

Antiretroviral drugs for the treatment of HIV infection in adults and adolescents in resource-limited settings



Recommendations for a Public Health Approach (2005-2006 Revision)

Guidelines Development Group

Brief Meeting Report

*Montreux, Switzerland
22- 23rd June 2005*

WHO convened a meeting of the Guideline Development Group (GDG) to review existing ART recommendations for resource poor settings. Simplified standardized guidelines for the use of ARV drugs as ART in resource poor settings are the cornerstone of the public health approach advocated by WHO. The GDG was asked to review the 2003 guidelines in the light of new data and considerable experience of scaling up ART and HIV care and make recommendations for revisions of the current WHO guidelines. The Guideline Development Group recognized the need for simple and evidence-based guidelines in order to continue to support the immense progress made in scaling up access to ART for the large numbers of HIV-infected adults and adolescents requiring HIV care including ART. ART has been shown to save lives and provide good outcomes for HIV infected individuals in a range of resource constrained settings. The GDG also considered the need to harmonize the guidelines with the ART guidelines for children and those for use of ARV in Prevention of Mother to Child Transmission (PMTCT), and to ensure consistency and applicability to align with existing recommendations used to scale up access to ART in resource poor settings.

The simplification of treatment and monitoring procedures for ARV use continue to be the prime consideration underpinning WHO recommendations for the use of ART, but needs to also consider important new evidence and progress made in developing new treatment options. The group also considered a WHO review of the use of the ART guidelines, and the consistency of national HIV programme treatment recommendations with the 2003 WHO recommendations with respect to:

- when ART should begin;
- which regimens should be introduced;
- reasons to substitute or switch ARVs; and
- how treatment should be monitored.

The review suggested recommendations could be improved for :

- for second-line options;
- special considerations of ART with major co-infections (TB, viral hepatitis), for injecting drug users and in pregnancy;
- specific considerations for ART side effects and drug adherence; and
- salvage strategies.

It was agreed that these should be better elaborated and revised in the 2005-06 guideline version.

The guidelines group recognized that while the guidelines are intended primarily to provide technical guidance at national level, the recommendations supported by evidence and experience are a powerful tool to advocate for greater access to ART for HIV infected person and can create pressure to increase production and lower cost of ARV drugs, diagnostics and laboratory technologies (including CD4 and viral load testing). The guidelines also need to

highlight the importance of preventing secondary transmission of the virus and that expanding access to ART offers opportunities to enhance prevention efforts.

The participants at the technical consultation agreed that the following key recommendations should be included in the revised guidelines:

General principles:

Emphasize and advocate for wider availability of CD4 testing to guide decision making about when initiate ART switch and salvage ART regimens in resource limited settings, with recommendations to seek a baseline CD4 if possible.

Continue to advocate for free or highly reduced prices of ART to HIV infected people and specific targeted efforts to ensure access for vulnerable populations.

When to start treatment

Clinical parameters:

- **WHO Clinical Stage IV Disease:** treat irrespective of laboratory parameters; or
- **WHO Stage III Disease:** consider treatment for all but guided by CD4 cell count where available, (especially for tuberculosis); or
- **WHO Clinical Stage II Disease:** treat guided by CD4 cell count or where CD4 cell assays are not available, guided by total lymphocyte count TLC ; or
- **WHO Clinical Stage I Disease:** only guided by CD4 cell count.

The Guidelines Development Group was keen to ensure that revised recommendations encourage the consideration of starting ART based on CD4 and that ART should be considered in all asymptomatic individuals when the CD4 falls below 350 cells /mm³, particularly if closer to 200-250 cells/mm³.

If CD4 is not available, total lymphocyte count (TLC) can be used to guide need for treatment in WHO stage II patients if < 1200 cells/mm³, although it is reported to be problematic and little used in the field. A CD4 cell count is very useful in deciding upon timing of ART initiation in certain WHO stage III conditions (e.g. TB).

Asymptomatic WHO Stage I patients should ideally not be treated if CD4 is not available. Where feasible having at least two CD4 values at baseline is desirable for better decision making as this can provide a firm baseline. In all situations where CD4 is < 200 cells/mm³, ART should be initiated. If CD4 count value is between 200-350 cells/mm³, treatment should be considered, and started before it falls to less than 200 cells/mm³. Where CD4 above higher than 350 cells/mm³, it is recommended is to observe and monitor the patient, and plan for clinical and lab follow.

Clinical staging and initiation of ART

Clinical stage	CD4 available	CD4 not available
I	CD4 guided	Do not treat
II	CD4 guided	TLC guided
III	Consider CD4	Treat
IV	Treat	Treat

CD4 criteria for initiation of ART

CD4 (cell /mm ³)	Actions
< 200	Treat irrespective of clinical stage
200- 350	Consider treatment; initiate before drop below 200 cell/mm ³
>350	Defer treatment in asymptomatic persons

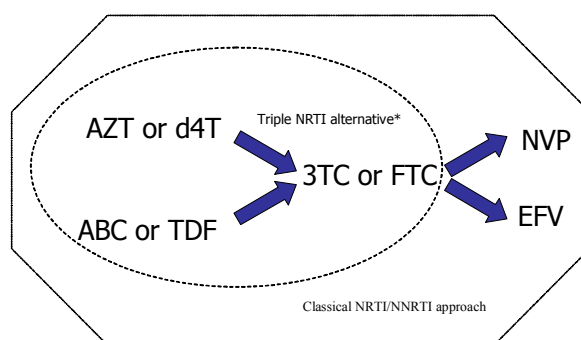
Where TLC is used to guide decision values less than 1200 cells/mm³ suggest initiation of ART is indicated in symptomatic persons.

Recommended 1st line regimens:

What to start:

The combination of two nucleosides (NRTI) plus one non-nucleoside (NNRTI) should continue to be the preferred 1st line ART regimen. In view of treatment outcomes, toxicity and threshold for resistance it was proposed to add TDF or ABC as additional RTI options in 1st line regimens, increasing the NRTI backbone options. The use of three nucleoside(tide)s should be retained as an option as it offers feasible treatment options for specific situations where NNRTIs options are compromised (negative drug interactions with concomitant medications, co-existing liver disease, pregnancy, concern for NNRTI resistance). Some of these regimens confer acceptable virologic response rates (e.g., AZT/3TC/ABC, AZT/3TC/TDF) while others should be avoided because of very high failure rates (e.g., ddI/3TC/TDF, ABC/3TC/TDF). Some specific combinations of nucleosides as d4T/ddI, TDF/ddI should be avoided because of the high risk of toxicity, significant pharmacological interactions or poor outcomes. 3TC and FTC are very similar and should be considered as interchangeable.

What to Start: Recommended 1st Line Regimens



* Triple NRTI should be considered as a simplification strategy for 1st line as suggested above, mainly for situations where NNRTIs options provide additional complications (e.g., pregnancy, viral hepatitis co-infection, TB co-infection).

Recommended 2nd line regimens:

Regardless of 1st line options selected, the GDG recommends selection of 2nd line regimens based on three new drugs including at least one new pharmacological class. Currently the best options are regimens containing a boosted PI, with two nucleosides. In 2nd line regimens adequate pharmacologic enhancement of the PI component is important. NFV or unboosted ATV can be used as an alternative PI in places without cold chain. AZT and d4T, despite different toxicity profiles share a high rate of cross resistance and the use of one of these drugs in the 1st line regimen generally precludes the use of the other in 2nd line combinations.

1st and 2nd Line ARV Regimens in Adults and Adolescents (2005-2006)

1 st Line Regimens	2 nd Line Regimens	
	RTI Component	PI Component*
(AZT or d4T) + (3TC or FTC) + (EFV or NVP)	ABC + ddl <u>or</u> ABC + TDF <u>or</u> TDF + AZT ± 3TC#	ATV/r <u>or</u> LPV/r <u>or</u> SQV/r
TDF + (3TC or FTC) + (EFV or NVP)	ABC + ddl <u>or</u> ddl + AZT ± 3TC#	
ABC + (3TC or FTC) + (EFV or NVP)	ddl + AZT ± 3TC# <u>or</u> TDF + AZT ± 3TC#	
(AZT or d4T) + (3TC or FTC) + (ABC or TDF)	EFV or NVP ± ddl <u>or</u> EFV or NVP ± 3TC#	

* NVP or ATV in places without cold chain. TDF cannot be used with unboosted ATV.

3TC can be considered to be maintained in 2nd line regimens to reduce the viral fitness.

Topics to be included in the new guidelines version:

The GDG established the need to include additional information about ART toxicity management, laboratory monitoring and drug-drug interactions. The GDG also emphasized that strategies to treat HIV should consider 1st line 2nd line regimens and salvage regimens as equally important for resource limited settings for the longer term. To better address this a new section outlining potential salvage strategies after 2nd line failure was proposed, although the details will need to be elaborated by the writing committee. Independent of the salvage approaches recommended, the necessity for careful evaluation of the benefits and adverse effects, and enhanced OI prevention were emphasized. Other important issues to be addressed in the revisions include the use of fixed dose combinations (FDCs), which have proved to be essential in the efforts at scaling up access to ART in resource limited settings.

Next Steps:

GDG members agreed to assist in the revision of the WHO guidelines and writing committees were established for the respective sections. The writing sub groups will now review and scrutinize further evidence and programme experience and develop the more detailed document. This will be compiled into a draft document to be discussed in WHO regional consultations and temporarily posted for public consultation in the Web prior to a global consensus meeting planned for Dec 2005. After that meeting, a final report with the major recommendations will be agreed and the final updated version launched in early 2006.