The basic concepts of the 2003 version of WHO antiretroviral treatment guidelines remain: a standardized formulary for first-line and second-line ART, with the use of two NRTIs (nucleoside reverse transcriptase inhibitors) and an NNRTI (non-nucleoside reverse transcriptase inhibitors) as the standard approach to first-line; maintenance of a boosted PI (protease inhibitor) as the mainstay of second-line regimens; and simplified patient management and standardized laboratory monitoring to indicate when to start, when to substitute an ARV drug for toxicity, and when to switch the regimen for failure or stop therapy (the “four Ss” of simplified clinical decision-making). The management of salvage therapy with third-line regimens for patients who failed on second line therapy is out of the scope of these guidelines.

WHO recognizes that, because access to basic laboratory services continues to be limited, many treatment decisions have to be based on clinical status alone. WHO continues to advocate wider access to laboratory monitoring tools, particularly CD4 testing, to guide the initiation and monitoring of ART. Viral load measurement is not currently recommended for decision making on the initiation or regular monitoring of ART in resource-limited settings. In this context, it has been recommended primarily for the definitive diagnosis of HIV infection in HIV-exposed children aged under 18 months and maybe considered in connection with diagnosing treatment failure earlier or to access discordant clinical and immunologic findings in patients in whom it is suspected that ART has failed. However, the availability of more simple and affordable methods of determining viral load in the near future can improve the standard of monitoring patients on ART, specially in situations where ART switching is being considered.

In addition to 3TC, AZT and d4T, other three new antiretrovirals (tenofovir, abacavir and emtricitabine) have been added as first-line ART options. With these changes, a triple NRTI therapy regimen can also be constructed as an alternative to complement the standard two NRTIs/NNRTI first-line approach for selected situations.

ART should be delivered as part of a package of care interventions, including the provision of co-trimoxazole prophylaxis, the management of opportunistic infections and comorbidities, nutritional support and palliative care.

When to start ART

- Current treatment guidelines suggest starting therapy in anyone with advanced or severe HIV-associated clinical disease or regardless of symptoms if the CD4 cell count is less than 200 /mm$^3$. The ideal starting point for treatment in asymptomatic patients with CD4 above this level is not established and requires consideration of a number of pros and cons, but if the value is between 200 and 350/mm$^3$, it should be considered and initiated before CD4 cell count drops below 200 cells/mm3. Treatment should not be initiated if CD4 cell count value is higher than 350/mm$^3$.

- Greater use of CD4 to guide decision in asymptomatic patients, but the absence or limited availability of CD4 cell count cannot be a barrier to start treatment in symptomatic patients. If CD4 cell count is not available TLC can be used to guide the decision to start ART in some situations (symptomatic patients with WHO clinical stage 2 disease), but with some clinical and operational limitations.
Recommended 1\textsuperscript{st} line ARV regimens

- 2 NRTI + 1 NNRTI as the preferential approach for 1\textsuperscript{st} line therapy.

- 3 NRTI as an alternative/simplified approach in 1\textsuperscript{st} line therapy, in situations where NNRTI options provide additional complications or are contraindicated.

- TDF or ABC as options in the initial regimen to compose the NRTI backbone of preferential approach or as a 3\textsuperscript{rd} drug in triple nuke approach.

- FTC is an equivalent alternative to 3TC as they are structurally related and shares the same efficacy and resistance profiles.

Additional consideration was given to the management of long-term toxicities of stavudine. WHO is now recommending that the 30 mg formulation of stavudine, dosed twice daily, should be used for all adult and adolescent patients, irrespective of body weight. This recommendation, which was previously considered an option, is now established as the preferred approach when d4T is used as part of an ARV therapeutic regimen. (See http://www.who.int/hiv/art/ARTadultsaddendum.pdf). WHO also recommends that zidovudine or tenofovir should be as one of the preferred NRTI options to be considered by countries as replacement for stavudine in their national formularies, in short to medium term, accordingly their programmatic capabilities.

Choice of ARV regimen for treatment failure of first line regimens

- Ideally use 3 new (i.e. which the patient has not previously been exposed to) drugs with at least 1 new class.

- Ritonavir-boosted PI (ATV/r, FPV/r, IDV/r, LPVr or SQV/r) as the key drug in 2\textsuperscript{nd} line regimens.

- Preferred 2\textsuperscript{nd} Line: 2 new NRTIs + boosted PI.

- Alternative 2\textsuperscript{nd} Line: 2 NRTI (at least 1 new) + PI (boosted or unboosted).

- Another alternative option is NNRTI + PI(r) if 3NRTI used in 1st line therapy.
• Limited options of NRTIs (extensive drug class cross resistance, particularly in patients with late switching), which mean boosted PI is cornerstone of potency.

• Among previously unused NRTIs, ddI, particularly as a enteric-coated formulation, has been considered as a key drug for construction of the 2nd line NRTI backbone.

Strategic maintenance of 3TC in second-line regimens has also been considered as an alternative to compose the NRTI backbone, because it confers residual viral activity maintains a mutation profile which decrease the viral replicative capacity and can induce some degree of resensitization to AZT and TDF. Add AZT can additionally improve the mutation profile delaying or preventing the emergence of K65R mutation, frequently induced by TDF and ABC.

**Clinical and laboratory monitoring**

• Clinical and immunologic parameters are recommended to assess new patients and monitor and evaluate response to ART. CD4 cell count monitoring, if available is recommended every six months. TLC is not recommended for monitoring treatment response.

• Toxicity of the majority of preferential drugs used in 1st line regimens monitored by clinical parameters (symptom-directed approach), with a minimum baseline laboratory assessment is recommended.

• Routine lab monitoring of toxicity is indicated in 2nd line regimens, particularly for PIs, as they can adversely affect glucose and lipid metabolism, which generally are asymptomatic.

**TB/HIV**

• Start ART earlier if possible (between 2 weeks-2 months) to reduce mortality, particularly in patients with low CD4 cell count.

• EFV based regimens preferred as 1st line approach in TB/HIV co-infected patients.

• Triple nukes or NVP-based regimens as alternatives in standard 1st line therapy in TB/HIV co-infected patients.

• Limited PI options for 2nd line ART in patients being treated for TB treatment with RMP. Use of extra dose of boosted ritonavir with some PIs (SQVr or LPVr) or replacement of rifampicin for rifabutin are the major options.

• IRS management as an important management aspect.

**ART in Hepatitis co-infection**

• Higher risk of drug-related hepatotoxicity is expected in co-infected patients using ART.

• In HCV co-infection, treatment of HCV should be preferentially started prior to developing severe immunodeficiency and preferably before ART, as significant drug interactions can occur.
• In HBV co-infection, ART using lamivudine (3TC) and tenofovir (TDF) are active against both HIV and HBV, and it is preferable to use both drugs together in situations where both HIV and HBV require treatment, as the use of only one of these drugs can result in more rapid development of HBV resistance.

ART in Women

• Pregnant women in 1st trimester of pregnancy or with childbearing potential should avoid EFV; However, if a woman of child-bearing age is on EFV use, then effective contraception should be used.

• NVP should be used with caution in women with nadir / baseline CD4>250/mm$^3$, because of an increased risk of hepatotoxicity.

• ART is recommended in pregnant women with the same eligibility criteria adopted in non pregnant adults, but is also recommended in pregnant women with a WHO clinical stage 3 disease and a CD4< 350/mm3. Pregnant women who do not yet need ART need to use prophylactic ARV regimens to prevent MTCT according to PMTCT guidelines.

ART in IDU

• The basic WHO recommended 1st and 2nd line ARV drug formulary can be used for large majority of patients.

• High prevalence of co-morbidities and co-treatment interactions should be taken in consideration in drug selection.

• The use of specific strategies (use of FDC/blister packs, once daily drugs, DOT/supervised treatment) should be strongly considered in order to improve the adherence to treatment.

• Link with prevention (including harm reduction).

ARV Adherence

• Minimize pill burden and complexity—FDC, blister packs, pill boxes.

• Avoid complicated regimens, i.e. food avoidance.

• Adherence "assessment and reinforcement" at follow up.

• Good adherence is most important driver of virologic and clinical outcome.

• Patients/family and treatment supporters need support before starting ART with ongoing support provided as needed thereafter.
Surveillance of transmitted HIV drug resistance; Monitoring of HIV drug resistance emerging in treatment

- Individual HIVDR testing to guide treatment is not recommended.
- Population based HIVDR surveillance of transmitted resistance in recently infected populations is recommended for specific areas within resource-restricted countries.
- Population-based monitoring of HIV drug resistance emerging in the first year of treatment, and evaluation of potentially associated ART program factors, is recommended at representative sentinel sites.

Early warning indicators for HIV Drug resistance - these are indicators targeted at ART facilities which, if collected will alert programme managers to programme factors which are also likely to be associated with poor outcomes of ART see: [http://www.who.int/hiv/drugresistance/EWItwopagertargets2006.pdf](http://www.who.int/hiv/drugresistance/EWItwopagertargets2006.pdf)

Children ART for infants and children


Detailed guidelines for ART in children were published in 2006 and are intended to direct national programmes in selecting the most feasible and context-appropriate first- and second-line ARV treatment regimens, based on the same criteria and classes outlined for adult ART above. Important aspects or differences in the revised guidelines include the following:

- How to establish diagnosis of HIV in infants and children.
- When to commence ART.
- Considerations for nutrition/ malnutrition and ART.

WHO also strongly promotes the use of virological testing for the early definitive diagnosis of HIV infection in HIV-exposed infants, or sick young infants where HIV is suspected being seen in health care facilities. Dried blood spots and centralized virological testing can be used to increase access to diagnostic testing for children. The guidelines also offer new recommendations on presumptive diagnosis of HIV where virological testing is not available, and immunological criteria for initiating ART. Annexes include guidance on drug-dosing schedules based on weight.

Specific additional technical tools related to ART care are also available related to on:

Patient Monitoring Guidelines for HIV Care and ART at : [http://www.who.int/3by5/capacity/ptmonguidelinesfinalv1.PDF](http://www.who.int/3by5/capacity/ptmonguidelinesfinalv1.PDF)


Other Key resources

http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf

http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf


http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf

http://www.who.int/hiv/pub/guidelines/pmtctguidelines3.pdf

http://www.who.int/hiv/pub/guidelines/ctxguidelines.pdf

Key Contacts

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<tr>
<th>HQ</th>
<th>Dr Charlie Gilks (Coordinator)</th>
<th><a href="mailto:gilksc@who.int">gilksc@who.int</a></th>
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<tr>
<td></td>
<td>Dr Marco Vitoria (adults/adolescents)</td>
<td><a href="mailto:vitoriam@who.int">vitoriam@who.int</a></td>
</tr>
<tr>
<td></td>
<td>Dr Siobhan Crowley (children/family care)</td>
<td><a href="mailto:crowleys@who.int">crowleys@who.int</a></td>
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<tr>
<td>AFRO</td>
<td>Dr. Rui Vaz</td>
<td><a href="mailto:vazr@afro.who.int">vazr@afro.who.int</a></td>
</tr>
<tr>
<td>AMRO</td>
<td>Dr. Patricio Rojas</td>
<td><a href="mailto:rojaspat@paho.org">rojaspat@paho.org</a></td>
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<tr>
<td>EMRO</td>
<td>Dr. Gabriele Reidner</td>
<td><a href="mailto:riednerg@emro.who.int">riednerg@emro.who.int</a></td>
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<tr>
<td>EURO</td>
<td>Dr. Irina Eramova</td>
<td><a href="mailto:ier@euro.who.int">ier@euro.who.int</a></td>
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<td>SEARO</td>
<td>Dr Ying Ru Lo</td>
<td><a href="mailto:loy@searo.who.int">loy@searo.who.int</a></td>
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<tr>
<td>WPRO</td>
<td>Dr. Massimo Ghidinelli</td>
<td><a href="mailto:ghidinelli@wpro.who.int">ghidinelli@wpro.who.int</a></td>
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