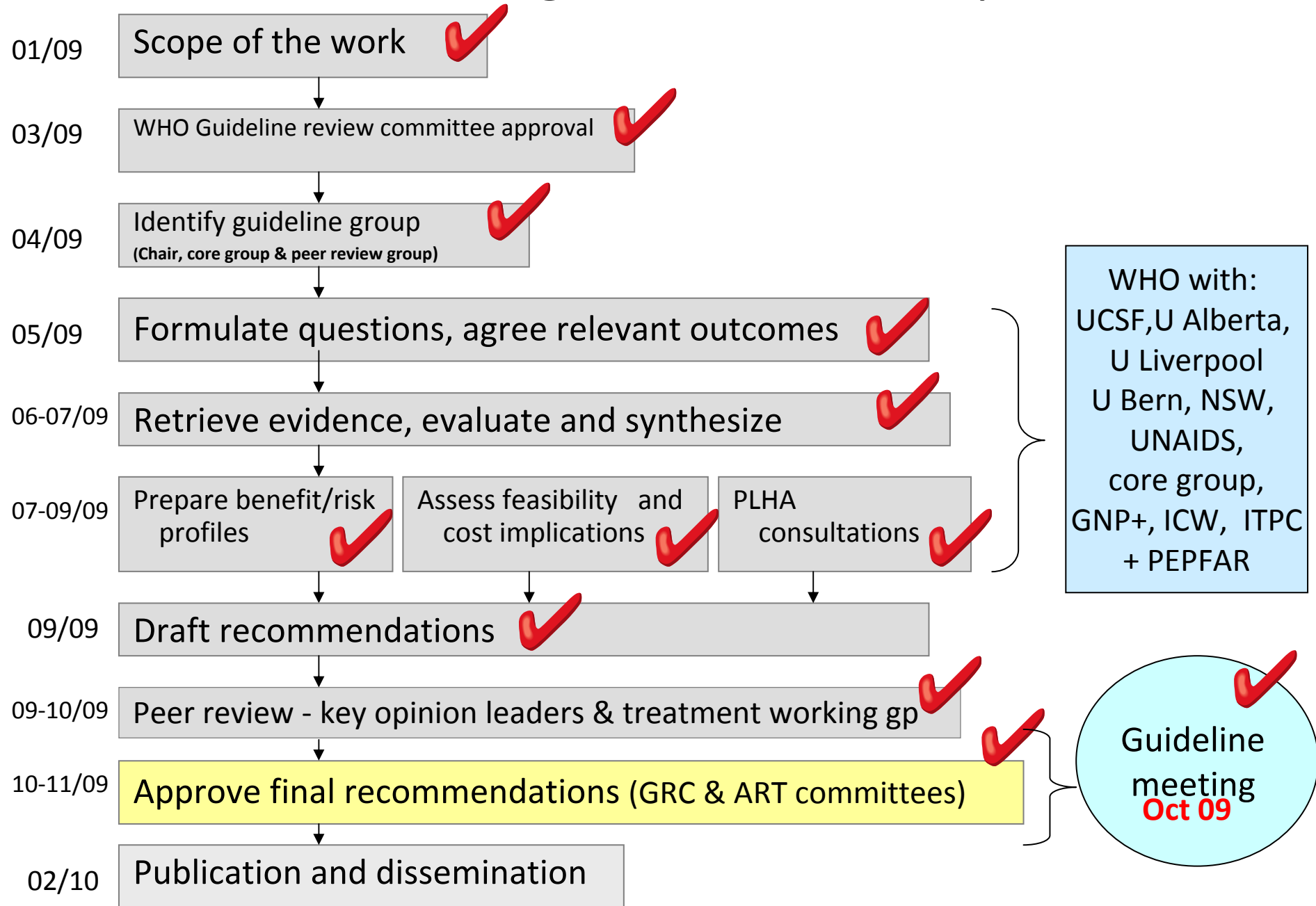


2009 Revisions of WHO ART Guidelines

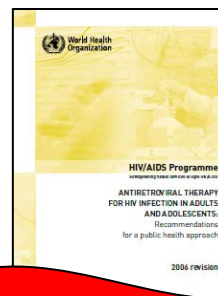
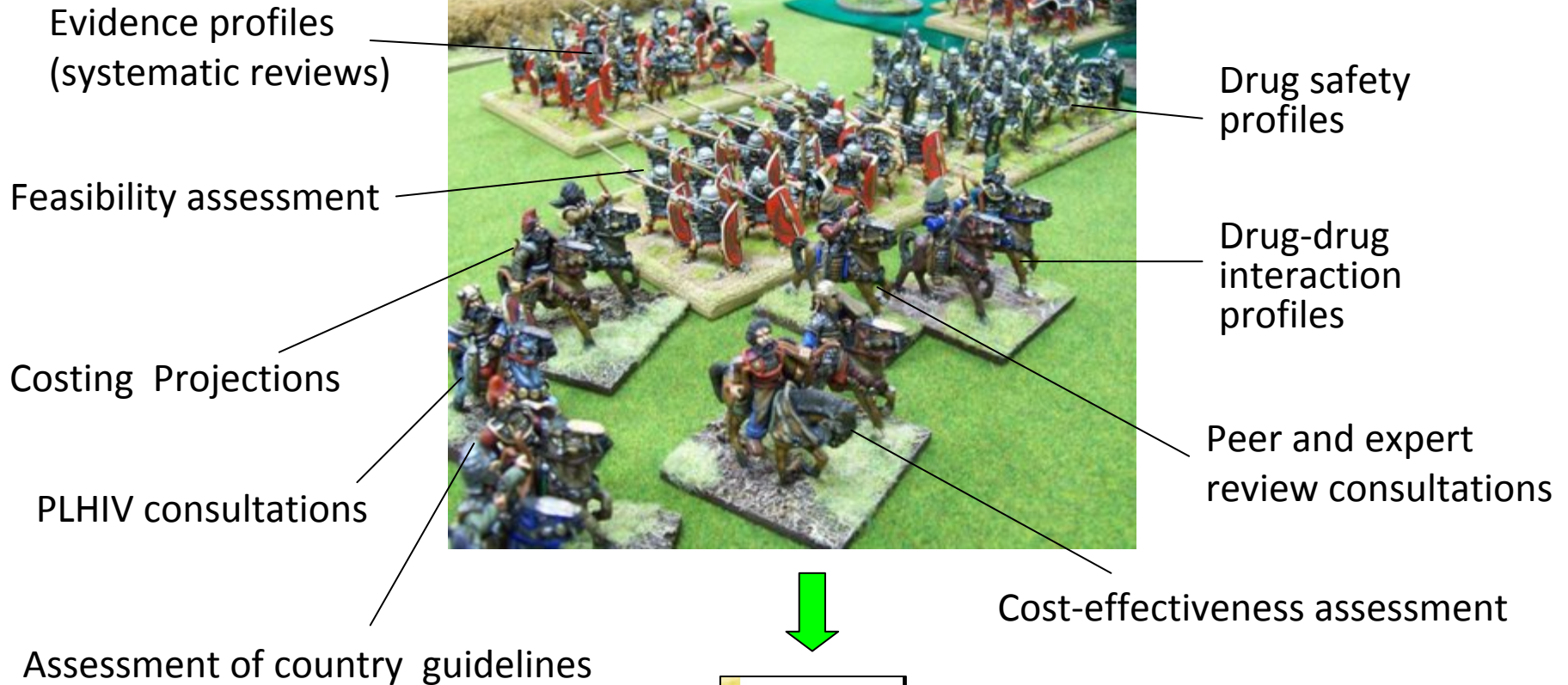
November 2009

Guidelines Development Process

2009 WHO ART guideline revision process

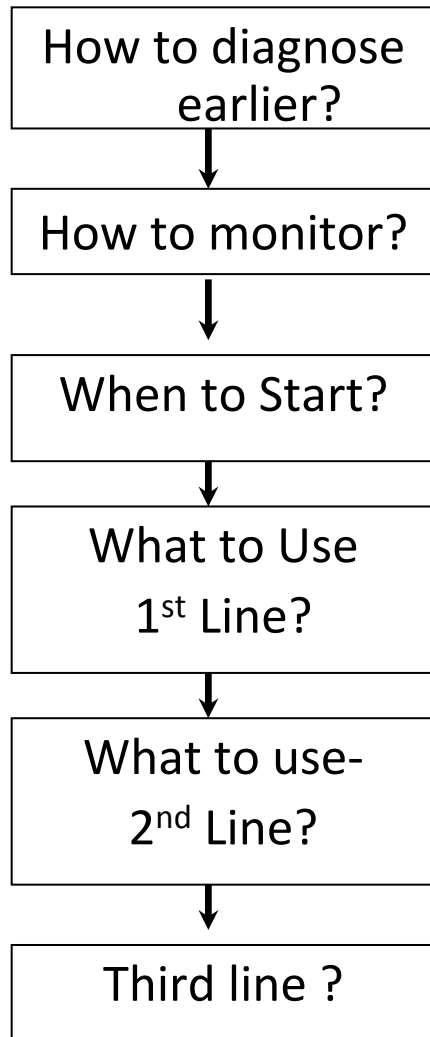


A cohort of preparatory activities....



2009 update

WHO ART treatment guidelines –the critical issues being reviewed



Critical patient & public health important outcomes:

- Mortality
- Disease progression (morbidity)
- Severe or regimen limiting adverse events
- Adherence & retention on ART
- Durability of regimen effect
- Reduction of HIV transmission
- Cost

Other outcomes evaluated:

- CD4
- HIV viral load
- HIV drug resistance
- HBV drug resistance
- HBV viral load

Major Populations being considered

- HIV+ve Adults & Adolescents
- HIV+ve Pregnant Women
- HIV+ve with TB Co-Infection
- HIV+ve with Hepatitis B Co-Infection

Quality of evidence using GRADE

The extent to which one can be confident that an estimate of effect or association is correct.

High	considerable confidence in estimate of effect
Moderate	further research likely to have impact on confidence in estimate, may change estimate
Low	further research is very likely to impact on confidence, likely to change the estimate
Very low	any estimate of effect is very uncertain

Factors to be considered to establish a recommendation

Factors	Comments
Quality of the evidence (GRADE)	Higher the quality of the evidence the more likely a strong recommendation can be made
Balance between desirable and undesirable effects	Larger the gap or gradient between these then more likely a strong recommendation will be made
Values and preferences (acceptability)	If there is a great deal of variability or strong reasons that the recommended course of action is unlikely to be accepted then it is more likely a weak recommendation will be made.
Costs/financial implications (resource use)	Higher the cost both financial and in terms of infrastructure, equipment or requirements, and more resource intensive requirements, then less likely to make a strong recommendation
Feasibility	Where the intervention is possible and practical in settings most affected and greatest impact being sought, a strong recommendation is more likely

Strength of recommendation

The degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects.



Desirable effects

- Health benefits
- Improved quality of life
- Cost efficiencies

Undesirable effects

- Adverse outcomes
- Decreased quality of life
- Increasing health costs

Drafting Recommendations: Risk Benefit Analysis

- Systematic reviews and GRADE profiles
- Impact assessment reports
- PLWH consultation reports
- Costing and feasibility analysis



DRAFT RECOMMENDATIONS



VALIDATION BY REVIEW GROUPS



FINAL RECOMMENDATIONS

Risk-Benefit Analysis:

Existing recommendation:	
Proposed recommendation	
Quality of Evidence (for outcomes deemed critical) High Moderate Low Very low	
Benefits/desired effects	
Risks/undesired effects	
Values/Acceptability	
Costs (consider actual costs, modeling; incremental cost of new recommendation; cost effectiveness analysis)	
Feasibility	
Suggested ranking of recommendation: • Strong (for or against) Or • Weak (for or against)	
Gaps, research needs, comments:	

Consensus Meeting on WHO ART
Guidelines for Adults and Adolescents
(14-16 October 2009)

Major Conclusions & Next Steps

2009 ART Revisions - General principles

- **Put best option first** then, what to do if best option not available
- Be clear when **strong evidence warrants strong recommendation**
- Be **explicit if limited data available** to support recommendations
- **Be somewhat aspirational** - thinking of what will likely be required & possible over next few years
- Encourage greater attention on **quality of HIV care**
- Emphasise value of **pre ART care** to good patient and programme outcomes
- Emphasise ART is part of combination **prevention package**

Start treatment earlier ...

- All symptomatic patients (WHO Clinical Stage 3 and 4) should initiate ART irrespective of CD4 cell count (including pregnant women)
- All patients with CD4 < 350 cells/mm³ should start treatment irrespective of clinical symptoms (including pregnant women)
- All patients who need TB or HBV treatment should start ART irrespective of CD4 cell count

Higher value on avoiding death, disease progression (including tuberculosis and HBV related cirrhosis) and likely HIV transmission (sexual and vertical)

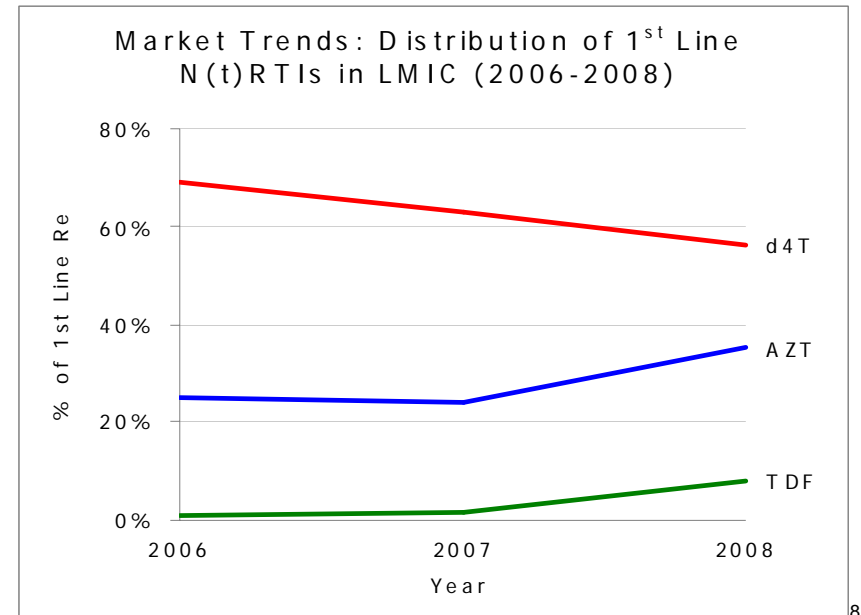
Use less toxic and more friendly 1st line regimens...

- Choose one of the following options to initiate ART
 - AZT+3TC+NVP
 - AZT+3TC+EFV
 - TDF+3TC/FTC+EFV
 - TDF+3TC/FTC+NVP
- **Fixed-dose combinations** wherever possible
- Countries should **minimize the number of options** and select the preferred regimen(s) likely to cover the majority of ART eligible patients (considering clinical, epidemiological and programmatic factors)

Higher value on phase out of d4T and overall comparability of these regimens in ART naive patients

d4T phase out and assessment risk

- Countries need to establish a phase out plan for d4T as **preferred 1st line NRTI** and undertake risk assessment for continued use (implement monitoring system if decide to continue to use d4T)
- Low dose d4T can have a **role as backup option** in case of time limited toxicity or temporary contraindication to AZT or TDF
- **Do not use d4T 40 mg formulations**



Higher value on move to less toxic alternatives considering the stigma associated with long term d4T side effects and low acceptability by PLHIV/clinicians

More friendly 2nd Line Regimens...

- **Boosted PI** based second line therapy will continue to be strongly recommended.
- Which boosted PI to use should be decided based on cost and availability of products esp. heat stable FDCs - **ATVr and LPVr are preferred options.**
- No clear benefits of using ATV/r over LPV/r .
- **TDF+3TC/FTC (if d4T/AZT used in 1st line) and AZT+3TC (if TDF used in 1st line)** as the preferred NRTI backbone options
- **NRTI choice determined by what used in first line** (in general non thymidine-based regimens lead to potentially more favourable NRTI options for second-line).

- TDF+3TC/FTC+ ATVr
- TDF+3TC/FTC+LPVr
- AZT+3TC+ATVr
- AZT+3TC+LPVr

Higher value on simplifying 2nd line regimens and availability of heat stable FDCs

What to Use in 1st and 2nd Line

Preferred 1 st Line Options	Preferred 2 nd Line Options
AZT + 3TC + EFV	TDF + 3TC or FTC + ATV/r or LPVr
AZT + 3TC + NVP	
TDF + 3TC or FTC + EFV	AZT + 3TC + ATV/r or LPVr
TDF + 3TC or FTC + NVP	

... and more strategic ART laboratory monitoring

Phase of HIV Management	Recommended Test	Desirable Test
At HIV diagnosis	CD4	HBsAg, anti-HCV?
Pre ART	CD4 (6 monthly)	Viral load?
At start of ART	CD4	Hb for AZT ¹ Creatinine clearance for TDF ² ALT for NVP ³
On ART	CD4	Hb for AZT ¹ Creatinine clearance for TDF ² ALT for NVP ³ Viral load
At clinical failure	CD4	Viral load
At immunological failure	Viral load	HIVDR test?

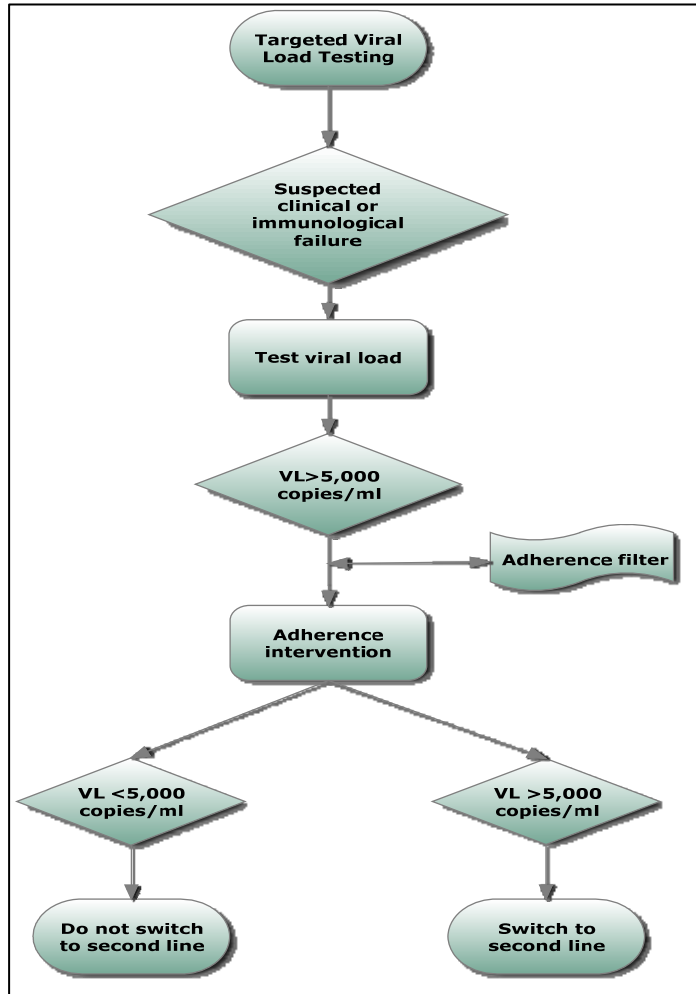
1 Recommended test in patients with high risk of adverse events associated with AZT (low CD4 or low BMI).

2 Recommended test in patients with 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 nephrotoxic drugs).

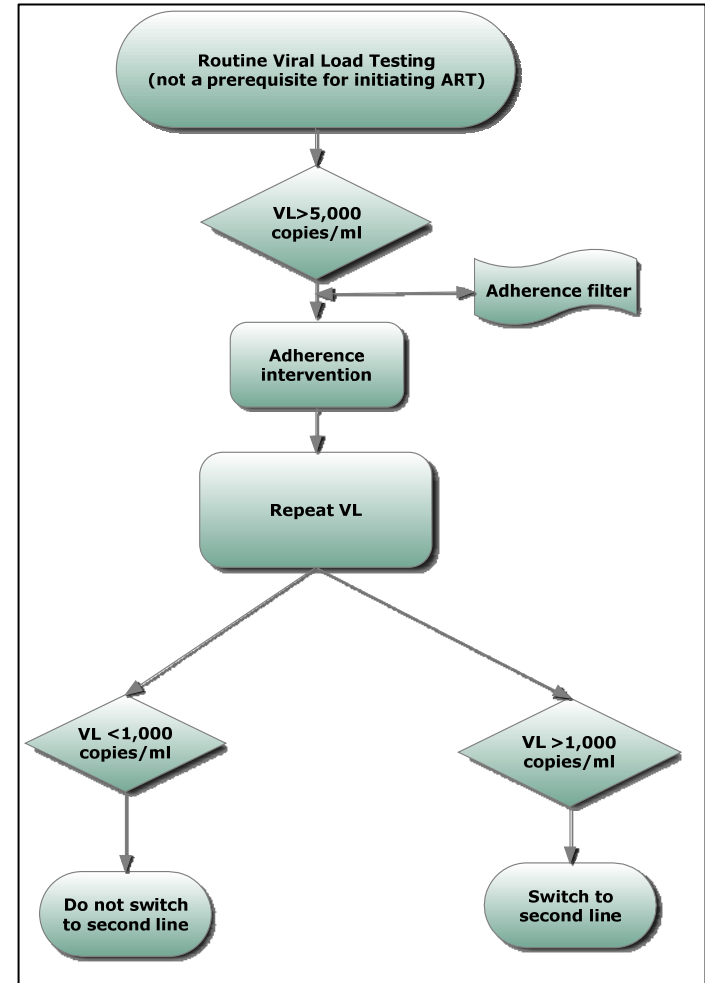
3 Recommended test in patients with high risk of adverse events associated with NVP (ART naive HIV+ women with CD4 > 250 cells/mm³, HCV co-infection)

Using VL to better decide when to switch ART: Two possible approaches...

Targeted Viral Load Monitoring



Routine Viral Load Monitoring



Additional Recommendations for Special HIV-Infected Populations

Pregnancy	TB/HIV	HBV/HIV	HCV/HIV
<p>1) AZT regimens preferred in pregnancy but TDF acceptable.</p> <p>2) Benefits of NVP for women with CD4 cell count between 250 to 350/mm³ likely to outweigh risk of not treating.</p> <p>3) EFV regimens should not be started in first trimester.</p>	<p>1) EFV based regimens preferred initial options</p> <p>2) All patients active TB disease should start ART as soon as tolerable.</p> <p>3) Rifabutin instead of Rifampicin in TB regimen if using concomitant PI regimen.</p>	<p>1) TDF/3TC or TDF/FTC as preferred NRTI backbone.</p> <p>2) In case of ART failure, TDF/3TC or TDF/FTC should be continued for anti-HBV activity and to reduce the risk of hepatic flares, irrespective of the selected second line ART regimen</p>	<p>1) Co infected patients should follow the same principles and recommendations as for its initiation in HIV monoinfected individuals.</p> <p>2) Patients should be closely monitored due to the increased risk of drug toxicities and drug interactions between some ARVs and anti-HCV drugs</p>

Choice of ART regimen for HIV+ women with prior exposure to MTCT regimens

Characteristics of previous ARV exposure	Recommendation
sdNVP (+/- short course AZT) with no AZT/3TC tail in last 12 months.	<ul style="list-style-type: none"> • Initiate a non-NNRTI regimen • PI preferred over 3 NRTI.
sdNVP (+/- short course AZT) with a AZT/3TC tail in last 12 months.	<ul style="list-style-type: none"> • Initiate a NNRTI regimen • Check viral load at 6 months and if > 5,000 copies/ml, switch to second-line ART with PI.
sdNVP (+/- short course AZT) with or without a AZT/3TC tail over 12 months ago.	<ul style="list-style-type: none"> • Initiate a NNRTI regimen • If possible, check viral load at 6 months and if > 5,000 copies/ml, switch to second-line ART with PI.
All triple ARV regimen irrespective of duration of exposure and time since exposure.	Initiate standard NNRTI regimen.

Summary of proposed WHO 2009 Criteria for the ART Initiation in adults and adolescents

(ART Guidelines Meeting, October/2009)

Clinical Situation	ART initiation Recommendations	Strength of Recommendation	Quality of Evidence
CD4 < 350 cells/mm ³	Start ART irrespective of WHO stage	Strong	Moderate
WHO clinical stage 1 or 2	Need CD4 to decide	Strong	Low
WHO clinical stage 3 or 4	Start ART irrespective of CD4	Strong	Low
Pregnancy	Start ART for stage 3 or 4 or CD4 < 350/mm ³	Strong	Low Moderate
Active TB disease	Start ART irrespective of CD4	Strong	Low
Active chronic hepatitis B	Start ART irrespective of CD4	Strong	Low

Summary of proposed WHO 2009 Preferred Regimens for ART initiation in adults and adolescents

(ART Guidelines Meeting, October/2009)

Clinical Situation	Preferred ART Regimen	Strength of Recommendation	Quality of Evidence
ARV naive HIV+ Adults	AZT+3TC+NVP or TDF+3TC/FTC+EFV	Strong Strong	Moderate Moderate
ARV naive HIV+ Adolescents	AZT+3TC+NVP or AZT+3TC+EFV	Strong Strong	Moderate Moderate
ARV naive HIV+ pregnant women	AZT+3TC+NVP or AZT+3TC+EFV (second trimester onwards)	Strong Strong	Moderate Moderate
NVP exposed HIV+ pregnant women (no ARV tail, < 12 months)	PI containing regimen 3 NRTI	Strong Conditional	Low Very Low
ART naive HIV + with active TB	AZT+3TC+EFV or TDF+3TC/FTC+EFV	Strong Strong	High High
ART naive HIV+ with HBV co-infection	TDF+3TC/FTC+ EFV or TDF+3TC/FTC+ NVP	Strong Strong	Moderate Moderate

To early to consider third-line ART?

- Mortality for patients on failing second line ART is high .
- Countries should develop a policy *vis a vis* third line options and consider providing a 3rd line regimen for patients failing 2nd line ART.
- Countries should consider use integrase inhibitors and 2nd generation NNRTIs and PIs as third-line drugs, if available.
- If 3rd line drugs are not available, a failing but tolerable 2nd line regimen should be continued.

Implementing new recommendations:

"First do not harm"

- Countries will need to prioritize increased CD4 threshold, transition to safer 1st line drugs and targeted use of laboratory monitoring in the context of equity & feasibility, sustaining scale up and quality of care.
- An adaptation/transition guide will be critical to assist countries in developing own ART recommendations without compromise access and exclude the most in need

Next Steps

- Meeting Report and review list of recommendations by guideline panel & peer review groups
- Develop adaptation/transition guide (November/2009)
- Develop draft of revised 2009 Guideline
- d4T phase out and risk assessment tool (to be developed by WHO)
- Issues to be reviewed/verified:
 - WHO clinical stage 2 – data on CD4 distribution and progression by condition (some stage 2 seems to be more “severe” than others)
 - Use of high dose folate to reduce risk of neural tube defects if EFV used in women of reproductive age.
 - How to prioritize introduction of revisions, notably increasing the CD4 threshold vs. transitioning away from d4T?
 - Low dose weight based d4T dosing (20 mg BID if < 60 kg)
 - Hep B - definition and assessment of active chronic hepatitis in RLS

Final Comments

- Some slight changes in relation to 2006 ART guidelines.
- Major Trends in 2009 version:
 - **Encourage earlier diagnosis**
 - Treat earlier
 - Promote less toxic/ more friendly regimens in 1st and 2nd line
 - Monitor more strategically
 - Will cost more (but will reduce deaths, avoid new infections and bring long term benefits)
- Burning unresolved issues- lack of WHO guideline for Hepatitis B and C clinical management.
- Next revision planned for **2012** (but interim recommendations can be done before this date)
- The major operational question is not if these recommendations should be followed or not, but how to do it safely and with equity...