

POLICY BRIEF

CONSOLIDATED GUIDELINES ON THE USE OF ANTIRETROVIRAL DRUGS FOR TREATING AND PREVENTING HIV INFECTION

WHAT'S NEW

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CONTENTS

1	WHAT ARE THE KEY FEATURES OF THE UPDATED CONSOLIDATED GUIDELINES ON THE USE OF ANTIRETROVIRALS?	2
	Updated recommendations based on new evidence, approaches and technologies	2
	Guidance based on the continuum of HIV testing, prevention, treatment and care	3
2	WHAT ARE THE NEW RECOMMENDATIONS AND GUIDANCE?	4
	HIV diagnosis and testing	4
	Antiretroviral drugs for HIV prevention	5
	Antiretroviral therapy for people living with HIV	6
	When to start ART	6
	What to start (first-line ART)	7
	Infant prophylaxis	8
	Monitoring the response to ART	8
	What ART to switch to (second and third line ART)	9
	Management of common coinfections and comorbidities	10
	Service delivery	11
	Differentiated care	11
	Linkage, retention and adherence to care	14
	Delivering HIV services to adolescents	14
	Improving the quality of HIV care services	15
	Monitoring and evaluation	15
	Publication, dissemination and evaluation	15
3	WHO WILL USE THESE GUIDELINES?	16
4	WHAT IS THE EXPECTED IMPACT OF THE NEW GUIDELINES?	16

1. WHAT ARE THE KEY FEATURES OF THE UPDATED CONSOLIDATED GUIDELINES ON THE USE OF ANTIRETROVIRALS?

Updated recommendations based on new evidence, approaches and technologies

The second edition of the World Health Organization (WHO) consolidated guidelines on the use of antiretrovirals (ARVs) updates the 2013 edition following an extensive review of evidence undertaken in 2015. Experience from country programmes, consultations with communities and modelling of potential impact have informed the new guidance.

The opportunities to use ARV drugs for treating and preventing HIV more effectively are growing rapidly. In recent years there has been a consistent trend towards initiating antiretroviral therapy (ART) earlier and expanding the use of ARV drugs for HIV prevention to achieve greater impact. New recommendations now support ART initiation in all adults, adolescents and children with HIV regardless of CD4 cell count or disease stage. Population considerations are addressed for all recommendations and, for the first time, recommendations specifically for adolescents (10 to 19 years old) have been included concerning when to start ART and service delivery approaches.

The review of evidence in 2015 concludes that:

- Earlier initiation of ART results in better clinical outcomes for people living with HIV.
- The ARV drug tenofovir disoproxil fumarate (TDF), alone or in combination with emtricitabine (FTC), is efficacious as pre-exposure prophylaxis (PrEP) to prevent HIV acquisition in all populations and settings.
- Safer and more efficacious ARV drugs are becoming available, and a newer class of drugs – integrase inhibitors – is becoming more affordable for low- and middle-income countries.

In addition, new approaches to diagnosis, treatment and patient monitoring are emerging:

- Innovative approaches to HIV testing are being implemented (home testing, community-based testing and self-testing).
- Many countries now provide lifelong ART to all pregnant and breastfeeding women.
- Many countries are implementing viral load (VL) testing as the preferred monitoring technology for people taking ART.
- New point-of-care viral load testing technologies have the potential to expand access to viral load testing.

The 2015 guidelines includes 10 new recommendations to improve the quality and efficiency of services to people living with HIV. Implementation of the recommendations in these guidelines on universal eligibility for ART will mean that more people will start ART earlier. As this expansion takes place, programmes must maintain the capacity to respond to the needs of all patients. New guidance on services covers the following:

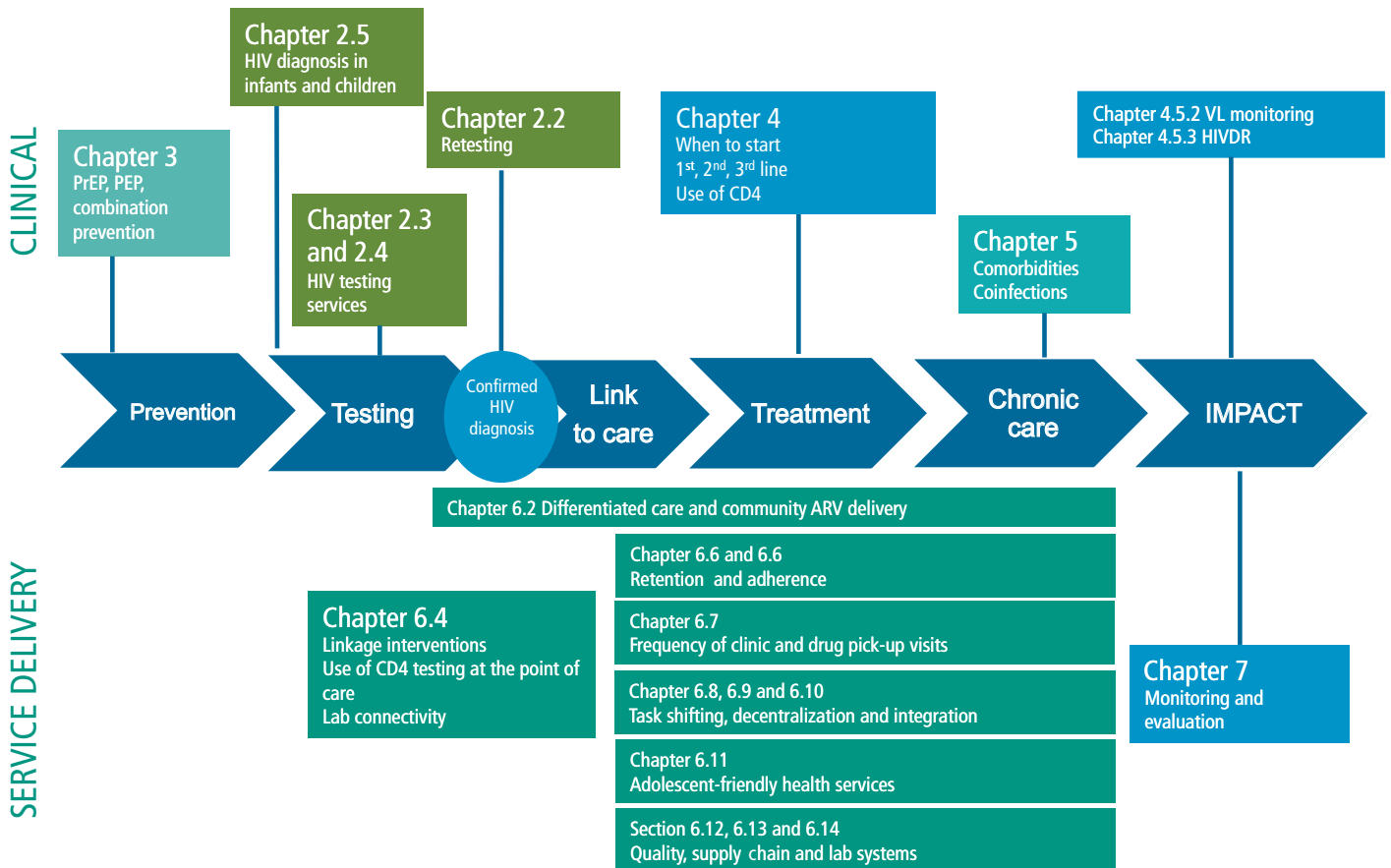
- the differentiated care framework to address the diverse needs of people living with HIV;
- alternative strategies for community delivery of ART to accommodate the growing number of people on ART;
- principles for improving the quality of care and providing people-centred care.

Accompanying these developments is recognition of the need to expand access to HIV testing, prevention, treatment and care in settings and populations with the highest burden of HIV. Meeting this need requires concerted efforts to support long-term adherence to ARV drugs and to eliminate stigma, discrimination and barriers to HIV services.

Guidance based on the continuum of HIV testing, prevention, treatment and care

The updated guidelines present both new recommendations and previous WHO guidance. They include clinical recommendations (“the what” of using ARVs for treatment and prevention) and service delivery recommendations to support implementation (“the how” of providing ARVs), organized according to the continuum of HIV testing, prevention, treatment and care (Fig.1). For the first time the guideline includes “good practice statements” on interventions whose benefits substantially outweigh the potential harms.

Fig.1. Guidance across the continuum of HIV testing, prevention, treatment and care in the updated *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*



2. WHAT ARE THE NEW RECOMMENDATIONS AND GUIDANCE?

New or updated guidance addresses the following topics:

- HIV diagnosis and testing
- ARVs for prevention
- ARVs for treatment
- managing coinfections and comorbidities
- service delivery.

For each of these topics, a table below summarizes the new and revised sections of the guidance updated since 2013. Recommendations are presented with their chapter numbers in the guideline.



HIV diagnosis and testing

New recommendations on HIV diagnosis address the timing of and approaches to virological testing in infants (using nucleic acid testing) and the use of rapid diagnostic tests (RDTs) in infants and young children. Also, new guidance outlines the provision of testing for infants and children presenting in clinic settings in generalized epidemics.

The guidelines summarize WHO guidance on HIV testing services, including the new recommendation on lay providers performing RDTs for HIV testing, drawn from the 2015 WHO *Consolidated guidelines on HIV testing services*.¹ These guidelines include information to be provided during pre- and post-test counselling, testing strategies, approaches to service delivery and considerations for priority populations and innovations such as self-testing.

2. CLINICAL GUIDELINES: HIV DIAGNOSIS	
2.4 Principles and approaches for service delivery	
2.4.1 Improving quality and efficiency	Lay providers who are trained and supervised to use rapid diagnostic tests (RDTs) can independently conduct safe and effective HIV testing services (<i>strong recommendation, moderate quality evidence</i>).
2.5 HIV diagnosis in infants and children	
2.5.2 Timing of virological testing	Addition of nucleic acid testing (NAT) at birth to existing early infant diagnosis (EID) testing approaches can be considered to identify HIV infection in HIV-exposed infants (<i>conditional recommendation, low quality evidence</i>).
2.5.3 Point-of-care technologies for the diagnosis of HIV infection in infants and children	Nucleic acid testing (NAT) technologies that are developed and validated for use at or near to point of care can be used for early infant HIV testing (<i>conditional recommendation, low quality evidence</i>).
	Rapid diagnostic tests for HIV serology can be used to assess HIV exposure only in infants less than four months of age. HIV-exposure status in infants and children four to 18 months of age should therefore be ascertained by undertaking HIV serological testing in the mother (<i>conditional recommendation, low quality evidence</i>).
	Rapid diagnostic tests for HIV serology can be used at nine months to rule out HIV infection in asymptomatic HIV-exposed infants (<i>conditional recommendation, low quality evidence</i>).
2.5.4 Provider-initiated HIV testing and counselling for infants and children	Rapid diagnostic tests for HIV serology can be used to diagnose HIV infection in children older than 18 months following the national testing strategy (<i>strong recommendation, moderate quality evidence</i>).
	In generalized epidemic settings, infants and children with unknown HIV status who are admitted for inpatient care or attending malnutrition clinics should be routinely tested for HIV (<i>strong recommendation, low quality evidence</i>).
Good practice statement	In generalized epidemic settings, infants and children with unknown HIV status should be offered HIV testing in outpatient or immunization clinics (<i>conditional recommendation, low quality evidence</i>).
	In all settings, children with a parent living with HIV should be routinely offered HIV testing and, if found to be either infected or at high risk of infection through breastfeeding, should be linked to services for treatment or prevention.

¹ Consolidated guidelines on HIV testing services. Geneva: World Health Organization; 2015. <http://who.int/hiv/pub/guidelines/hiv-testing-services/en/>.

Antiretroviral drugs for HIV prevention

The updated guidelines include a new recommendation on the use of oral pre-exposure prophylaxis (PrEP) to prevent the acquisition of HIV. WHO has expanded its earlier recommendations to offer PrEP to selected key populations. PrEP is now recommended for all populations at substantial risk of acquiring HIV, provisionally defined as an incidence of HIV greater than three per 100 person-years in the absence of PrEP.

Recommendations on post-exposure prophylaxis (PEP), published in the 2014 WHO ARV guideline supplement¹ also are summarized in the table that follows.



3. CLINICAL GUIDELINES: ANTIRETROVIRAL DRUGS FOR HIV PREVENTION	
3.1 Oral pre-exposure prophylaxis for preventing the acquisition of HIV	Oral pre-exposure prophylaxis (PrEP) containing TDF should be offered as an additional prevention choice for people at substantial risk ² of HIV infection as part of combination HIV prevention approaches (<i>strong recommendation, high quality evidence</i>).
3.2 Post-exposure prophylaxis	<p>A two-drug PEP regimen is effective, but three drugs are preferred (<i>conditional recommendation, low quality evidence</i>).</p> <p>Preferred antiretroviral regimen for adults and adolescents:</p> <ul style="list-style-type: none"> TDF + 3TC³ (or FTC⁴) is recommended as the preferred backbone regimen for HIV PEP in adults and adolescents (<i>strong recommendation, low to moderate quality evidence</i>). LPV/r⁵ or ATV/r⁶ are suggested as the preferred third drug for HIV PEP in adults and adolescents. Where available, RAL,⁷ DRV/r⁸ or EFV⁹ can be considered as alternative options (<i>conditional recommendation, very low quality evidence</i>). Preferred antiretroviral regimen for children ≤10 years: ZDV¹⁰ + 3TC is recommended as the preferred backbone for HIV PEP in children aged ≤10 years. ABC¹¹ + 3TC or TDF + 3TC (or FTC) can be considered as alternative regimens (<i>strong recommendation, low quality evidence</i>). LPV/r is recommended as the preferred third drug for HIV PEP in children aged ≤10 years. An age-appropriate alternative regimen can be identified among ATV/r, RAL, DRV, EFV, and NVP.¹² (<i>conditional recommendation, very low quality of evidence</i>). <p>Prescribing practices:</p> <ul style="list-style-type: none"> A full 28-day prescription of antiretrovirals should be provided for HIV PEP following initial risk assessment (<i>strong recommendation, very low quality evidence</i>). Enhanced adherence counselling is suggested for all individuals initiating HIV PEP (<i>conditional recommendation, moderate quality evidence</i>).

1 Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children. Geneva: World Health Organization 2014; http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013supplement_dec2014/en/.

2 Substantial risk is provisionally defined as HIV incidence greater than three per 100 person-years in the absence of PrEP.

3 lamivudine

4 emtricitabine

5 lopinavir with low-dose ritonavir

6 atazanavir

7 raltegravir

8 darunavir with low dose ritonavir

9 efavirenz

10 zidovudine

11 abacavir

12 Nevirapine (NVP) should not be used in children above the age of two years.

Antiretroviral therapy for people living with HIV

The updated guidelines address when to start ART, what to start (preferred first-line ART regimens) and what regimens to switch to (second- and third-line ART). These recommendations are presented for adults, pregnant and breastfeeding women, adolescents and children. New recommendations are also included on infant prophylaxis and the monitoring of treatment response and failure. Further guidance is provided on the management of ARV-related toxicities and key ARV drug interactions, incorporating new evidence emerging since 2013.

When to start ART

New recommendations on when to start ART now support ART initiation in all adults, adolescents and children with HIV at any CD4 cell count or disease stage. Efforts should be made to reduce the time between diagnosis and ART initiation to improve health outcomes. Recommendations on the timing of ART initiation in people living with HIV and active tuberculosis (TB) have been reviewed in the 2015 guideline process; these recommendations are maintained with upgraded quality of evidence (high quality).

4. CLINICAL GUIDELINES: ANTIRETROVIRAL THERAPY	
4.1 Preparing people living with HIV for ART	
4.1.1 Accelerated ART initiation Good practice statement	Efforts should be made to reduce the time between HIV diagnosis and ART initiation based on an assessment of a person's readiness.
4.3 When to start ART	
4.3.1 When to start ART in adults (>19 years old)	ART should be initiated in all adults living with HIV regardless of WHO clinical stage and at any CD4 cell count (<i>strong recommendation, moderate quality evidence</i>). As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count ≤ 350 cells/mm ³ (<i>strong recommendation, moderate quality evidence</i>).
4.3.2 When to start ART in pregnant and breastfeeding women	ART should be initiated in all pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count and continued lifelong (<i>strong recommendation, moderate quality evidence</i>).
4.3.3 When to start ART in adolescents (10–19 years of age)	ART should be initiated in all adolescents living with HIV regardless of WHO clinical stage and at any CD4 cell count (<i>conditional recommendation, low quality evidence</i>). As a priority, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adolescents with CD4 count ≤ 350 cells/mm ³ (<i>strong recommendation, moderate quality evidence</i>).
4.3.4 When to start ART in children younger than 10 years of age	ART should be initiated in all children living with HIV, regardless of WHO clinical stage or at any CD4 cell count. Infants diagnosed in the first year of life (<i>strong recommendation, moderate quality evidence</i>). Children living with HIV one year old to less than 10 years old (<i>conditional recommendation, low quality evidence</i>). As a priority, ART should be initiated in; all children ≤ 2 years old or children younger than 5 years with WHO HIV clinical stage 3 or 4 or CD4 count ≤ 750 cells/mm ³ or CD percentage $< 25\%$ and children 5 years and older with WHO HIV clinical stage 3 or 4 or with CD4 count ≤ 350 cells/mm ³ .
4.3.5 Timing of ART for adults and children with TB	ART should be started in all TB patients living with HIV regardless of CD4 count (<i>strong recommendation, high quality evidence</i>). TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (<i>strong recommendation, high quality evidence</i>). HIV-positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm ³) should receive ART within the first two weeks of initiating TB treatment. ART should be started in any child with active TB disease as soon as possible and within eight weeks following the initiation of anti-tuberculosis treatment regardless of the CD4 count and clinical stage (<i>strong recommendation, low quality evidence</i>).

What to start (first-line regimens)

New guidance on preferred ART regimens for adults and adolescents allows for a reduced dosage of efavirenz to improve tolerability and reduce costs and for the option of using the integrase inhibitor class of drugs in first-line ART. WHO re-emphasizes the discontinuation of stavudine (d4T) in first-line regimens and encourages the use of fixed-dose combinations and once-daily regimens. Evidence for recommended first-line regimens for children up to three years of age and three to 10 years of age have been reviewed, and the quality of evidence upgraded to high. The table below outlines the preferred and alternative recommended first-line regimens for all age groups.



PREFERRED AND ALTERNATIVE FIRST-LINE ART REGIMENS		
First-line ART	Preferred first-line regimen	Alternative first-line regimens ^{1,2}
Adults	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTG ^{3,4} TDF + 3TC (or FTC) + EFV ₄₀₀ ^{3,4,5} TDF + 3TC (or FTC) + NVP
Pregnant/breastfeeding women	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF (or ABC) + 3TC (or FTC) + DTG ^{3,4} TDF (or ABC) + 3TC (or FTC) + EFV ₄₀₀ ^{3,4,5} TDF (or ABC) + 3TC (or FTC) + NVP
Children 3 years to less than 10 years	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + EFV (or NVP)
Children less than 3 years	ABC (or AZT) + 3TC + LPV/r	ABC (or AZT) + 3TC + NVP

4.4 What to start: first-line ART	Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities (<i>strong recommendation, moderate quality evidence</i>).
	Fixed-dose combinations and once-daily regimens are preferred for antiretroviral therapy (<i>strong recommendation, moderate quality evidence</i>).

1 For adults and adolescents d4T should be discontinued as an option in first-line treatment.

2 ABC or boosted protease inhibitors (PIs) (ATV/r, DRV/r, LPV/r) can be used in special circumstances.

3 Safety and efficacy data on use of DTG and EFV₄₀₀ in pregnant women, people with HIV/TB coinfection and children and adolescents younger than 12 years of age are not yet available.

4 Conditional recommendation, moderate quality evidence. Refer to full guideline for more detail.

5 EFV at lower dose (400 mg/day).

Infant prophylaxis

Guidance from 2010 on infant prophylaxis has been updated with a definition of high risk infants and recommendations on duration and number of ARV drugs, for both breastfed and formula-fed infants born to mothers with HIV. Infant feeding guidance remains unchanged from 2010; updated guidance is anticipated in early 2016, following a recent review of the evidence.



4.4.7 Infant prophylaxis	Infants born to mothers with HIV who are at high risk of acquiring HIV ¹ should receive dual prophylaxis with daily AZT and NVP for the first 6 weeks of life, whether they are breastfed or formula-fed (<i>strong recommendation, moderate quality evidence</i>).
	Breastfed infants who are at high risk of acquiring HIV, ¹ including those first identified as exposed to HIV during the postpartum period, should continue infant prophylaxis for an additional 6 weeks (total of 12 weeks of infant prophylaxis) using either AZT and NVP or NVP alone (<i>conditional recommendation, low quality evidence</i>).
	Infants of mothers who are receiving ART and are breastfeeding should receive 6 weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given 4 to 6 weeks of infant prophylaxis with daily NVP (or twice-daily AZT) (<i>strong recommendation, moderate quality evidence for breastfeeding infants; strong recommendation, low quality evidence for infants receiving only replacement feeding</i>).
Good practice statement	ART should be initiated urgently in all pregnant and breastfeeding women, even if they are identified late in pregnancy or postpartum, because the most effective way to prevent mother-to-child HIV transmission is to reduce maternal viral load.

Monitoring the response to ART

Clinical assessment and laboratory tests play a key role in assessing individuals following a positive diagnosis of HIV. Viral load is the preferred monitoring approach to diagnose and confirm treatment failure.² New recommendations encourage routine viral load testing to be carried out at six and 12 months after initiating ART and, if the patient is stable on ART,³ every 12 months thereafter. The guidelines include a new recommendation for the use of dried blood spot specimens using venous or capillary blood for viral load testing.

WHO supports stopping routine CD4 count testing where viral load testing is available and can be used instead. This section of the guideline also outlines recommended tests for HIV screening and monitoring and for screening of coinfections and non-communicable diseases.

4.5 Monitoring the response to ART and diagnosing treatment failure	
4.5.1 Laboratory monitoring before and after initiating ART	Dried blood spot specimens using venous or capillary whole blood can be used to determine HIV viral load. A threshold of 1000 copies/ml can be used to determine virological failure when using dried blood spot samples, as defined for testing in plasma (<i>conditional recommendation, low quality evidence</i>).
	Routine viral load monitoring can be carried out at 6 months, at 12 months, and then every 12 months thereafter if the patient is stable on ART to synchronize with routine monitoring and evaluation reporting (<i>conditional recommendation, very low quality evidence</i>).
	In settings where routine viral load monitoring is available, CD4 cell count monitoring can be stopped in individuals who are stable on ART and virologically suppressed (<i>conditional recommendation, low quality evidence</i>).

¹ High-risk infants are defined as those:

- born to women with established HIV infection who have received less than four weeks of ART at the time of delivery, OR
- born to women with established HIV infection with VL >1000 copies/mL in the four weeks before delivery, if VL available, OR
- born to women with incident HIV infection during pregnancy or breastfeeding, OR
- identified for the first time during the postpartum period, with or without a negative HIV test prenatally.

² Virological failure is defined by a persistently detectable viral load exceeding 1000 copies/ml (that is, two consecutive viral load measurements within a 3-month interval, with adherence support between measurements) after at least six months of starting a new ART regimen.

³ WHO defines people stable on ART according to the follow criteria: on ART for at least one year, no current illnesses or pregnancy, good understanding of lifelong adherence and evidence of treatment success (two consecutive viral load measures below 1000 copies/ml).

What ART to switch to (second- and third-line ART)

WHO emphasizes a public health approach to second- and third-line ART. Preferred second-line regimens and alternatives are proposed, consistent with ART optimizing principles, availability of fixed-dose combinations, tolerability and the risk of resistance mutation. New recommendations include the use of DRV/r or RAL with LPV/r as alternative ART regimens for adults and adolescents. A RAL-based second-line regimen is recommended for children after failure of a first-line LPV/r-based regimen. The principles for third-line regimens are consistent with the 2013 guidelines; they should include new drugs with minimal risk of cross-resistance to previously used regimens, and patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen.

POPULATION	1 ST LINE REGIMEN	2 ND LINE REGIMENS	3 RD LINE REGIMENS
Adults	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r 2 NRTIs + DRV/r	DRV/r ¹ + DTG (or RAL) ± 1–2 NRTIs
	2 NRTIs + DTG	2 NRTIs + ATV/r or LPV/r 2 NRTIs + DRV/r	DRV/r + 2 NRTIs ± NNRTI Optimize regimen using genotype profile
Pregnant/breastfeeding women	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r 2 NRTIs + DRV/r	DRV/r + DTG (or RAL) ± 1–2 NRTIs
Children	2 NRTIs + LPV/r	If less than 3 years: 2 NRTIs + RAL ² If older than 3 years: 2 NRTIs + EFV or RAL	DTG ⁴ + 2 NRTIs DRV/r ³ + 2 NRTIs DRV/r ³ + DTG ⁴ ± 1–2 NRTIs
	2 NRTIs + EFV	2 NRTIs + ATV/r ⁵ or LPV/r	

Note: NRTI = nucleoside analog reverse-transcriptase inhibitor; NNRTI = non-nucleoside reverse-transcriptase inhibitor.

- 1 In PI-experienced patients, the recommended DRV/r dose should be 600mg/100 mg twice daily.
- 2 If RAL is not available, no change is recommended unless in the presence of advanced clinical disease progression or lack of adherence specifically because of poor palatability of LPV/r. In this case, switching to a second-line NVP-based regimen should be considered. Based on approval of the use of EFV in children less than three years of age, an EFV-based regimen could be considered as an alternative. However, more data are needed to inform how best to use EFV in this population.
- 3 DRV/r should not be used in children younger than three years of age.
- 4 RAL can be used in children failing PI-based second-line treatment when DTG is not available and when RAL has not been used in a previous regimen. DTG is currently only approved for children 12 years and older, however studies are ongoing to determine dosing in younger children and approval to lower age groups is expected in the near future.
- 5 ATV/r can be used as an alternative to LPV/r in children older than 3 months of age, however the limited availability of suitable formulations for children younger than 6 years of age, the lack of a fixed-dose formulation and the need for separate administration of RTV booster should be considered when choosing this regimen.



Management of common coinfections and comorbidities

The guidelines include a summary of previously published WHO guidance on the use of co-trimoxazole prophylaxis¹ and the diagnosis and management of TB (including the use of isoniazid preventive therapy (IPT)). New recommendations are included on the use of Xpert MTB/RIF² and lateral flow urine lipoarabinomannan assays (LF-LAM)³ for the diagnosis of active TB. This chapter also outlines recommendations on the diagnosis and prevention of cryptococcal disease and links to guidance on conditions that are common in people living with HIV (for example, hepatitis, skin and oral infections) as well as to approaches to general care.

5. CLINICAL GUIDELINES: MANAGING COMMON COINFECTIONS AND COMORBIDITIES

5.2 Prevention, screening and management of common coinfections

<p>5.2.1 Co-trimoxazole prophylaxis</p>	<p>Co-trimoxazole prophylaxis is recommended for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with CD4 \leq350 cells/mm³ (<i>strong recommendation, moderate quality evidence</i>).</p> <ul style="list-style-type: none"> In settings where malaria and/or severe bacterial infections (SBIs) are highly prevalent, co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage (<i>conditional recommendation, moderate quality evidence</i>). <p>Co-trimoxazole prophylaxis may be discontinued in adults (including pregnant women) with HIV who are clinically stable on ART, with evidence of immune recovery and virologic suppression (<i>conditional recommendation, low quality evidence</i>).</p> <ul style="list-style-type: none"> In settings where malaria and/or SBIs are highly prevalent, co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage (<i>conditional recommendation, moderate quality evidence</i>). <p>Co-trimoxazole prophylaxis is recommended for infants, children and adolescents with HIV, regardless of clinical and immunological conditions. Priority should be given to all children less than 5 years old regardless of CD4 cell count or clinical stage, and children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with CD4 \leq350 cells/mm³ (<i>strong recommendation, high quality evidence</i>).</p> <ul style="list-style-type: none"> In settings where malaria and/or SBIs are highly prevalent, co-trimoxazole prophylaxis should be continued until adulthood whether or not ART is being taken (<i>conditional recommendation, moderate quality evidence</i>). In settings of low prevalence for both malaria and bacterial infections, co-trimoxazole prophylaxis may be discontinued for children 5 years of age and older who are clinically stable and/or virologically suppressed on ART for at least 6 months and CD4 $>$350 cells/mm³ (<i>strong recommendation, very low quality evidence</i>). <p>Co-trimoxazole prophylaxis is recommended for HIV-exposed infants from 4 to 6 weeks of age and should be continued until HIV infection has been excluded by an age-appropriate HIV test to establish final diagnosis after complete cessation of breastfeeding (<i>strong recommendation, very low quality evidence</i>).</p> <p>Routine co-trimoxazole prophylaxis should be given to all HIV-infected patients with active TB disease regardless of CD4 cell count (<i>strong recommendation, high quality evidence</i>).</p>
<p>5.2.2 Tuberculosis</p>	<p>Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST⁴ as the initial diagnostic test in adults and children suspected of having HIV-associated TB or multi-drug resistant TB (<i>strong recommendation, adults: high quality evidence; children: very low quality evidence</i>).</p> <p>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>).</p> <p>Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture or histopathology) for testing specific non-respiratory specimens (lymph nodes and other tissues) from patients suspected of having extrapulmonary TB (<i>conditional recommendation, very low quality evidence</i>).</p> <p>Except as specifically described below for persons with HIV infection with low CD4 counts or who are seriously ill,⁵ LF-LAM should not be used for the diagnosis of TB (<i>strong recommendation, low quality evidence</i>).</p> <p>LF-LAM may be used to assist in the diagnosis of active TB in adult in-patients living with HIV, with signs and symptoms of TB (pulmonary and/or extrapulmonary), who have a CD4 cell count less than or equal to 100 cells/mm³, or people living with HIV who are seriously ill regardless of CD4 count or with unknown CD4 count (<i>conditional recommendation, low quality evidence</i>)⁶.</p> <p>LF-LAM should not be used as a screening test for active TB (<i>strong recommendation, low quality evidence</i>).</p>

1 Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children. Geneva: World Health Organization 2014; http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013supplement_dec2014/en/

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

3 The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV. Geneva: World Health Organization 2015; <http://www.who.int/tb/publications/use-of-lf-lam-tb-hiv/en/>.

4 Drug-susceptibility testing.

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

6 This recommendation also applies to adults living with HIV who are out-patients with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/mm³, or who are seriously ill regardless of CD4 count or with unknown CD4 count, based on the generalization of data from in-patients. This recommendation also applies to children living with HIV, with signs and symptoms of TB (pulmonary and/or extrapulmonary) based on the generalization of data from adults while acknowledging that data are very limited and that there are concerns regarding low specificity of the LF-LAM assay in children.

The new guidance highlights the growing incidence of noncommunicable diseases in people living with HIV and makes new recommendations on the need to assess and manage cardiovascular disease and depression. References are provided to relevant WHO guidance on the management of drug use, provision of nutritional care and palliative care for people living with HIV.



5.3 Prevention, screening and management of other comorbidities and chronic care for people living with HIV	
5.3.1 Assessment and management of cardiovascular diseases	Assessment and management of cardiovascular risk should be provided for all individuals living with HIV according to standard protocols recommended for the general population ¹ (<i>conditional recommendation, very low quality evidence</i>).
Good practice statement	Strategies for prevention and risk reduction of cardiovascular diseases by addressing modifiable factors such as blood pressure, smoking status, obesity, unhealthy diet and lack of physical activity should be applied to all people living with HIV.
5.3.2 Diagnosis and management of depression in people living with HIV	Assessment and management of depression should be included in the package of HIV care services for all individuals living with HIV (<i>conditional recommendation, very low quality evidence</i>).

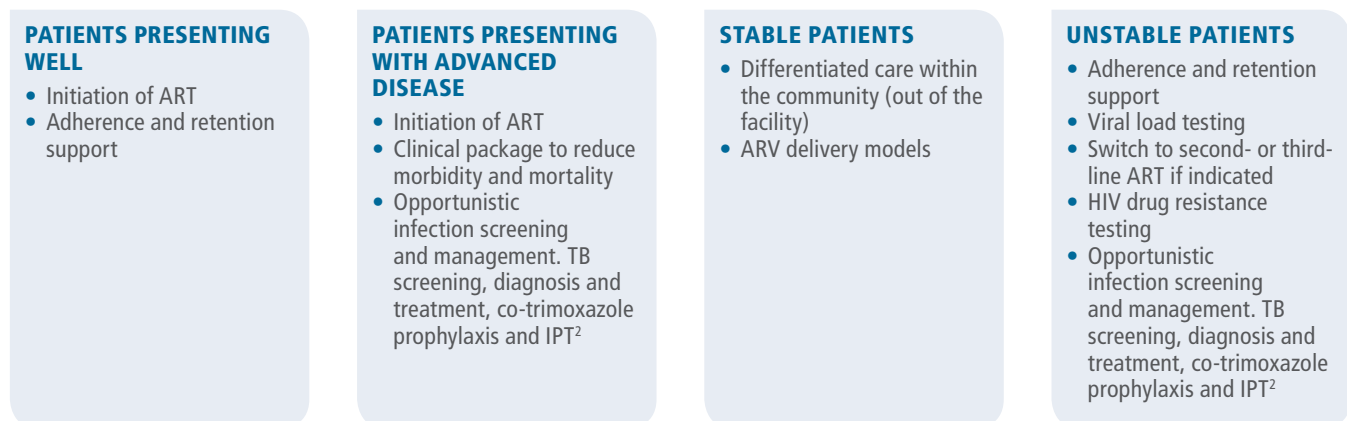
Service delivery

The service delivery guidance expands on the implementation aspects of the clinical recommendations in the guidelines. This chapter presents recommendations and guidance to strengthen the continuum of care and improve the quality and efficiency of service delivery, including clinical and community-based care, procurement and supply chain management and laboratory services.

Differentiated care

The new, second edition of the ARV guidelines introduces the concept of differentiated care and care packages for stable and unstable patients. The differentiated care framework recognizes that, as national guidelines evolve towards ART initiation for all people with HIV regardless of clinical and immunological status, HIV programmes will be challenged to manage an increasing number of patients on ART and an increasingly diverse set of patient needs. Differentiated care involves the provision of different care packages to patients on ART based on their care needs (Fig. 2).

Fig. 2. Diversity of care needs for people living with HIV



¹ The WHO package of essential noncommunicable disease (PEN) protocols target the following populations for CVD screening: age >40 years, smokers, people with known hypertension or diabetes mellitus, waist circumference >90 cm in women and >110 cm in men, and family history of DM or premature CVD. PEN is available at http://www.who.int/cardiovascular_diseases/publications/pen2010/en.

² Isoniazid preventive therapy.

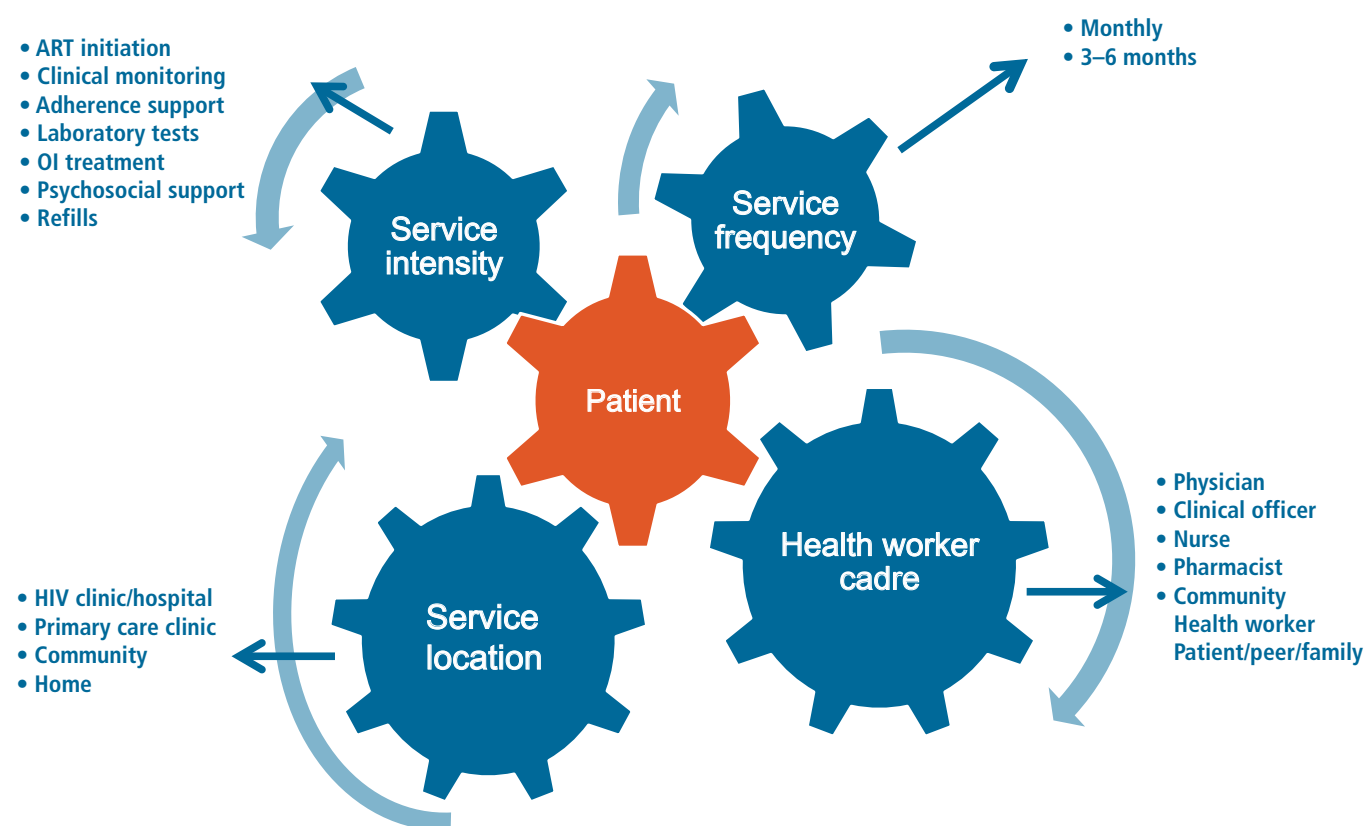
People engaged in care will move among groups and settings over the course of their lifetime on treatment. Patients who are stable on ART may safely move their care to one of many different community ARV delivery models. This approach will relieve overburdened health-care functions and enable more attention to be paid in clinical settings to patients who are unwell either because they are unstable on ART or because they present to the clinic with advanced disease. People who present and initiate treatment when well may require additional support for adherence and retention in care, as Option B+ programmes for prevention of mother-to-child transmission have found.

The differentiated care framework is characterized by the combination of the four delivery components shown in Fig. 3:

1. the intensity of services delivered
2. the location of service delivery
3. the provider of services and
4. the frequency of services.

How these components are combined into a service delivery framework will vary across countries and populations, but the intention common to all programmes should be to improve the acceptability and outcomes of care.

Fig. 3. Key factors in differentiated approaches to HIV care



Under the differentiated care model, new recommendations to support patients include reducing the frequency of clinic visits and medication pickups for those who are stable on ART and the introduction of distribution of ARVs by trained and supervised lay providers. Previous recommendations are maintained on the role of trained non-physicians in initiation and maintenance and dispensing of ART to all adults, adolescents and children, and a new good practice statement supports blood finger prick by lay providers for sample collection. A recommendation on the integration of sexually transmitted infection and family planning services into HIV care settings has the potential to expand access to all those accessing these overlapping services.

6. SERVICE DELIVERY	
6.7 Frequency of visits	Less frequent clinical visits (3–6 months) are recommended for people stable on ART (<i>strong recommendation, moderate quality evidence</i>). ¹ Less frequent medication pickups (3–6 months) are recommended for people stable on ART (<i>strong recommendation, low quality evidence</i>). ²
6.8 Task shifting and sharing	Trained and supervised lay providers can distribute ART to adults, adolescents and children living with HIV (<i>strong recommendation, low quality evidence</i>).
Good practice statement	Trained and supervised non-laboratory staff including lay persons can undertake blood finger prick for sample collection.
6.10 Integrating and linking services	
6.10.4 STI and family planning in HIV care settings	Sexually transmitted infection (STI) and family planning services can be integrated within HIV care settings (<i>conditional recommendation, very low quality evidence</i>).



1 When routine clinical consultations are due, they should be coordinated with planned medicine pickups to reduce visit frequency.

2 ARV supply management should be strengthened to ensure availability of ARV medicine and prevent stock-outs in the context of less frequent medication pickups.

Linkage, retention and adherence to care

New guidance to strengthen the continuum of care promotes timely linkage to care, point-of-care CD4 testing, electronic communication of test results and evidence-informed approaches to strengthening adherence to treatment and retention in care.

6.4 Linkage from HIV testing to enrolment in care	
6.4.1 Interventions to ensure timely linkage	<p>Following an HIV diagnosis, a package of support interventions should be offered to ensure timely linkage to care for all people living with HIV (<i>strong recommendation, moderate quality evidence</i>).</p> <p>The following interventions have demonstrated benefit in improving linkage to care following an HIV diagnosis:</p> <ul style="list-style-type: none"> streamlined interventions to reduce time between diagnoses and engagement in care, including (i) enhanced linkage with case-management; (ii) support for HIV disclosure; (iii) tracing; (iv) training staff to provide multiple services, and (v) streamlined services (<i>moderate quality evidence</i>); peer support¹ & navigation approaches for linkage (<i>moderate quality evidence</i>), and quality improvement approaches using data to improve linkage (<i>low quality evidence</i>).
6.4.2 CD4 cell count testing at the point of care	CD4 cell count testing at the point of care can be used to prioritize patients for urgent linkage to care and ART initiation (<i>conditional recommendation, low quality evidence</i>).
6.4.3 Laboratory connectivity	Electronic communication can be considered to transfer test results and reduce delays in acting on results of early infant diagnosis and other essential laboratory tests (<i>conditional recommendation, low quality evidence</i>).
6.5 Retention in care	<p>Programmes should provide community support for people living with HIV to improve retention in HIV care (<i>strong recommendation, low quality evidence</i>).</p> <p>The following community-level interventions have demonstrated benefit in improving retention in care:</p> <ul style="list-style-type: none"> package of community-based interventions² (<i>children: low quality evidence, adults: very low quality evidence</i>) adherence clubs³ (<i>moderate quality evidence</i>) extra care for high risk persons (<i>very low quality evidence</i>).
6.6 Adherence	<p>Adherence support interventions should be provided to people on ART (<i>strong recommendation, moderate quality evidence</i>).</p> <p>The following interventions have demonstrated effectiveness in improving adherence and virological suppression:</p> <ul style="list-style-type: none"> peer counsellors (<i>moderate quality evidence</i>) mobile phone text messages (<i>moderate quality evidence</i>) reminder devices (<i>moderate quality evidence</i>) cognitive behavioural therapy (<i>moderate quality evidence</i>) behavioural skills training / medication adherence training (<i>moderate quality evidence</i>) fixed-dose combinations and once-daily regimens (<i>moderate quality evidence</i>).

Delivering HIV services to adolescents

The updated guidelines emphasize providing adolescent-friendly health services within HIV settings to increase engagement with adolescents, improve outcomes and promote the integration of services for sexually transmitted infections and family planning into HIV care settings. A new recommendation builds on existing approaches to providing adolescent-friendly care and WHO-defined characteristics of adolescent-friendly health services.⁴

6.11 Delivering HIV services to adolescents	Adolescent-friendly services should be implemented in HIV services to ensure engagement and improved outcomes (<i>strong recommendation, low quality evidence</i>).
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¹ Peer support includes peer counselling.

² Includes patient advocates, and peer supporter interventions providing adherence and psychosocial support in the community.

³ Includes peer support, distribution of ARVs, assessment by nonclinical or lay providers.

⁴ Global standards for quality health-care services for adolescents: a guide to implement a standards-driven approach to improve the quality of health-care services for adolescents. Volume 1: Standards and criteria. Geneva: World Health Organization; 2015, http://apps.who.int/iris/bitstream/10665/183935/1/9789241549332_vol1_eng.pdf?ua=1

Improving the quality of HIV care services

Strategies to improve the quality of HIV care services are needed at all levels of the health system. The updated guidance on improving the quality of HIV services focuses on key principles and provides examples of quality assurance and quality improvement.

<p>6.12 Improving the quality of HIV care services</p> <p>Good practice statements</p>	<p>HIV programmes should:</p> <ul style="list-style-type: none"> • provide people-centred care that is focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity and respect, especially for vulnerable populations, and engage and support people and families for informed decision-making to play an active role in their own care; • offer safe, acceptable and appropriate clinical and nonclinical services in a timely fashion, aiming to reduce morbidity and mortality associated with HIV infection and to improve health outcomes and quality of life in general; • promote efficient and effective use of resources.
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Monitoring and evaluation

The updated ARV guidelines summarize a range of recommended approaches for monitoring and evaluating HIV programmes along the continuum of testing, prevention, treatment and care, based on the 2015 WHO *Consolidated guidelines on strategic information for HIV in the health sector*.¹ The strategic information guidelines recommend national and global HIV programme indicators, focusing on 10 indicators identified for global reporting. The guidelines also propose specific strategies to monitor ARV toxicity and ARV drug resistance.

Publication, dissemination and evaluation

Chapter 8 of the updated guidelines provides guiding principles and tools for planning the implementation of the new guidance. Four country examples of the use of costing in implementation decision-making may help countries to estimate the costs and budgeting of their HIV response and related interventions and services. A logical framework for implementing HIV policies is provided to support sequencing of implementation, to be used in conjunction with key data for decision-making.

Annexes to the guidelines include testing algorithms, ARV dosing tables and a table of drug interactions. A checklist for decision-making and implementation is included to support adaptation. **Web supplements** provide evidence-to-decision frameworks, systematic reviews of the evidence, consultation reports and relevant information collected during the guideline development process.



¹ Consolidated strategic information guidelines for HIV in the health sector. Geneva: World Health, <http://who.int/hiv/pub/guidelines/strategic-information-guidelines/en/>

3. WHO WILL USE THESE GUIDELINES?

The primary audience for these guidelines is national HIV programme managers, particularly those in low- and middle-income countries. The guidelines will also be a valuable resource for health-care providers and should help to shape the priorities of policy-makers in development agencies, international organizations, nongovernmental organizations and other implementing partners over the coming years. The guidelines will also be of value to people living with HIV and communities and civil society organizations, whose meaningful engagement is essential to successful implementation.

4. WHAT IS THE EXPECTED IMPACT OF THE NEW GUIDELINES?

By March 2015 global ART coverage for all people living with HIV had reached approximately 41% – 15 million people (1). According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), expanding ART to all 35 million people currently living with HIV is projected to avert 28 million new HIV infections and 21 million AIDS-related deaths by 2030 (2). Thus, implementing these guidelines will have unprecedented impact.

These benefits require high levels of testing uptake and treatment coverage, sustained adherence to ART and high rates of retention in care. The cost implications at the regional and country levels will vary and need to be further explored, since countries have different levels of current treatment coverage and cost considerations depending on their context and resources. Additional ARV drug costs may be at least partially offset by increased efficiencies, such as implementation of the differentiated care approach, task shifting and integration of HIV and related services. Greater investments by countries and responsibility for implementing these recommendations will be needed to maximize their impact.



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