

INTRODUCTION

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1 INTRODUCTION

1.1 Context

These guidelines provide guidance on the diagnosis of human immunodeficiency virus (HIV) infection, the care of people living with HIV and the use of antiretroviral (ARV) drugs for treating and preventing HIV infection. They are structured along the continuum of HIV testing, prevention, treatment and care. This edition updates the 2013 WHO consolidated guidelines on the use of antiretroviral drugs (1), based on an extensive review of new evidence conducted in 2015.

Although countries are at different stages of ART coverage and implementation of the 2013 edition of the guidelines, in 2016 there is a consistent trend towards further expanding access to ART, initiating treatment earlier and expanding the use of ARV drugs for HIV prevention. These guidelines present several new recommendations, including the recommendations to provide lifelong ART to all children, adolescents and adults living with HIV, including all pregnant and breastfeeding women living with HIV, regardless of CD4 cell count. WHO has also expanded earlier recommendations to offer pre-exposure prophylaxis (PrEP) to selected key populations, to all populations with an incidence of HIV above 3 per 100 person-years.¹ A newer class of ARV drugs is now recommended as an option for first-line treatment option in resource-limited settings, as well as a reduced dosage of a previously recommended drug, efavirenz, to improve tolerability.

Implementing the new recommendations and approaches in these guidelines at the national and global levels will have important implications for programme priority setting, funding and service delivery. Similar to the 2013 edition, the guidelines provide operational and service delivery guidance to help countries as they work to implement new approaches, including guidance on effective integration of HIV and other services and strategies to optimize the quality of services along the continuum of care, including linkage, retention, adherence to treatment and adolescent-friendly health services. Importantly, the service delivery guidance in 2016 (Chapter 6) emphasizes the need for countries to provide differentiated care through reduced frequency of clinic visits and community ART distribution to help countries manage the growing cohort of people who are stable on ART and reduce the burden on people receiving treatment and health facilities as more people become eligible for treatment in accordance with these guidelines.

¹ Due to the anticipated public health impact, the new recommendations in these guidelines on when to start ART and pre-exposure prophylaxis (PrEP) were published in September 2015 (Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization, 2015 (<http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en>, accessed 6 October 2015).

1.2 Objectives

The objectives of these guidelines are:

- to provide updated, evidence-based clinical recommendations outlining a public health approach to providing ARV drugs for HIV prevention and treatment in all age groups and populations in the context of the continuum of HIV care, focusing on settings with limited health system capacity and resources;
- to provide guidance on key operational and service delivery issues that need to be addressed to increase access to HIV services, strengthen the continuum of HIV care and further integrate the provision of ARV drugs into health systems; and
- to provide programmatic guidance for decision-makers and planners at the national level on adapting, setting priorities for and implementing the clinical and operational recommendations and monitoring their implementation and impact.

1.3 Target audience

The guidelines are primarily intended for use by national HIV programme managers. They will also be of interest to the following audiences:

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

1.4 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 and expedite the achievement of key global and national HIV goals for 2016–2021 (2) and to realizing the Sustainable Development Goals (3).
- The guidelines are based on a public health approach to scaling up the use of ARV drugs along the continuum of HIV prevention, treatment and care.
- Developing and implementing the guidelines should realize the rights and responsibilities of people living with HIV and promote the greater involvement of people

living with HIV (GIPA) and meaningful involvement of people living with HIV (MIPA) principles.

- In addition to strengthening the continuum of HIV services, the recommendations in the guidelines should be implemented with a view to strengthening broader health systems and provision of universal health care.
- Implementation of the guidelines needs 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, availability of resources and comorbidities, the organization and capacity of the health system and anticipated cost–effectiveness.

1.5 Methods for developing the guidelines

1.5.1 Guideline contributors

WHO convened five groups to perform specific guideline development functions:

- An internal WHO Guideline Steering Group coordinated the overall guideline development process.
- A Core Group of external experts provided strategic guidance to the guideline development process. Members of the Core Group also performed external review of the guidelines.
- A Clinical Guideline Development Group reviewed the evidence and developed clinical recommendations related to HIV testing and the use of ARV drugs for prevention and treatment.
- An Operational Guideline Development Group reviewed the evidence and developed recommendations related to package of care and service delivery components in these guidelines.
- An External Review Group provided peer review of the full guideline document.

The composition of both Guideline Development Groups was in accordance with WHO procedures for developing guidelines (4) and included HIV experts, researchers, programme managers, epidemiologists, human rights experts, representatives of United Nations agencies and representatives of civil society organizations and networks of people living with HIV. Appropriate representation by region and sex was considered. Representatives from civil society were selected from a call for nominations; eight participants were selected from more than 90 applications. The WHO HIV Civil Society Reference Group contributed to the selection process of civil society participants. The Chairs of both Guideline Development Groups also participated in the Core Group to ensure consistency. The members of the External Review Group were selected to provide further geographical representation.

1.5.2 Competing interests

Conflicts of interests were managed as follows:

1. All external contributors to the development of these guidelines, including members of the Core Group, the Clinical and Operational Guideline Development Groups and the External Review Group, were required to complete a WHO Declaration of Interests (DOI) form before engaging in the guideline development process and before participating in the Guideline Development Group meetings. All contributors were requested to promptly notify WHO if any change in the disclosed information occurred during the course of this work.
2. In accordance with the WHO DOI policy for experts, a brief biography of all members of the Guideline Development Groups was published on the WHO HIV website for a period of 14 days with a description of the objective of the Groups' meetings. No public comments or objections were received concerning the Groups' membership.
3. The completed DOI forms were reviewed by the WHO Guideline Steering Group with a view to managing disclosed interests in the use of antiretroviral drugs for treating and preventing HIV infection. Where any conflict of interest was declared, the WHO Guideline Steering Group determined whether such conflicts were serious enough to affect the expert's objective judgement on the guideline development process and recommendations. To ensure consistency, the WHO Guideline Steering Group applied the criteria for assessing the severity of conflict of interests in the *WHO handbook for guideline development* (4).
4. The procedures for the management of declared conflicts of interests were undertaken in accordance with the *WHO guidelines for declaration of interests (experts)*. Conflicts of interest that warranted actions by the WHO Guideline Steering Group arose where experts had obtained funding from a body or an institution to perform primary research directly related to any of the guideline recommendations. At the Guideline Development Group meetings, the concerned experts were restricted from participating in discussions and/or formulating recommendations pertaining to their academic conflicts of interest.
5. All relevant declared interests (x out of x for Clinical Guideline Development Group and x out of x for Operational Guideline Group) are summarized with the agreed management plan (Annexes 1 and 2). The majority of the participants of the Guideline Development Groups did not declare significant conflicts of interest for either meeting.
6. Declared interests were shared with all participants at the meeting of the Guideline Development Groups so that the Groups were aware of any existing interests among the members.
7. Comments on the guidelines received from the External Review Group were reviewed in relation to the interests declared by the individual members.
8. All Declaration of Interests forms are on electronic file at the WHO Department of HIV/AIDS and will be maintained for 10 years.

The WHO Guideline Steering Group acknowledges that limiting the participation of key experts is challenging given the significant contribution of pharmaceutical companies in the HIV research and ARV drug trials and the involvement of several experts as investigators in relevant trials.

Funding from the Bill & Melinda Gates Foundation, the United States President's Emergency Plan for AIDS Relief, the United States Agency for International Development and the United States Centers for Disease Control and Prevention supported the development of these guidelines.

1.5.3 Evidence synthesis

Systematic reviews of the evidence

The WHO Guideline Steering Group formulated PICO questions to guide the systematic reviews. The following technical advisory meetings held in 2014 and 2015 contributed to this process:

- a consultation on the treatment of HIV among adolescents (5);
- a consultation on new strategies to optimize care in the postnatal period: infant prophylaxis, feeding and diagnosis;
- Paediatric ARV Drug Optimization 2 (6);
- The future with PrEP in combination HIV prevention, WHO and UNAIDS; Scoping for the development of further recommendations on the use of PrEP for the prevention of sexual transmission of HIV and the Technical Advisory Group for Pre-Exposure Prophylaxis;
- a scoping consultation on care packages for people living with HIV (7);
- a scoping consultation on chronic comorbidities in people living with HIV (8);
- a scoping consultation on priority areas and required work on ARV toxicity (9);
- a scoping meeting on the use of viral load and CD4 testing in the management of HIV; and
- a consultation on strengthening the quality of HIV clinical services in resource-limited settings.

Systematic review teams (Web Supplement B) developed protocols and conducted reviews. PRISMA guidelines for systematic reviews and meta-analyses were used for reporting of reviews (10). Web Supplement B includes search strategies, quality assessment and synthesis of findings for all systematic reviews conducted in 2015. Data from the systematic reviews were summarized and presented as evidence profiles using the GRADE (Grading of Recommendation, Assessment, Development and Evaluation) approach (11).

Several reviews were conducted using a network meta-analysis to evaluate the inference of the comparative effectiveness of interventions that may or may not have been evaluated against each other. The WHO GRADE working group was consulted on the interpretation of findings and use of GRADE in evaluating the overall quality of evidence from these reviews.

Diagnostic test accuracy reviews were conducted following Cochrane methods. Summary-of-evidence profiles were developed using an adapted GRADE approach in consultation with the WHO Guidelines Review Committee and the methodologist in the Clinical Guideline Development Group.

Values of outcomes

A list of potential outcomes of interest was circulated to members of both Guideline Development Groups. The members were asked to score the importance on a scale of 1 (not important) to 9 (critical) from the perspective of individuals living with HIV, to consider the importance of the values to service users. The average of the scores and variability for each outcome were used to determine the outcomes critical to decision-making.

Overall quality of the evidence

The GRADE method was used to rate the overall quality of the evidence (Table 1.1).

The quality of evidence is defined as the confidence that the reported estimates of effect are adequate to inform a specific recommendation. The GRADE system classifies the quality of evidence as high, moderate, low and very low. Randomized controlled trials are initially rated as high-quality evidence but may be downgraded for several reasons, including risk of bias, inconsistency of results, indirectness of evidence, imprecision and publication bias. Observational studies are initially rated as low-quality evidence but may be upgraded if the magnitude of the treatment effect is very large, if evidence indicates a dose–response relationship or if all plausible residual confounding would reduce the demonstrated effect or increase the effect if no effect were observed.

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 (12). Desirable effects (potential benefits) may include beneficial health outcomes (such as reduced incidence of HIV and reduced morbidity and mortality); reduction of the burden on the individual and/or health services; and potential cost savings for the individual, communities, programme and/or health system. Undesirable effects (potential harm) include those affecting individuals, families, communities or health services. Harm may include the resource use and cost implications

Table 1.1. GRADE quality of evidence

Quality of evidence	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Middle	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

of implementing the recommendations; adverse clinical outcomes (such as drug resistance or drug toxicity); and legal ramifications, in which certain practices are criminalized.

Strength of the recommendations

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

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

A conditional recommendation is one for which 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 Groups are not confident about these trade-offs in all situations. At implementation, monitoring and rigorous evaluation is needed to address these uncertainties, which are likely to provide new evidence that may change the calculation of the balance of trade-offs and to suggest how to overcome any implementation challenges.

Key information sources

Modelling of potential impact

Modelling data on the impact of interventions were used to support decision-making. A causal modelling analysis comparing the effect of various treatment initiation criteria on death and growth response for children and adolescents aged 5–16 years old was used to support the recommendation on when to start ART for children and adolescents. Models developed to simulate how immediate ART initiation regardless of CD4 cell count could affect HIV mortality and transmission in sub-Saharan Africa contributed to decision-making on the recommendation on when adults should start ART.

The benefits of alternative approaches to monitoring people receiving ART were also modelled, including prediction of one-year mortality using the current CD4 percentage and count among children receiving ART. The results of this work informed the CD4 criteria for switching therapy in children without access to viral load monitoring. The costs and consequences of viral load monitoring with dried blood spot versus plasma specimens in low- and middle-income countries were also used to support decision-making.

Resource use

The prices for drugs in ART regimens were collected from the WHO Global Price Reporting Mechanism: <http://apps.who.int/hiv/amds/price/hdd/>.

Equity and acceptability

Evidence on the acceptability and views of service users was collected using a mixed-methods approach. The WHO Guideline Steering Group reviewed all PICO questions to identify those for which collecting service user data would best inform decision-making. The service users considered were people living with HIV, caregivers of children living with HIV and health workers.

Table 1.2. Components of CERQual used to assess confidence in findings

Component	Description
Methodological limitations	The extent to which there are problems in the design or conduct of primary studies that contributed to the evidence review.
Relevance	The extent to which the body of evidence from the primary studies supporting a review finding is applicable to the context in the review question.
Adequacy of data	Overall determination of the degree of richness and quantity of data supporting a review finding.
Coherence	The coherence of the review finding addresses the question of whether the finding is well grounded in data from the primary studies

Four qualitative evidence syntheses were conducted on the following topics: 1) the role of ARV drug toxicity in influencing adherence among people living with HIV; 2) barriers to and facilitators of interventions to improve linkage to care; 3) barriers to and facilitators of interventions to improve ARV adherence; and 4) barriers to and facilitators of interventions to improve retention in care for people receiving ART. The Confidence in the Evidence from Reviews of Qualitative Research (CERQual) (13) approach was used to assess the confidence in the findings from the qualitative evidence syntheses, using four factors (Table 1.2).

Qualitative literature reviews (published and grey literature) were conducted on the following topics: 1) the timing of ART initiation for all populations (including pregnant and breastfeeding women); 2) the duration of infant prophylaxis; 3) PrEP; 4) the frequency of clinic visits and medication pickups; 5) initiating ART on the same day as HIV testing; 6) task shifting for sample collection and diagnostic tests, and 7) delivering sexual transmitted infection and family planning services in HIV clinic settings.

A community consultation was conducted on when to start ART and the use of viral load testing for monitoring of people living with HIV. Seven networks of people living with HIV, supported by a global research organization, conducted 24 workshops to assess the acceptability of initiating ART earlier for people living with HIV, caregivers and service providers in eight countries (India, Indonesia, Kenya, Peru, Portugal, Ukraine, Zambia and Zimbabwe). An additional global consultation on adolescent treatment and care and a facility-based situational analysis also contributed to the evidence base on the acceptability of initiating ART earlier among adolescents.

Community networks conducted focus group discussions to explore the views on early infant diagnosis of women living with HIV and the mothers of infants exposed to HIV on in Kenya, Namibia and Nigeria. An online survey on the quality of HIV care experienced by people living with HIV collated responses from 534 individuals and was used to support the guidance on quality of care in Chapter 6.

Feasibility

Programmatic data from country implementation experience were used to support decision-making. Programme data from Brazil, Rwanda, Thailand, Uganda and VietNam were presented to the Guideline Development Groups (14). Qualitative interviews and an

online survey were used to ascertain the views of HIV programme managers in three WHO regions and the conclusions from these assisted discussions on the feasibility of interventions.

WHO also conducted a survey in low- and middle-income countries on the availability and use of HIV diagnostics (15) and ARV drugs. The outcomes from a meeting with diagnostic manufacturers informed the decision-making (16).

Meetings of the Guideline Development Groups

The Clinical and Operational Guideline Development Groups met in Geneva, Switzerland in June 2015 to review evidence and formulate recommendations. The Operational Guideline Development Group met following the Clinical Guideline Development Group so that participants could consider the implementation considerations of decisions made in the clinical meeting.

The Clinical Guideline Development Group considered evidence for PICO questions A1.1 to E1.1. The Operational Guideline Development Group considered evidence for PICO questions F1.1 to F6.2. The Clinical Guideline Development Group held an additional virtual meeting in September 2015 to review two PICO questions that were not fully reviewed in June. A quorum of the Clinical Guideline Development Group attended this meeting and a 'round-robin' approach was used to gain consensus on the recommendations. Email communication followed to ensure that all members of the Clinical Guideline Development Group agreed with the recommendations made by virtual discussion.

The systematic reviews and evidence-to-decision-making tables prepared in accordance with the GRADE process (Table 1.3) were presented at the meetings, and the respective methodologist facilitated discussions. Web Supplement A provides all evidence-to-decision-making tables, including GRADE evidence profile tables for all PICO questions that led to a recommendation.

The Guideline Development Groups made decisions by consensus. The Clinical Guideline Development Group voted as a decision-making aid for the question of when adults should initiate ART in relation to the strength of the recommendation (with a majority vote of 70%). No other votes were held to decide strength or directionality of recommendations.

Good practice statements

Good practice statements were made when the Guideline Development Groups considered the benefits to substantially outweigh any undesirable consequences, in many cases considering a large body of indirect evidence with indirect comparisons to strongly support the decision. Principles for developing good practice statements were applied (17). Formal GRADE methods have not been applied to these statements. Where statements have been referenced from other guidelines (often referred to as good practice principles or practices), the source is noted.

Table 1.3. Criterion for consideration in evidence-to-decision-making tables

Domain	Rationale
Quality of the evidence	This is an assessment of the degree of confidence in the estimate of the effect: that is, the likelihood that the effect will differ substantially from what the research found. "Differ substantially" means a large enough difference that it might affect a decision.
Benefits and risks	When a new recommendation is developed, desirable effects (benefits) need to be weighed against undesirable effects (risks), considering any previous recommendation or another alternative. The larger the gap or gradient in favour of the benefits over the risks, the more likely that a strong recommendation will be made.
Values of outcomes	This is a judgement of how much the people affected by an intervention or option value each of the outcomes. How much people value outcomes in relation to each other needs to be considered when weighing up the desirable effects of a treatment against the undesirable effects.
Costs and resource implications	How large the requirements are in resource use of the intervention and the alternative. Costs: the value of the resources that are consumed (such as staff time, drugs and use of equipment) as the consequences of an intervention or option. Cost-effectiveness: the cost of a treatment in relation to its effects. Lower costs (monetary, infrastructure, equipment or human resources) or greater cost-effectiveness is more likely to support a strong recommendation.
Equity	The absence of avoidable or remediable health differences among groups of people that may be defined socially, economically, demographically or geographically.
Acceptability	How much a treatment or recommendation is accepted by the people who are affected by it or who are implementing it. If the recommendation is likely to be widely accepted or valued highly, it is likely that a strong recommendation will be made. A great deal of variability or strong reasons that the recommended course of action is unlikely to be accepted make a conditional recommendation more likely.
Feasibility	Is it feasible to implement an intervention and to sustain it? If an intervention is achievable in a setting where the greatest impact is expected, a strong recommendation is appropriate.

1.5.4 External review

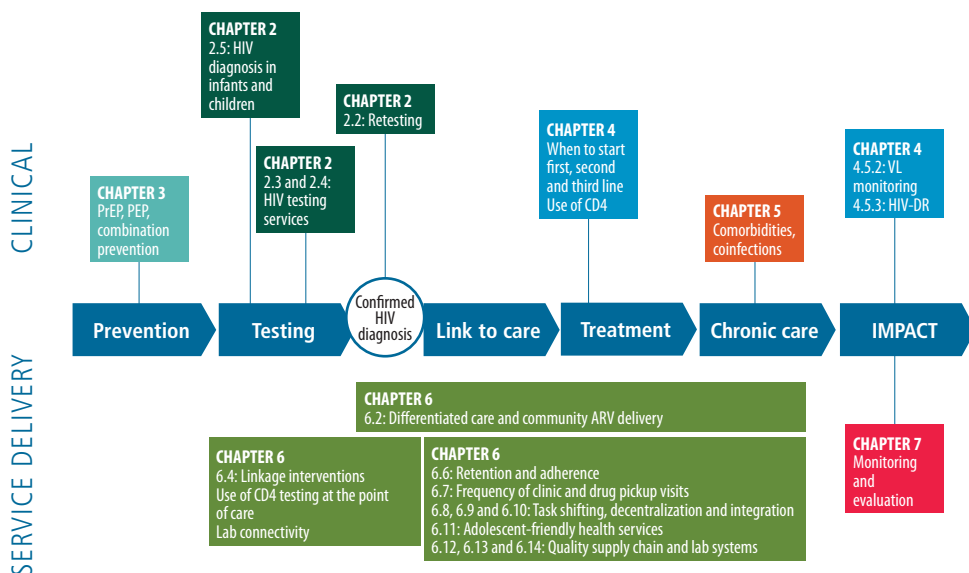
Members of the External Review Group were invited and selected to ensure geographical and gender balance, ensuring that members with a broad expertise in public health, programme management and community representation reviewed a draft of the guidelines for comments on validity, reliability and feasibility. An online format was used to compile comments and suggested revisions. This format enabled all external reviewers to see other comments from reviewers and agree or disagree to form consensus. All comments were then reviewed by a relevant member of the WHO Guideline Steering Group. All comments received were recorded with subsequent action; indicating whether specific changes had been made to the guideline in response to the comments. The draft guideline was reviewed by members of the Guideline Development Groups and the Core Group.

1.6 Organization of the guidelines

1.6.1 Chapter contents

The structure of the guidelines is based on the continuum of HIV testing, prevention, treatment and care (Fig.1.1).

Fig. 1.1. Continuum of care and relevant sections of the guideline



The chapters of the guidelines include the following information:

Chapter 2 discusses and summarizes existing WHO guidance on HIV testing services, including information to be provided during pre- and post-test counselling, approaches to service delivery and considerations for priority populations. Detailed analysis is provided of new evidence on HIV diagnosis in infants and children, together with new recommendations on the timing of and approaches to virological testing among infants and the use of new testing technologies.

Chapter 3 addresses the use of ARV drugs for HIV prevention. A new recommendation for 2015 is presented on the use of oral PrEP to prevent the acquisition of HIV. Existing recommendations on post-exposure prophylaxis are summarized and the importance of combination HIV prevention approaches is discussed.

Chapter 4 addresses ART for people living with HIV, including when to start treatment (first-line regimens for adults, adolescents and children) and what regimens to switch to (second- and third-line treatment). The chapter contains the new recommendations that all adults, adolescents and children should initiate ART regardless of CD4 cell count or

disease stage, including lifelong treatment for pregnant and breastfeeding women. Preferred first-line regimens for adults and adolescents include newly recommended options for a reduced dosage of efavirenz and, for the first time, use of the integrase inhibitor class of drugs. The evidence for the recommended approaches to first-line regimens for children up to three years of age and 3–10 years of age have also been reviewed. Revised recommendations are presented on options for second- and third-line ART for adults and children and infant ARV drug prophylaxis. Existing recommendations on timing of ART for people with TB and infant feeding by women living with HIV are summarized. The chapter includes new recommendations on stopping CD4 count testing where viral load testing is available and the use of new technologies for viral load testing and a detailed summary of guidance on managing toxicities related to ARV drugs and key ARV drug interactions.

Chapter 5 summarizes existing WHO guidance on the management of common coinfections and comorbidities associated with HIV, including the use of co-trimoxazole preventive therapy, TB case finding, treatment of active TB, and managing cryptococcal infection and viral hepatitis. The importance of assessing and managing the risk of noncommunicable diseases among people living with HIV is highlighted in two new recommendations on cardiovascular disease and depression.

Chapter 6 discusses key service delivery issues related to providing ART and supports the concept of differentiated care for people with advanced HIV disease and people who are stable on ART. Reducing the frequency of clinic visits and medication pickups for people who are stable on ART and more convenient and accessible approaches to distributing ARV drugs are newly recommended to reduce the growing burden on people receiving ART and health facilities. New recommendations are also provided to help to strengthen linkage to care following HIV diagnosis and long-term retention in care, including community-based approaches and measures to support adherence. Existing guidance on task shifting and integrating and decentralizing services is summarized. New guidance in this chapter emphasizes the importance of providing adolescent-friendly health services to meet the particular needs of adolescents.

Chapter 7 summarizes a range of recommended approaches to monitoring and evaluating programmes along the continuum of testing, prevention and care, including using recommended programme indicators and strategies to monitor ARV drug toxicity and ARV drug resistance.

Chapter 8 outlines how the guideline will be published and disseminated to stakeholders. Guidance on adoption and adaptation is given and reference made to tools to support implementation.

The **annexes** include algorithms, reference tables to support key recommendations and checklists and case studies to support country adaptation.

The **web supplements** present evidence-to-decision frameworks, summaries of evidence reviews, consultations and other relevant information collected in developing these guidelines.

1.6.2 Presentation of the recommendations

New recommendations developed in 2015 are highlighted and are typically presented in the following format to reflect the review of the evidence and other considerations by the Guideline Development Groups.

- **Recommendation.** The recommendation and the strength and quality of evidence assessed are stated.
- **Background.** Previous WHO guidance in this area and developments since the recommendations were last reviewed are described. When the recommendation relates to a specific population, key issues for that population may be briefly summarized.
- **Rationale and supporting evidence.** New evidence on which the recommendation is based and other key operational and programmatic considerations that informed the development of the recommendation are summarized.
- **Implementation considerations.** Key implementation issues specific to the recommendation are discussed.
- **Research gaps.** Issues requiring further research are briefly described.

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