation is carried out for these recommendations. Important upcoming guideline reviews related to these recommendations include updating the guidelines for the prevention, diagnosis and management of cryptococcal disease and reviewing the monitoring algorithm for people receiving ART.

These guidelines will be incorporated into the next full update of the WHO consolidated ARV guidelines. The consolidated ARV guidelines are planned to be reviewed and updated every 2–3 years. The technical update of each section is reviewed as the evidence base and users' needs change.

An evaluation process will be conducted in 2018 to assess the uptake of the recommendations in national guidelines.

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ANNEX 1. RECOMMENDATIONS FOR THE PACKAGE OF DIAGNOSTIC AND SCREENING INTERVENTIONS FOR PEOPLE WITH ADVANCED HIV DISEASE

Intervention	CD4 cell count	Adults	Adolescents	Children
Use of Xpert® MTB/RIF test for diagnosing TB ^a	Any	Xpert® MTB/RIF should be used rather than conventional microscopy, culture and drug susceptibility testing as the initial diagnostic test of having HIV-associated TB or multidrug-resistant TB. <i>Strong recommendation, high-quality evidence</i>	Same as adults <i>Strong recommendation, high-quality evidence</i>	Same as adults <i>Strong recommendation, very-low-quality evidence</i>
	Any	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. <i>Strong recommendation, very-low-quality evidence</i>	Same as adults <i>Strong recommendation, very-low-quality evidence</i>	Same as adults <i>Strong recommendation, very-low-quality evidence</i>
	Any	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, pus and other tissues) from people suspected of having extrapulmonary TB. <i>Conditional recommendation, very-low-quality evidence</i>	Yes	No
Use of LF-LAM for diagnosis of TB ^a	≤100 cells/mm ³	LF-LAM may be used to assist in diagnosing active TB among adult hospital inpatients living with HIV with signs and symptoms of TB (pulmonary and /or extrapulmonary, who have a CD4 count ≤100 cells/mm ³ or people living with HIV who are seriously ill (respiratory rate >30 breaths per minute, temperature >39°C, heart rate >120 beats per minute and/or unable to walk unaided) regardless of CD4 cell count or with unknown CD4 cell count. <i>Conditional recommendation, low-quality evidence</i> Note: This recommendation may be applied to outpatients with signs and symptoms of TB (pulmonary and /or extrapulmonary) who have a CD4 cell count ≤100 cells/mm ³ or who are seriously ill regardless of CD4 cell count or with unknown CD4 cell count. LF-LAM test should not be used as a screening test for active TB. <i>Strong recommendation, low-quality evidence</i>	This recommendation applies to adolescents based on a generalization of data from adults.	Note: This recommendation also applies to children living with HIV with signs and symptoms of TB (pulmonary and /or extrapulmonary) while acknowledging that data are very limited and the concerns regarding the low specificity of the LF-LAM assay in children.
Use of cryptococcal antigen screening	≤100 cells/mm ³	The routine use of serum or plasma cryptococcal antigen screening among ART-naïve adults may be considered before ART initiation (or re-initiation) among people with a CD4 cell count of less than 100 cells/mm ³ <i>Conditional recommendation, low-quality evidence</i>	Cryptococcal antigen screening for adolescents is recommended <i>Conditional recommendation, low-quality evidence</i>	Not recommended <i>Conditional recommendation, low-quality evidence</i>

^a A negative Xpert® MTB/RIF test (especially on CSF) or negative LF-LAM test does not exclude TB.

Recommendations for the package of prophylaxis interventions for people with advanced HIV disease

Intervention	Indication to start			Indication to stop		
	Adults	Adolescents	Children	Adults	Adolescents	Children
Co-trimoxazole prophylaxis	<p>Severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or with a CD4 cell count <350 cells/mm³.</p> <p><i>Strong recommendation, moderate-quality evidence</i></p> <p>Malaria and/or severe bacterial infections highly prevalent: co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage.</p> <p><i>Conditional recommendation, moderate-quality evidence</i></p>	<p>Same as children</p>	<p>Regardless of clinical and immune conditions. Priority should be given to all children younger than five years old regardless of CD4 cell count or clinical stage, those with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with CD4 count \leq350 cells/mm³.</p> <p><i>Strong recommendation, high-quality evidence</i></p>	<p>Clinically stable on ART, with evidence of immune recovery and viral suppression.</p> <p><i>Conditional recommendation, low-quality evidence</i></p> <p>Malaria and /or severe bacterial infections are highly prevalent: co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage.</p> <p><i>Conditional recommendation, moderate-quality evidence</i></p>	<p>Same as children</p>	<p>High prevalence of malaria and/or severe bacterial infections: continued regardless of whether ART is provided.</p> <p><i>Conditional recommendation, moderate-quality evidence</i></p> <p>Low prevalence of malaria and/or severe bacterial infections: discontinued for children who are clinically stable and/or virally suppressed on ART for at least 6 months and with a CD4 cell count >350 cells/mm³.</p> <p><i>Strong recommendation, very-low-quality evidence</i></p>

Intervention	Indication to start		Indication to stop		
	Adolescents	Children	Adults	Adolescents	
TB preventive treatment	<p>Adults</p> <p>Screen with a clinical algorithm; those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered isoniazid preventive therapy. <i>Strong recommendation, moderate-quality evidence</i></p> <p>Unknown or positive tuberculin skin test status and unlikely to have active TB: at least six months of isoniazid preventive therapy regardless of the degree of immunosuppression, ART status, prior TB treatment, or pregnancy status. <i>Strong recommendation, high-quality evidence</i></p> <p>In resource-limited settings with high TB incidence and transmission, adults with unknown or positive tuberculin skin test status and in whom active TB has been ruled out: at least 36 months of isoniazid preventive therapy regardless of the degree of immunosuppression, ART status, prior TB treatment, or pregnancy. <i>Strong recommendation, moderate-quality evidence</i></p>	<p>Adolescents</p> <p>Same as adults</p>	<p>Children</p> <p>Older than 12 months and unlikely to have TB disease on symptom-based screening and no contact with a TB case: six months of isoniazid preventive therapy (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day) if they are living in a high TB prevalence setting. <i>Strong recommendation, low-quality evidence</i></p> <p>Younger than 12 months: only those who have contact with a TB case and TB disease has been ruled out (using investigations) should receive six months of isoniazid preventive therapy. <i>Strong recommendation, low-quality evidence</i></p> <p>Older than 12 months: those unlikely to have TB disease on symptom-based screening and no contact with a TB case might be offered six months of isoniazid preventive therapy (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day) if living in a medium- or low- TB prevalence setting. <i>Conditional recommendation, low-quality evidence</i></p> <p>All children living with HIV, after successfully completing treatment for TB, should receive isoniazid preventive therapy for an additional 6 months. <i>Conditional recommendation, low-quality evidence</i></p>	<p>Adults</p> <p>After six or at least 36 months according to the recommendation adopted</p>	<p>Children</p> <p>After six months</p>

Intervention	Indication to start			Indication to stop	
	Adults	Adolescents	Children	Adults	Adolescents
Pre-emptive anti-fungal therapy: fluconazole 800 mg/day for two weeks, then 400 mg/day for eight weeks and continued maintenance with fluconazole 200 mg/day	Blood cryptococcal antigen screening positive among people with CD4 counts <100 cells/mm ³ (where lumbar puncture is negative or not feasible or if lumbar puncture excludes cryptococcal meningitis) ^a <i>Conditional recommendation, low-quality evidence</i>	Same as adults	Not applicable since screening is not recommended	If HIV viral load monitoring is not available: When people are stable and adherent to ART and receiving antifungal maintenance therapy for at least one year and have a CD4 cell count ≥200 cells/mm ³ (two measurements six months apart). <i>Strong recommendation, low-quality evidence</i> If viral load monitoring is available: When people are stable and adherent to ART and antifungal maintenance treatment for at least one year and with a CD4 cell count ≥100 cells/mm ³ (two measurements six months apart) and a suppressed viral load. <i>Conditional recommendation, low-quality evidence</i>	Same as adults ^b
					Children Not applicable since screening is not recommended

^a Everyone with headache or confusion should undergo lumbar puncture. ^b Dosing of fluconazole for adolescents should be reviewed based on weight

ANNEX 2. METHODS FOR DEVELOPING THE GUIDELINES

Declarations of interest

All external contributors to the guidelines, including members of the Guideline Development Group and the External Review Group completed a WHO declaration of interests form. In accordance with WHO policy for experts,⁷ a web-based search was conducted of Guideline Development Group members to identify any potential competing interest. The results of the web-based search were recorded. A brief biography of each Guideline Development Group member was published on the WHO HIV website for a period of 14 days with a description of the objectives of the meeting. No public comments or objections were received concerning Guideline Development Group members.

Disclosure of interests and management plan

The responsible technical officer reviewed the declaration of interests forms as well as the results of the web-based search for each member of the Guideline Development Group. The results were shared with the Guideline Steering Group, which reviewed the results, and a management plan was agreed and recorded for each individual (Annex 3).

At the start of the guideline development meeting, all conflicts of interest identified and the management plan for any conflicts of interest were shared with the meeting participants. During the meeting, the GRADE methodologist and the WHO Guideline Steering Group closely monitored participation by members of the Guideline Development Group to ensure that this was in accordance with the agreed management plan.

The responsible technical officer reviewed the declaration of interest forms from members of the External Review Group in accordance with WHO guideline development policy,⁸ and the results were shared with the Guideline Steering Group. Any conflicts of interest identified were considered when interpreting comments from External Review Group members during the external review process.

Methods for evidence synthesis

Key information sources

The Guideline Steering Group formulated PICO questions (population, intervention, comparator and outcome) to guide the systematic reviews to support the development of the guidelines. The following two PICO questions of relevance to these guidelines were identified.

1. Do packaged interventions (two or more interventions delivered together) improve outcomes among people presenting with advanced HIV disease compared with standard care? (WHO definition of advanced disease: CD4 count <200 cells/mm³ and/or WHO stage 3 or 4 disease.)

⁷ Guidelines for declaration of interests (WHO experts). Geneva: World Health Organization; 2017 (http://www.who.int/medicines/news/2017/Guidelines_for_Declaration_of_Interests_WHO_Experts_51b2CRD.pdf, accessed 22 May 2017)

⁸ WHO handbook for guideline development. 2nd ed. Geneva: World Health Organization; 2014 (<http://apps.who.int/iris/handle/10665/145714>, accessed 22 May 2017).

2. Does rapid initiation of ART, including same-day start, lead to better outcomes for people newly diagnosed with HIV?

A list of potential outcomes of interest for each question was circulated to all members of the Guideline Development Group, and members scored the importance on a scale of 1 (not important) to 9 (critical). The median of the score for each outcome was used to inform the decision-making.

Systematic review teams developed protocols and conducted reviews in accordance with PRISMA reporting guidelines for systematic reviews and meta-analyses. These are available in the Web Annex to these guidelines.

Values and preferences

To explore values and preferences, an online survey of people living with HIV was conducted regarding the acceptability of packaged interventions for advanced HIV disease and the acceptability of rapid or same-day initiation of ART. The survey was disseminated through networks of civil society organizations and representative organizations of people living with HIV.

To further support the evidence for rapid or same-day initiation of ART, a qualitative literature review was conducted. The results of a community-led global consultation of people living with HIV on same-day or rapid ART initiation were also reviewed (see Web Annex).

Feasibility and acceptability

To explore the feasibility and acceptability for both packaged interventions for advanced HIV disease and rapid or same-day initiation of ART, online surveys were conducted of health-care workers and of HIV programme managers. Health-care workers were contacted through existing networks of organizations of health-care workers. Programme managers were contacted through WHO regional advisers, who disseminated the surveys to country programme managers in their region (see Web Annex).

Cost

The systematic review for packaged interventions identified evidence of the costs of the packaged interventions. Unit costs and cost-effectiveness (where this was available) were assessed as part of the review.

Quality of the evidence and the strength of the recommendations

The GRADE method was used to rate the quality of the evidence and determine the strength of the recommendations. The GRADE approach to recommendation development, which WHO has adopted, defines the quality of evidence as the extent to which one can be confident that the reported estimates of effect (desirable or undesirable) available from the evidence are close to the actual effects of interest. The strength of a recommendation reflects the degree of confidence of the Guideline Development Group that the desirable effects of the recommendation outweigh the undesirable effects. Desirable effects (potential benefits) may include beneficial health outcomes (such as reduced morbidity and mortality), reduction of burden on the individual and/or health services and potential cost savings. Undesirable effects (potential harm) include those affecting individuals, families, communities or health services. Additional burdens considered include the resource use and cost implications of implementing the recommendations and clinical outcomes (such as drug resistance and drug toxicity).

The strength of a recommendation can be either strong or conditional.

⁹ The community-led global consultation of people living with HIV on same-day or rapid ART initiation was carried out in 2015 for the development of the 2016 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.

A strong recommendation (for or against) is one for which there is confidence that the desirable effects of adherence to the recommendation clearly outweigh the undesirable effects.

A conditional recommendation (for or against) is one for which the quality of evidence may be low or may apply only to specific groups or settings; or the Guideline Development Group concludes that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects or are closely balanced, but the Guideline Development Group is not confident about these trade-offs in all situations.

The quality of the evidence, values and preferences of the end-users, feasibility, resource implications as well as consideration of potential benefits and harms contribute to determining the strength of a recommendation.

Guideline Development Group meeting

The Guideline Development Group met for three days in Geneva, Switzerland on 22–24 March 2017. The systematic reviews and supportive evidence, including values and preferences, acceptability, feasibility and cost, were presented to the Group. Evidence-to-decision-making tables were prepared in accordance with the GRADE process and presented to the Guideline Development Group, and the methodologist facilitated discussions. The Guideline Development Group made decisions by unanimous consensus. Voting was not required (but the Group agreed at the start of the meeting that 60% of the votes would be required for a decision).

Peer review

A draft of the guidelines were circulated for review to members of the Guideline Development Group and the External Review Group. The Guideline Steering Group reviewed the comments and incorporated them into the final document with due consideration of any conflicts of interest of External Review Group members.

ANNEX 3. DECLARATIONS OF INTERESTS

All external contributors to the development of these guidelines completed a WHO declaration of interests form. In accordance with the WHO declaration of interests policy for experts, a brief biography of each Guideline Development Group member was published on the WHO HIV website for a period of 14 days with a description of the objective of the meeting. No public comments or objections were received concerning the Group members.

The responsible technical officer reviewed all the declaration of interests forms completed by the Guideline Development Group members and undertook a web search as a complementary assessment. A management plan for each declared conflict was agreed. All declared interests and management strategies were discussed with the chairs and methodologist. Conflicts of interest were shared at the start of the Guideline Development Group meeting, with participation closely monitored by the Guideline Steering Group and GRADE methodologist. The majority of the members of the Guideline Development Group did not declare significant conflicts of interest for this meeting.

Every effort was made to ensure that the representation of the Guideline Development Group minimized conflicts of interest. The Guideline Steering Group acknowledges that limiting the participation of key experts is challenging since pharmaceutical companies significantly contribute to HIV research and ARV drug trials and several experts participate as investigators in relevant trials.

The Guideline Steering Group assessed all completed declaration of interests forms for other external contributors to the guidelines. Individual participation was reviewed in respect of the interests declared. All declaration of interests forms are on electronic file at the WHO Department of HIV and will be maintained for at least 10 years.

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