

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

RECOMMENDATIONS FOR A PUBLIC HEALTH APPROACH

JUNE 2013

SUMMARY OF NEW RECOMMENDATIONS

The following table summarizes the new WHO recommendations formulated for the 2013 guidelines on HIV testing and counselling, antiretroviral therapy (ART) and HIV service delivery. It also summarizes the guidance provided in Chapter 10 for programme managers. Where the recommendations remain unchanged from 2010 ART guidelines, this is clearly stated in the table.

The table is not comprehensive and does not include all WHO recommendations referred to in these guidelines, specifically recommendations that have been drawn from other, already existing WHO guidelines. The existing WHO recommendations referred to can be found in: Chapter 5 on HIV testing and counselling and HIV prevention, Chapter 6 on general care for people living with HIV, Chapter 8 on the management of common coinfections and other comorbidities and in section 7.4 on monitoring and management of drug toxicities.

HIV testing and counselling	
Topic and population	Recommendations
Community-based testing	<ul style="list-style-type: none"> ● In generalized HIV epidemics, community-based HIV testing and counselling with linkage to prevention, care and treatment services is recommended, in addition to provider-initiated testing and counselling (<i>strong recommendation, low-quality evidence</i>). ● In all HIV epidemic settings, community-based HIV testing and counselling for key populations, with linkage to prevention, care and treatment services is recommended, in addition to provider-initiated testing and counselling (<i>strong recommendation, low-quality evidence</i>).
HIV testing and counselling of adolescents ^a	<ul style="list-style-type: none"> ● HIV testing and counselling, with linkages to prevention, treatment and care, is recommended for adolescents from key populations in all settings (generalized, low and concentrated epidemics) (<i>strong recommendation, very-low-quality evidence</i>). ● HIV testing and counselling with linkage to prevention, treatment and care is recommended for all adolescents in generalized epidemics (<i>strong recommendation, very-low-quality evidence</i>). ● We suggest that HIV testing and counselling with linkage to prevention, treatment and care be accessible to all adolescents in low and concentrated epidemics (<i>conditional recommendation, very-low-quality evidence</i>). ● We suggest that adolescents be counselled about the potential benefits and risks of disclosure of their HIV status and empowered and supported to determine if, when, how and to whom to disclose (<i>conditional recommendation, very-low-quality evidence</i>).

When to start ART in people living with HIV

Topic and population	Recommendations
When to start ART in adults and adolescents^a	<ul style="list-style-type: none"> ● As a priority, ART should be initiated in all individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤ 350 cells/mm³ (<i>strong recommendation, moderate-quality evidence</i>). ● ART should be initiated in all individuals with HIV with CD4 count >350 cells/mm³ and ≤ 500 cells/mm³ regardless of WHO clinical stage (<i>strong recommendation, moderate-quality evidence</i>). ● ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count in the following situations: <ul style="list-style-type: none"> ● Individuals with HIV and active TB disease (<i>strong recommendation, low-quality evidence</i>). ● Individuals coinfectd with HIV and HBV with evidence of severe chronic liver disease (<i>strong recommendation, low-quality evidence</i>). ● Partners with HIV in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners (<i>strong recommendation, high-quality evidence</i>).
When to start ART in pregnant and breastfeeding women	<ul style="list-style-type: none"> ● All pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART (<i>strong recommendation, moderate-quality evidence</i>). ● For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women with HIV should initiate ART as lifelong treatment (<i>conditional recommendation, low-quality evidence</i>). ● In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of mother-to-child transmission risk has ceased (<i>conditional recommendation, low-quality evidence</i>).

^aAn adolescent is a person aged 10 to 19 years inclusive.

When to start ART in people living with HIV (continued)

Topic and population	Recommendations
ARVs and duration of breastfeeding	<p>The key principles and recommendations established in 2010 remain, including:</p> <p>National or subnational health authorities should decide whether health services will mainly counsel and support mothers known to be infected with HIV to either breastfeed and receive ARV interventions or avoid all breastfeeding given their particular context.</p> <p>In settings where national authorities have decided that maternal and child health services will mainly promote and support breastfeeding and ARV interventions as the strategy that will most likely give infants born to mothers known to be infected with HIV the greatest chance of HIV-free survival:</p> <ul style="list-style-type: none"> ● Mothers known to be infected with HIV (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast-milk can be provided (<i>strong recommendation, high-quality evidence for the first 6 months; low-quality evidence for the recommendation of 12 months</i>).
When to start ART in children	<ul style="list-style-type: none"> ● ART should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count. <ul style="list-style-type: none"> ● Infants diagnosed in the first year of life (<i>strong recommendation, moderate-quality evidence</i>) ● Children infected with HIV one year to less than five years of age (<i>conditional recommendation, very-low-quality evidence</i>). ● ART should be initiated in all children infected with HIV five years of age and older with CD4 cell count ≤ 500 cells/mm³, regardless of WHO clinical stage. <ul style="list-style-type: none"> ● CD4 count ≤ 350 cells/mm³ (<i>strong recommendation, moderate-quality evidence</i>) ● CD4 count between 350 and 500 cells/mm³ (<i>conditional recommendation, very-low-quality evidence</i>). ● ART should be initiated in all children infected with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 cell count (<i>strong recommendation, moderate-quality evidence</i>). ● ART should be initiated in any child younger than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection (<i>strong recommendation, low-quality evidence</i>).

What ART regimens to start with

Topic and population	Recommendations
First-line ART regimens for adults	<ul style="list-style-type: none"> ● First-line ART should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI). ● TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (<i>strong recommendation, moderate-quality evidence</i>). ● If TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following options is recommended: <ul style="list-style-type: none"> ● AZT + 3TC + EFV ● AZT + 3TC + NVP ● TDF + 3TC (or FTC) + NVP <i>(strong recommendation, moderate-quality evidence)</i>. ● Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities (<i>strong recommendation, moderate-quality evidence</i>).
First-line ART for pregnant and breastfeeding women and their infants	<ul style="list-style-type: none"> ● A once-daily fixed-dose combination of TDF + 3TC (or FTC) + EFV is recommended as first-line ART in pregnant and breastfeeding women, including pregnant women in the first trimester of pregnancy and women of childbearing age. The recommendation applies both to lifelong treatment and to ART initiated for PMTCT and then stopped (<i>strong recommendation, low- to moderate-quality evidence: moderate-quality evidence for adults in general but low-quality evidence for the specific population of pregnant and breastfeeding women and infants</i>). ● Infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given four to six weeks of infant prophylaxis with daily NVP (or twice-daily AZT). Infant prophylaxis should begin at birth or when HIV exposure is recognized postpartum (<i>strong recommendation, moderate-quality evidence for breastfeeding infants; strong recommendation, low-quality evidence for infants receiving only replacement feeding</i>).

What ART regimens to start with (continued)

Topic and population	Recommendations
<p>First-line ART for children younger than 3 years of age</p>	<ul style="list-style-type: none"> ● A LPV/r-based regimen should be used as first-line ART for all children infected with HIV younger than three years (36 months) of age, regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with an NVP-based regimen (<i>strong recommendation, moderate-quality evidence</i>). ● Where viral load monitoring is available, consideration can be given to substituting LPV/r with an NNRTI after virological suppression is sustained (<i>conditional recommendation, low-quality evidence</i>). ● For infants and children infected with HIV younger than three years, ABC + 3TC + AZT is recommended as an option for children who develop TB while on an ART regimen containing NVP or LPV/r. Once TB therapy has been completed, this regimen should be stopped and the initial regimen should be restarted (<i>strong recommendation, moderate-quality evidence</i>). ● For infants and children infected with HIV younger than three years, the NRTI backbone for an ART regimen should be ABC + 3TC or AZT + 3TC (<i>strong recommendation, low-quality evidence</i>).
<p>First-line ART for children 3 years of age and older (including adolescents)</p>	<ul style="list-style-type: none"> ● For children infected with HIV three years of age and older (including adolescents), EFV is the preferred NNRTI for first-line treatment and NVP is the alternative (<i>strong recommendation, low-quality evidence</i>). ● For children infected with HIV three years to less than 10 years old (and adolescents weighing less than 35 kg), the NRTI backbone for an ART regimen should be one of the following, in preferential order: <ul style="list-style-type: none"> ● ABC + 3TC ● AZT or TDF + 3TC (or FTC) <i>(conditional recommendation, low-quality evidence)</i>. ● For adolescents infected with HIV (10 to 19 years old) weighing 35 kg or more, the NRTI backbone for an ART regimen should align with that of adults and be one of the following, in preferential order: <ul style="list-style-type: none"> ● TDF + 3TC (or FTC) ● AZT + 3TC ● ABC + 3TC <i>(strong recommendation, low-quality evidence)</i>.

Monitoring ART response and diagnosis of treatment failure

Topic and population	Recommendations
All populations	<ul style="list-style-type: none"> ● Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure (<i>strong recommendation, low-quality evidence</i>). ● If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure (<i>strong recommendation, moderate-quality evidence</i>).

Second-line ART: what ART regimen to switch to

Topic and population	Recommendations
<p>What ART regimen to switch to in adults and adolescents</p> <p><i>(includes pregnant and breastfeeding women)</i></p>	<ul style="list-style-type: none"> ● Second-line ART for adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) + a ritonavir-boosted protease inhibitor (PI). ● The following sequence of second-line NRTI options is recommended: <ul style="list-style-type: none"> • After failure on a TDF + 3TC (or FTC)-based first-line regimen, use AZT + 3TC as the NRTI backbone in second-line regimens. • After failure on an AZT or d4T + 3TC-based first-line regimen, use TDF + 3TC (or FTC) as the NRTI backbone in second-line regimens. ● Use of NRTI backbones as a fixed-dose combination is recommended as the preferred approach (<i>strong recommendation, moderate-quality evidence</i>). ● Heat-stable fixed-dose combinations ATV/r and LPV/r are the preferred boosted PI options for second-line ART (<i>strong recommendation, moderate-quality evidence</i>).

Second-line ART: what ART regimen to switch to (continued)

Topic and population	Recommendations
<p>What ART regimen to switch to in children (including adolescents)</p>	<ul style="list-style-type: none"> ● After failure of a first-line NNRTI-based regimen, a boosted PI plus two NRTIs are recommended for second-line ART; LPV/r is the preferred boosted PI (<i>strong recommendation, moderate-quality evidence</i>). ● After failure of a first-line LPV/r-based regimen, children younger than 3 years should remain on their first-line regimen, and measures to improve adherence should be undertaken (<i>conditional recommendation, very-low-quality evidence</i>). ● After failure of a first-line LPV/r-based regimen, children 3 years or older should switch to a second-line regimen containing an NNRTI plus two NRTIs; EFV is the preferred NNRTI (<i>conditional recommendation, low-quality evidence</i>). ● After failure of a first-line regimen of ABC or TDF + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is AZT + 3TC (<i>strong recommendation, low-quality evidence</i>). ● After failure of a first-line regimen containing AZT or d4T + 3TC (or FTC) the preferred NRTI backbone option for second-line ART is ABC or TDF + 3TC (or FTC) (<i>strong recommendation, low-quality evidence</i>).
<h3>Third-line ART</h3>	
Topic and population	Recommendations
All populations	<ul style="list-style-type: none"> ● National programmes should develop policies for third-line ART (<i>conditional recommendation, low-quality evidence</i>). ● Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as integrase inhibitors and second-generation NNRTIs and PIs (<i>conditional recommendation, low-quality evidence</i>). ● Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen (<i>conditional recommendation, very low-quality evidence</i>).
Special considerations for children	<p>Strategies that balance the benefits and risks for children need to be explored when second-line treatment fails. For older children and adolescents who have more therapeutic options available to them, constructing third-line ARV regimens with novel drugs used in treating adults such as ETV, DRV and RAL may be possible. Children on a second-line regimen that is failing with no new ARV drug options should continue with a tolerated regimen. If ART is stopped, opportunistic infections still need to be prevented, symptoms relieved and pain managed.</p>

Table 5.2 Summary of HIV testing and counselling recommendations for generalized epidemics

Who to test	When to test	Where to test	Relevant WHO guidance
Everyone attending health facilities	Integrate in all health care encounters	All settings, including primary health care, outpatient medical and surgical wards, antenatal care and maternal and child health, TB, family planning and sexually transmitted infection clinics	<i>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</i>
Partners and couples	Premarital, pregnancy, after separations, new partnerships and at the start of care and ART For the HIV-negative person in serodiscordant couples, offer re-testing every 6–12 months	Primary health care settings, voluntary counselling and testing sites, ART clinics, antenatal care, family planning clinics, sexually transmitted infection clinics, community and mobile outreach, home	<i>Couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples (26)</i> <i>Delivering HIV test results and messages for re-testing and counselling in adults (32)</i>
Families of index cases	As soon as possible after the family member is diagnosed	Primary health care settings, ART clinics, maternal and child health and antenatal care settings, homes and community and mobile outreach	<i>Service delivery approaches to HIV testing and counselling (HTC): a strategic HTC programme framework (1)</i> <i>Planning, implementing and monitoring home-based HIV testing (33)</i>
Key populations: people who inject drugs, men who have sex with men, transgender people, sex workers, prisoners, and partners of people who inject drugs	Every 6–12 months	Primary health care settings, sexually transmitted infections clinics and outreach services, including harm reduction and other sites providing services to key populations	<i>Prevention and treatment of HIV and other sexually transmitted infections for sex workers in low- and middle-income countries: recommendations for a public health approach (30)</i> <i>Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people: recommendations for a public health approach (31)</i> <i>Service delivery approaches to HIV testing and counselling (HTC): a strategic HTC programme framework (1)</i> <i>Delivering HIV test results and messages for re-testing and counselling in adults (32)</i>

Table 5.2 (continued)

Who to test	When to test	Where to test	Relevant WHO guidance
Pregnant women and male partners	At first antenatal care visit Re-test in third trimester or peripartum Offer partner testing	Antenatal care, delivery, postpartum	<i>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</i> <i>Delivering HIV test results and messages for re-testing and counselling in adults (32)</i> <i>Couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples (26)</i>
Infants and children <18 months old	Early infant diagnosis at 4–6 weeks for all infants whose mothers are living with HIV or if maternal HIV status is unknown; determine the final infant HIV infection status after 18 months and/or when breastfeeding ends	Maternal and child health services Paediatric clinics Immunization clinics	<i>WHO recommendations on the diagnosis of HIV infection in infants and children (27)</i>
Children	Establish HIV status for all health contacts	Child inpatients and outpatients, immunization clinics	<i>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</i>
Adolescents	Integrate into all health care encounters Annually if sexually active; with new sexual partners	Primary health care, outpatients, inpatients, voluntary counselling and testing sites, youth-friendly services, family planning and sexually transmitted infections clinics	<i>Delivering HIV test results and messages for re-testing and counselling in adults (32)</i> <i>Guidelines on HIV testing and counselling for adolescents and care and treatment for adolescents living with HIV (29)</i>

Table 5.3 Summary of HIV testing and counselling recommendations for low-level and concentrated epidemics

Who to test	When to test	Where to test	Relevant WHO guidance
People with signs or symptoms of HIV infection	Integrate in health care encounter	Sexually transmitted infection clinics, TB clinics, medical wards, other clinics	<i>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</i>
Partners of people with HIV	As soon after partner diagnosis as possible For the negative person in serodiscordant couples, offer re-testing every 6–12 months	Clinical settings including primary health care settings, ART, TB, sexually transmitted infection clinics, voluntary counselling and testing	<i>Couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples (26)</i> <i>Delivering HIV test results and messages for re-testing and counselling in adults (32)</i>
Families of index cases	As soon as possible after the family member is diagnosed	ART clinics, maternal and child health and antenatal care settings, homes, community outreach	<i>Service delivery approaches to HIV testing and counselling (HTC): a strategic HTC programme framework (1)</i> <i>Planning, implementing and monitoring home-based HIV testing (33)</i> <i>Couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples (26)</i>
Key populations: people who inject drugs, men who have sex with men, transgender people and sex workers	Every 6–12 months	Sexually transmitted infection clinics, outreach services for key populations and harm-reduction services	<i>Prevention and treatment of HIV and other sexually transmitted infections for sex workers in low- and middle-income countries: recommendations for a public health approach (30)</i> <i>Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people: recommendations for a public health approach (31)</i> <i>Service delivery approaches to HIV testing and counselling (HTC): a strategic HTC programme framework (1)</i> <i>Delivering HIV test results and messages for re-testing and counselling in adults (32)</i>

Table 5.3 (continued)

Who to test	When to test	Where to test	Relevant WHO guidance
Pregnant women	At the first antenatal care visit	Antenatal care	<i>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</i>
Infants and children <18 months old	Early infant diagnosis at 4-6 weeks for all infants whose mothers are living with HIV or if maternal HIV status is unknown; determine the final infant HIV infection status after 18 months and/or when breastfeeding ends	Maternal and child health services Paediatric clinics Immunization clinics	<i>WHO recommendations on the diagnosis of HIV infection in infants and children (27)</i>
Children with signs or symptoms of HIV infection or who have a family member living with HIV	Integrate in health care encounter	In all health settings	<i>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</i>
Adolescents from key populations	Every 6–12 months	Youth-friendly services, sexually transmitted infection clinics, outreach	<i>Delivering HIV test results and messages for re-testing and counselling in adults (32)</i> <i>Guidelines on HIV testing and counselling for adolescents and care and treatment for adolescents living with HIV (29)</i>

5.2 HIV prevention based on ARV drugs¹

5.2.1 Oral pre-exposure prophylaxis

Background

Oral pre-exposure prophylaxis of HIV (PrEP) is the daily use of ARV drugs by HIV-uninfected people to block the acquisition of HIV. Clinical trials of daily oral PrEP have shown evidence of effectiveness with serodiscordant heterosexual couples (34), men and transgender women who have sex with men (35), high risk heterosexual couples (36), people who inject drugs (37).

Source for recommendations

- *Guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV: recommendations for use in the context of demonstration projects. Geneva, World Health Organization, 2012 (http://apps.who.int/iris/bitstream/10665/75188/1/9789241503884_eng.pdf) (38).*

Existing recommendations (38)

Existing WHO recommendations (38) are for the use of oral PrEP in demonstration projects for serodiscordant couples and men and transgender women who have sex with men.

- *Serodiscordant couples.* When serodiscordant couples are identified and where additional HIV prevention choices for them are needed, daily oral pre-exposure prophylaxis (either TDF or the combination of TDF + FTC) may be considered as a possible additional intervention for the uninfected partner (*conditional recommendation, high-quality evidence*).

If oral pre-exposure prophylaxis is to be provided for the HIV-negative partner in same-sex, male serodiscordant couples, the combination of TDF + FTC should be used, as evidence of effectiveness and safety in male-to-male penetrative sex is available for this regimen only.

- *Men and transgender women.* Where HIV transmission occurs among men and transgender women who have sex with men and additional HIV prevention choices for them are needed, daily oral pre-exposure prophylaxis (specifically the combination of TDF + FTC) may be considered as a possible additional intervention (*conditional recommendation, high-quality evidence*).

¹ Chapter 7 covers other aspects of ARV drugs as prevention, including PMTCT.

5.2.2 ART for prevention among serodiscordant couples



Source for recommendations

- *Couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples. Geneva, World Health Organization, 2012 (http://whqlibdoc.who.int/publications/2012/9789241501972_eng.pdf) (26).*

Existing recommendations (26)

- People with HIV in serodiscordant couples who start ART for their own health should be advised that ART is also recommended to reduce HIV transmission to the uninfected partner (*strong recommendation, high-quality evidence*).
- HIV-positive partners with a CD4 count ≥ 350 cells/mm³ in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners (*strong recommendation, high-quality evidence*).

5.2.3 Post-exposure prophylaxis for occupational and non-occupational exposure to HIV



Background

Post-exposure prophylaxis is short-term ART to reduce the likelihood of acquiring HIV infection after potential exposure either occupationally or through sexual intercourse. Within the health sector, post-exposure prophylaxis should be provided as part of a comprehensive package of universal precautions that reduces the exposure of personnel to infectious hazards at work. WHO post-exposure prophylaxis guidelines for occupational exposure have not been reviewed since 2006 and will be updated by 2014. The current recommended duration of post-exposure prophylaxis for HIV infection is 28 days, and the first dose should be offered as soon as possible within 72 hours after exposure. The choice of post-exposure prophylaxis drugs should be based on the country's first-line ART regimen for HIV. A recent recommendation (39) relates specifically to post-exposure prophylaxis in the case of sexual assault.

Source for recommendation

- *Responding to intimate partner violence and sexual violence against women: clinical and policy guidelines. Geneva, World Health Organization, in press (39).*

Existing recommendation (2013) (39)

- Consider HIV post-exposure prophylaxis for women presenting within 72 hours of a sexual assault. Use shared decision-making with the survivor to determine whether HIV post-exposure prophylaxis is appropriate (*strong recommendation, very-low-quality evidence*).



7.3 Monitoring response to ART and the diagnosis of treatment failure



7.3.1 Laboratory monitoring before and after initiating ART

Clinical assessment and laboratory tests play a key role in assessing individuals before ART is initiated and then monitoring their treatment response and possible toxicity of ARV drugs. Table 7.13 summarizes recommended laboratory tests for HIV screening and monitoring, as well as approaches to screen for coinfections and noncommunicable diseases.

Table 7.13 Recommended and desirable laboratory tests at HIV diagnosis and monitoring on ART

Phase of HIV management	Recommended	Desirable (if feasible)
HIV diagnosis	HIV serology, CD4 cell count TB screening	HBV (HBsAg) serology ^a HCV serology <i>Cryptococcus</i> antigen if CD4 count ≤ 100 cells/mm ³ ^b Screening for sexually transmitted infections Assessment for major noncommunicable chronic diseases and comorbidities ^c
Follow-up before ART	CD4 cell count (every 6–12 months)	
ART initiation	CD4 cell count	Haemoglobin test for AZT ^d Pregnancy test Blood pressure measurement Urine dipsticks for glycosuria and estimated glomerular filtration rate (eGFR) and serum creatinine for TDF ^e Alanine aminotransferase for NVP ^f
Receiving ART	CD4 cell count (every 6 months) HIV viral load (at 6 months after initiating ART and every 12 months thereafter)	Urine dipstick for glycosuria and serum creatinine for TDF ^c
Treatment failure	CD4 cell count HIV viral load	HBV (HBsAg) serology ^a (before switching ART regimen if this testing was not done or if the result was negative at baseline)

^a If feasible, HBsAg testing should be performed to identify people with HIV and HBV coinfection and who therefore should initiate TDF-containing ART.

^b Can be considered only in settings with a high prevalence of cryptococcal antigenaemia (>3%) (180).

^c Consider assessing the presence of chronic conditions that can influence ART management such as hypertension and other cardiovascular diseases, diabetes and TB.

^d Among children and adults with a high risk of adverse events associated with AZT (low CD4 or low BMI).

^e Among people with a high risk of adverse events associated with TDF: underlying renal disease, older age group, low BMI, diabetes, hypertension and concomitant use of a boosted PI or potential nephrotoxic drugs.

^f Among people with a high risk of adverse events associated with NVP, such as being ART-naïve, women with HIV with a CD4 count >250 cells/mm³ and HCV coinfection. However, liver enzymes have low predictive value for monitoring NVP toxicity.

7.3.2 Monitoring the response to ART and the diagnosis of treatment failure

New recommendations



- Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure (*strong recommendation, low-quality evidence*).
- If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure (*strong recommendation, moderate-quality evidence*).

Special notes: Treatment failure is defined by a persistently detectable viral load exceeding 1000 copies/ml (that is, two consecutive viral load measurements within a three-month interval, with adherence support between measurements) after at least six months of using ARV drugs. Viral load testing is usually performed in plasma; however, certain technologies that use whole blood as a sample type, such as laboratory-based tests using dried blood spots and point-of-care tests, are unreliable at this lower threshold, and where these are used a higher threshold should be adopted.

Viral load should be tested early after initiating ART (at 6 months) and then at least every 12 months to detect treatment failure. If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure, with targeted viral load testing to confirm virological failure where possible.

Background

Monitoring individuals receiving ART is important to ensure successful treatment, identify adherence problems and determine whether and which ART regimens should be switched in case of treatment failure. Before 2010, WHO guidelines on ART recommended using clinical outcomes and CD4 count for routinely monitoring the response to ARV drugs. However, the value of viral load testing as a more sensitive and early indicator of treatment failure is increasingly recognized and is the gold standard for monitoring the response to ARV drugs in high-income settings.

The 2010 WHO guidelines recommended that countries consider phasing in viral load testing to monitor the response to ART and use a viral load threshold above 5000 copies/ml in an adherent person with no other reasons for an elevated viral load (such as drug interactions, poor absorption and intercurrent illness). However, most ART programmes in resource-limited settings still do not have access to viral load testing and continue to rely on clinical and immunological monitoring. This limited use of viral load monitoring has been identified as a key reason for the lower than expected rates for switching ART regimens in resource-limited settings.

Rationale and supporting evidence

Although evidence from clinical trials for a survival benefit of viral load testing is limited, it can provide an early indication of treatment failure, and the 2013 guidelines strongly recommend using it for detecting virological failure and/or confirming treatment failure among people with evidence of clinical and/or immunological failure (Table 7.14). Since several clinical and epidemiological studies show that the risk of HIV transmission is very low when the viral load is lower than 1000 copies/ml (181), the Guidelines Development Group also recommended reducing the viral load threshold for treatment failure from 5000 copies/ml to 1000 copies/ml.




Table 7.14 WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens

Failure	Definition	Comments
Clinical failure	<p>Adults and adolescents</p> <p>New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition)^a after 6 months of effective treatment</p>	<p>The condition must be differentiated from immune reconstitution inflammatory syndrome^b occurring after initiating ART</p> <p>For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure^a</p>
	<p>Children</p> <p>New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment</p>	
Immunological failure	<p>Adults and adolescents</p> <p>CD4 count falls to the baseline (or below)</p> <p>or</p> <p>Persistent CD4 levels below 100 cells/mm³</p>	<p>Without concomitant or recent infection to cause a transient decline in the CD4 cell count</p> <p>A systematic review found that current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure (182). The predicted value would be expected to be even lower with earlier ART initiation and treatment failure at higher CD4 cell counts. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure</p>
	<p>Children</p> <p>Younger than 5 years</p> <p>Persistent CD4 levels below 200 cells/mm³ or <10%</p> <p>Older than 5 years</p> <p>Persistent CD4 levels below 100 cells/mm³</p>	
Virological failure	<p>Plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support</p>	<p>The optimal threshold for defining virological failure and the need for switching ART regimen has not been determined</p> <p>An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed</p> <p>Assessment of viral load using DBS and point-of-care technologies should use a higher threshold</p>

^a See the list of clinical conditions associated with advanced or severe HIV disease in Annex 1.

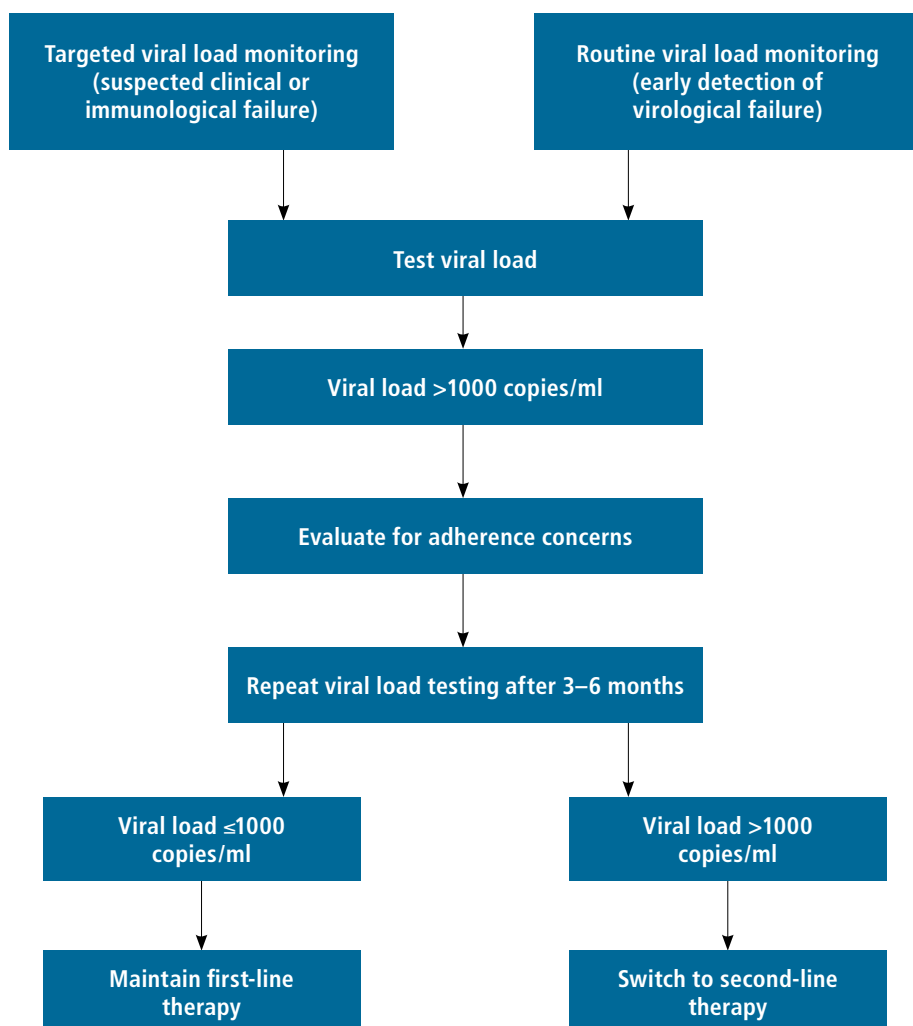
^b Section 6.1 discusses immune reconstitution inflammatory syndrome.

Threshold for defining virological failure

The optimal threshold for defining virological failure and for switching ART regimens has not been established. The rationale for the threshold of 1000 copies/ml was based on two main sources of evidence. First, viral blips or intermittent low-level viraemia (50–1000 copies/ml) can occur during effective treatment but have not been associated with an increased risk of treatment failure unless low-level viraemia is sustained (207). Second, clinical and epidemiological studies show that the risk of HIV transmission and disease progression is very low when the viral load is lower than 1000 copies/ml (181,208,209).

Most standard blood and plasma viral load platforms available and being developed have good diagnostic accuracy at this lower threshold. However, the sensitivity of dried blood spots for viral load determination at this threshold may be reduced (210,211). Programmes relying on dried blood spot technology for viral load assessment may therefore consider retaining the higher threshold (3000–5000 copies/ml) until sensitivity at lower thresholds is established (212–214).

Fig. 7.1 Viral load testing strategies to detect or confirm treatment failure and switch ART regimen in adults, adolescents and children



7.4 Monitoring and substitutions for ARV drug toxicities



7.4.1 Guiding principles

- The availability of laboratory monitoring is not required for initiating ART.
- Symptom-directed laboratory monitoring for safety and toxicity can be used for those receiving ART.

7.4.2 Major types of ARV toxicities

The 2010 WHO ART guidelines recommended a symptom-directed approach to laboratory monitoring of the safety and toxicity of ART regimens. At the same time, several laboratory tests for monitoring ARV toxicity were advised (but not required) for specific high-risk people using certain drugs. Table 7.15 lists key types of toxicity and associated risk factors for the major ARV drugs.

Monitoring drug toxicity using a symptom-directed approach needs to be investigated further to optimize treatment. More data are needed on whether routine or periodic laboratory monitoring for specific types of toxicity (such as renal function monitoring among TDF users) is required for all individuals or only people at higher risk.

Table 7.15 Types of toxicities associated with first-, second- and third-line ARV drugs

ARV drug	Major types of toxicity	Risk factors	Suggested management
ABC	Hypersensitivity reaction	Presence of HLA-B*5701 gene	If ABC is being used in first-line ART, substitute with TDF or AZT or d4T If ABC is being used in second-line ART, substitute with TDF
	Electrocardiographic abnormalities (PR interval prolongation)	Pre-existing conduction disease Concomitant use of other drugs that may prolong the PR interval	LPV/r or DRV/r. If boosted PIs are contraindicated and NNRTIs have failed in first-line ART, consider integrase inhibitors
ATV/r	Indirect hyperbilirubinaemia (clinical jaundice)	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	
	Nephrolithiasis and risk of prematurity	Risk factors unknown	
AZT	Anaemia, neutropaenia, myopathy, lipoatrophy or lipodystrophy	Baseline anaemia or neutropaenia CD4 count ≤ 200 cells/mm ³	If AZT is being used in first-line ART, substitute with TDF or ABC If AZT is being used in second-line ART, substitute with d4T
	Lactic acidosis or severe hepatomegaly with steatosis	BMI >25 (or body weight >75 kg) Prolonged exposure to nucleoside analogues	

Table 7.15 (continued)

ARV drug	Major types of toxicity	Risk factors	Suggested management
d4T	Peripheral neuropathy, lipatrophy or lipodystrophy	Older age CD4 count ≤ 200 cells/mm ³ Concomitant use of isoniazid or ddl	If d4T is being used in first-line ART, substitute with TDF or AZT or ABC
	Lactic acidosis or severe hepatomegaly with steatosis, acute pancreatitis	BMI >25 (or body weight >75 kg) Prolonged exposure to nucleoside analogues	If d4T is being used in second-line ART (after TDF or ABC are used in first-line ART), substitute with AZT
DRV/r	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	If DRV/r is being used in second-line ART, substituting with ATV/r or LPV/r can be considered. When it is used in third-line ART, limited options are available
	Severe skin and hypersensitivity reactions	Sulfonamide allergy	
EFV	Persistent central nervous system toxicity (such as abnormal dreams, depression or mental confusion)	Depression or other mental disorder (previous or at baseline) Daytime dosing	NVP. If the person cannot tolerate either NNRTI, use boosted PIs
	Hepatotoxicity	Underlying hepatic disease – HBV and HCV coinfection Concomitant use of hepatotoxic drug	
	Convulsions	History of seizure	
	Hypersensitivity reaction, Stevens-Johnson syndrome	Risk factors unknown	
	Potential risk of neural tube birth defects (very low risk in humans) (122,140)		
Male gynaecomastia			
ETV	Severe skin and hypersensitivity reactions	Unknown	Limited options are available



Table 7.15 (continued)

ARV drug	Major types of toxicity	Risk factors	Suggested management
LPV/r	Electrocardiographic abnormalities (PR and QT interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR interval	If LPV/r is used in first-line ART for children, use an age-appropriate NNRTI (NVP for children younger than 3 years and EFV for children 3 years and older). ATV can be used for children older than 6 years
	QT interval prolongation	Congenital long QT syndrome Hypokalaemia Concomitant use of drugs that may prolong the QT interval	
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	If LPV/r is used in second-line ART for adults, use ATV/r or DRV/r. If boosted PIs are contraindicated and the person has failed on treatment with NNRTI in first-line ART, consider integrase inhibitors
	Pancreatitis	Advanced HIV disease	
	Risk of prematurity, lipoatrophy or metabolic syndrome, dyslipidaemia or severe diarrhoea	Risk factors unknown	
NVP	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs CD4 >250 cells/mm ³ in women CD4 >400 cells/mm ³ for men First month of therapy (if lead-in dose is not used)	EFV. If the person cannot tolerate either NNRTI, use boosted PIs
	Severe skin rash and hypersensitivity reaction (Stevens-Johnson syndrome)	Risk factors unknown	
RAL	Rhabdomyolysis, myopathy, myalgia	Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis	Limited options are available

Table 7.15 (continued)

ARV drug	Major types of toxicity	Risk factors	Suggested management
TDF (169)	Tubular renal dysfunction, Fanconi syndrome	Underlying renal disease Older age BMI <18.5 (or body weight <50 kg) Untreated diabetes mellitus Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI	If TDF is being used in first-line ART, substitute with AZT or d4T or ABC If TDF is being used in second-line ART (after d4T + AZT use in first-line ART), substitute with ABC or ddl
	Decreases in bone mineral density	History of osteomalacia and pathological fracture Risk factors for osteoporosis or bone loss	
	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity	
	Exacerbation of hepatitis B (hepatic flares)	Discontinuation of TDF due to toxicity	Use alternative drug for hepatitis B treatment (such as entecavir)

7.5 What ART regimen to switch to (second-line ART)

Using a boosted PI + two NRTI combination is recommended as the preferred strategy for second-line ART for adults, adolescents and also for children when NNRTI-containing regimens were used in first-line ART. In children using a PI-based regimen for first-line ART, switching to NNRTI or maintaining the PI regimen is recommended according with age (Table 7.17).

Table 7.17 Summary of preferred second-line ART regimens for adults, adolescents, pregnant women and children

Second-line ART			Preferred regimens	Alternative regimens
Adults and adolescents (≥10 years), including pregnant and breastfeeding women			AZT + 3TC + LPV/r ^a AZT + 3TC + ATV/r ^a	TDF + 3TC (or FTC) + ATV/r TDF + 3TC (or FTC) + LPV/r
Children	If a NNRTI-based first-line regimen was used		ABC + 3TC + LPV/r ^b	ABC + 3TC + LPV/r ^b TDF + 3TC (or FTC) + LPV/r ^b
	If a PI-based first-line regimen was used	<3 years	No change from first-line regimen in use ^c	AZT (or ABC) + 3TC + NVP
		3 years to less than 10 years	AZT (or ABC) + 3TC + EFV	ABC (or TDF) + 3TC + NVP

^a DRV/r can be used as an alternative PI and SQV/r in special situations; neither is currently available as a heat-stable fixed-dose combination, but a DRV + RTV heat-stable fixed-dose combination is currently in development.

^b ATV/r can be used as an alternative to LPV/r for children older than six years.

^c Unless failure is caused by lack of adherence resulting from poor palatability of LPV/r.

7.5.1 Second-line ART for adults and adolescents



New recommendations

NEW

- Second-line ART for adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) + a ritonavir-boosted protease inhibitor (PI).
 - The following sequence of second-line NRTI options is recommended:
 - After failure on a TDF + 3TC (or FTC)–based first-line regimen, use AZT + 3TC as the NRTI backbone in second-line regimens.
 - After failure on an AZT or d4T + 3TC–based first-line regimen, use TDF + 3TC (or FTC) as the NRTI backbone in second-line regimens.
 - Use of NRTI backbones as a fixed-dose combination is recommended as the preferred approach (*strong recommendation, moderate-quality evidence*).
- Heat-stable fixed-dose combinations of ATV/r and LPV/r are the preferred boosted PI options for second-line ART (*strong recommendation, moderate-quality evidence*).