

Report of the Consensus Meeting on
WHO Antiretroviral Therapy Guidelines for Adults and Adolescents
Ramada Encore Hotel, Geneva Switzerland
14-16 October 2009

Executive Summary

In October 2009 WHO convened a multidisciplinary guidelines panel group for the Consensus Meeting on WHO Antiretroviral Therapy Guidelines for Adults and Adolescents. The consultation and review of available evidence considered recommendations for when to start ART, laboratory monitoring before and while on ART, what first, second and third line regimens to use, co-infection with TB and hepatitis, and adherence to ART.

Generally, the consultation resulted in encouraging earlier diagnosis, earlier treatment, promote less toxic and more friendly regimens, more strategic monitoring, which will cost more but will likely result in long term savings for health systems. The group also described simple tools to accompany the guidelines that will be important for helping countries prioritize otherwise limited resources and capacity as they work towards full implementation of the revised guidelines over time without compromising access, excluding those most in need, threatening adherence, disrupting existing scale up efforts.

This report details the new recommendations, summarizes findings of the GRADE evidence profiles, and describes the advisors' decision making process behind the revisions they recommended to the WHO guidelines for ART for adults and adolescents.

Meeting Background

WHO ART Guidelines for Adults and Adolescents were originally published in 2002, revised in 2003 and in 2006. Significant experience and evidence has accumulated since the last revisions were made. Important new evidence on when to initiate ART, what drug regimens to use and how to manage ARV toxicities and failure need to be revised. The risk-benefits, acceptability, cost and financial implications, and feasibility aspects need to be clearly considered in the update of these recommendations. The impact of specific co-morbidities such as tuberculosis and hepatitis need also to be better evaluated.

The WHO/HIV Department is revising the current recommendations on antiretroviral management in adults and adolescents in accordance with procedures outlined by the WHO Guidelines Review Committee and based on the GRADE approach.

The specified purpose of this meeting was to update the WHO recommendations for ART management in adults and adolescents.

Meeting Objectives

1. Review the draft list of the revised WHO recommendations for ART use in adults and adolescents.
2. Review evidence summaries and evaluations of risk benefit, acceptability, feasibility and costs related to these recommendations.
3. Develop consensus and ranking the strength of final WHO recommendations for ART use in adults and adolescents.
4. Identify simple implementation tools required.
5. Identify key recommendations for future research.

Meeting Outcomes

1. Consensus on revised recommendations for ART use in adults and adolescents.
2. Implementation steps and required simple implementation tools described.
3. Recommendations, research, and other issues requiring urgent attention articulated.

Preparatory Work

The questions to be considered in this guideline review were agreed upon by the core WHO guideline working group in May 2009 .WHO then undertook a series of activities to prepare for this October 2009 consensus meeting.

1. Systematic reviews were conducted on:
 - ARV drug interactions with drugs for TB, hepatitis, malaria, and with opioids;
 - ART management for HIV-hepatitis B co-infection;
 - HIV-hepatitis C co-infection;
 - ART toxicity summary (TDF, AZT, NVP and d4T);
 - Safety of EFV;
 - Teratogenicity of EFV;
 - Low dose d4T safety profile;
 - CD4 and viral load technologies.
2. GRADE profiles we prepared for:
 - When to start ART;
 - What to use 1st line and 2nd line;
 - When to switch to 2nd line.
3. An impact assessment was conducted to estimate the number of patients in need of treatment according to various proposed CD4 thresholds.

4. Consultations were conducted with PLHIV and the findings summarized in reports from three organizations representing PLHIV.
5. Costing information was prepared based on studies of procurement and production of ARVs.
6. Feasibility analysis was conducted for the introduction proposed guidelines in Malawi (other countries in process or pending).
7. A report on issues related to adherence to ARTs for HIV+ patients, including adolescents.
8. A review was undertaken to study and compare ART Guidelines from 26 countries.
9. ART failure criteria were reviewed using data from ART-LINC and other studies.

Based on this preparatory work, recommendations were drafted by the Guidelines Drafting Group in early September 2009. These draft recommendations, grade profiles, risk benefit analysis tables (see below), and supporting data were circulated to a Peer Review Group, which had the opportunity to express any issues, suggest any changes, and to validate the draft recommendations prior to the 14-16 October Consensus Meeting.

Meeting Participants

Members of the Guidelines Panel Group were selected from global experts and invited to participate along with methodological, economic and non-HIV experts, in accordance with WHO procedures for guideline development. Regional advisers nominated suitable experts from within countries to provide perspectives from all WHO regions.

Meeting Process

At the consensus meeting the guidelines panel group reviewed and agreed on the ART recommendations for adults and adolescents. The same group is also expected to advocate for implementation of the new guidelines at regional and country levels.

For each subject area examined, a series of plenary presentations and discussion sessions were followed by working group sessions where specific recommendations and the evidence for them were discussed. Working groups were tasked with changing or supporting the proposed recommendation and ranking the final recommendation (strong, or conditional/weak).

The proposed recommendations, which had been slightly revised by the Peer Review Group, were considered by the guidelines panel group using a Risk-Benefit Analysis Tool consisting of a table exploring the following points:

- Existing recommendation;
- Proposed recommendation;

- Quality and grade of evidence (including GRADE profiles, systematic reviews and other supporting data) for the outcomes deemed critical;
- Benefits/desired effects;
- Risks/undesired effects;
- Values/Acceptability: split per those In favor and those against.
- Costs (consider actual costs, modeling; incremental cost of new recommendation; cost effectiveness analysis);
- Feasibility;
- Suggested ranking of recommendation (strong, or conditional/weak);
- Gaps, research needs, comments.

The following general principles were followed in this process:

- 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 supports recommendations;
- Be somewhat aspirational thinking of what will be required over next few years.

See in annex:

- Summary of major recommendations;
- Comments on what ART to start for women with prior exposure to MTCT regimen;
- Special note on HIV-HCV co-infection.

SUMMARY OF MAJOR RECOMMENDATIONS (2009 WHO ART Guidelines for Adults and Adolescents)

When to start

Recommendations

1. It is recommended to treat all patients with CD4 count <350 cells/mm³, irrespective of WHO clinical stage. (Strong recommendation, moderate quality of evidence)
2. It is recommended that all patients with WHO Clinical Stage 1 and 2 should have access to CD4 testing to decide when to initiate treatment (Strong recommendation, low quality of evidence)
3. It is recommended to treat all patients with WHO HIV clinical stage 3 and 4, irrespective of CD4 count. (Strong recommendation, moderate quality of evidence)

Domains and considerations

Quality of evidence

Moderate quality of evidence supports strong recommendations for these clinical and immunological criteria for ART initiation for the critical outcomes of reduction in absolute risk of death, disease progression, including tuberculosis, occurrence of severe adverse events and the important outcome of HIV transmission (sexual and mother-to-child).

One randomized clinical trial (RCT) specifically aimed to answer the PICO question: *When is the optimal time to initiate ART in asymptomatic, treatment-naïve, HIV-infected adults?* (CIPRA-HT001 2009; a single-centre trial in Haiti. One sub-group post hoc analysis nested in a RCT (SMART trial; a multicentre study in 33 predominantly high income countries) reported reduction of disease progression and serious non-AIDS events when ART was initiated at a CD4 cell count <350 cells/mm³ compared with <200 - 250 cells/mm³.

In the GRADE profile, pooled data from the RCT (816 participants) and the sub-group post hoc analysis (248 participants) provide moderate evidence that starting ART at CD4 levels higher than 200 or 250 cells/mm³ reduces mortality rates in asymptomatic, ART-naïve, HIV-infected people.

Evidence regarding a reduction in morbidity is less strong as the number of severe adverse events was low.

As the CIPRA HT-001 2009 trial was conducted in a resource-limited setting (RLS), the applicability of these results in determining a change in WHO guidelines is high.

Imprecision (only one RCT), indirectness (post hoc subset analysis) and reporting bias (there may be other trials which did not conduct or publish similar analyses of potential sub-sets within the original trials) are reported in the GRADE profile.

The RCT results are consistent with previous observational cohort studies both from high-income and low-income countries, which showed that early initiation of ART reduces morbidity and mortality. (Sterne 2009; Moh 2007; Badri 2004; Wong 2007). No GRADE tables were produced for these four studies identified in the systematic review as it was felt unlikely that they would increase the overall quality of evidence.

Considering the uncertain prognostic value of some WHO clinical stage 2 conditions and modelling and observational data suggesting that more than 50% of HIV-infected patients with this clinical stage can have a CD4 count of <350 cells/mm³, the panel recommended HIV-infected individuals with WHO clinical stage 1 and 2 should have access to CD4 testing to decide if treatment should be

<p>initiated.</p> <p>No uncertainty about the quality of evidence</p>
<p>Risks/Benefits</p> <p>Benefits</p> <ul style="list-style-type: none"> • A more permissive CD4 count threshold may provoke a change in treatment seeking behaviour, with a reduction in late presentation and an actual increase in CD4 count at ART initiation. • Modeling data suggests there is additional transmission benefit (including mother-to-child transmission) from earlier start of ART in populations with high treatment coverage. • Decreased risk of TB (observational and modeling studies) • Estimated reduction in mortality of 20% 2010-2015 (if ART coverage is >85%) <p>Risks</p> <ul style="list-style-type: none"> • Concerns that starting patients earlier will add burdens to countries and programs by increasing the numbers eligible for ART • Risk of inequity in ART access and potential displacement of sicker patients • Estimated increased ART cost of 57% 2010-2015 (if ART coverage is >85%) <p>Benefits outweigh risks</p>
<p>Values and acceptability</p> <p>In favour</p> <ul style="list-style-type: none"> • PLHIV highly value earlier initiation of ART • Opportunity to reduce the apparent disparity between high- and low-middle income country (LMIC) ART recommendations • The recommendations on <i>when to start</i> are the same for pregnant women <p>Against</p> <ul style="list-style-type: none"> • Will appear to decrease treatment coverage • Potential increased cost needs to be balanced against the high value placed on continued access • Potential for more ART related adverse events with earlier start <p>Uncertainty NO</p>
<p>Cost</p> <ul style="list-style-type: none"> • Cost effectiveness of ART is well established • Overall costs will increase if initiation of ART is earlier. Long-term incremental benefits seem to justify the cost <p>Uncertainty YES</p>
<p>Feasibility</p> <ul style="list-style-type: none"> • Implementation is dependent on capacity to perform CD4 cell count • Need drug combinations which are less toxic if starting patients earlier • Feasible with a phased introduction, speed and completeness determined by health system, HIV burden, coverage, capacity & funding <p>Uncertainty YES</p>
<p>Gaps, research needs, comments</p> <ul style="list-style-type: none"> • Currently no commercial point of care CD4 testing • Significant level of uncertainty for cost issues exists and needs further refinement • Retention in care/adherence implications of earlier start • Impact on health services and health economics • WHO will prepare tools to assist countries/programs in the transition to and implementation of the recommendations

- There are ongoing RCTs evaluating early ART initiation (PROMISE, START, TEMPRANO) some of which will be concluded by 2011/2012.

Final comment

Strong recommendations

In developing these recommendations, the panel placed high value on avoiding death, disease progression including tuberculosis and likely HIV transmission over and above cost and feasibility concerns.

What to start

Recommendations

1. It is recommend that one the following regimens is used to initiate ART in ART-naïve individuals. (Strong recommendation, moderate quality of evidence)
AZT+3TC+EFV
AZT+3TC+NVP
TDF+3TC or FTC+EFV
TDF+3TC or FTC+NVP
2. Fixed dose combinations or co-packaged formulations are recommended wherever possible. (Strong recommendation, moderate quality of evidence)

Domains and considerations

Quality of evidence

The PICO question addressed the **critical** outcomes of mortality, clinical response, (disease progression) and serious adverse events, and the **important** outcomes of virological response, adherence, tolerance and retention.

On the question of whether **d4T causes more toxicity compared to AZT**, the quality of evidence for the critical outcome of serious adverse events is low with no difference reported from 9 RCTs and 3 observational studies with maximum follow-up of 52 weeks. However, the panel noted a serious limitation of available data and short follow-up.

There is no evidence from randomized controlled trials, non-randomized trials or observational studies from LMIC that clearly indicate the superiority of d4T over AZT, EFV over NVP, TDF over AZT or d4T or TDF over ABC in triple-drug antiretroviral regimens for treatment-naïve patients.

On the question of whether **d4T is superior to AZT** in a dual NRTI backbone, the overall quality of evidence for critical outcomes is low (very low for mortality) and there is no evidence of superiority from 9 RCTs and 6 observational studies. Indirectness (5 of 9 RCTs reported indirect comparisons) and, to a lesser degree, imprecision (small sample sizes and few patients enrolled in RLS) were reported in the GRADE profile.

On the question of whether **TDF is superior AZT** in a dual NRTI backbone, the quality of evidence for all but mortality outcomes is moderate to high with no evidence of superiority from 3 RCTs (Gallant 2004, Rey 2009, Arribas 2008) and 1 observational study with regard to mortality, serious adverse events or virological response. Taken together, this literature is of moderate quality, with two large studies with 144-week follow up adding to its precision and at least some patients enrolled from Latin American countries. The PEARLS study (AACTG 5175), a RCT of once-daily PI/NNRTI-containing therapy in Africa, Asia, Haiti, South America, USA (estimated completion December 2009) will add to this literature by providing a direct comparison of AZT and TDF in dual NRTI backbones with EFV.

On the question of whether **EFV is superior to NVP** in combination with two NRTIs, the quality of evidence is moderate with no evidence of superiority from 6 randomized controlled trials and 24 observational studies. The observational studies reviewed from LMIC were unable to confirm the superiority of EFV which has been reported from some studies in high-income countries.

In the GRADE profiles, only the RCTs were downgraded for imprecision. Three ongoing studies due for completion in 2011/2012 will add to this literature [CARINEMO (ANRS 12146) in Mozambique, DAYANA (ARNS 12115) in Senegal and Cameroon, and the NCT00332306 trial in India].

Current evidence suggests that these regimens are comparable in terms of efficacy, with better

overall toxicity profile than d4T based regimens

No uncertainty about the quality of evidence

[see more details on the replacement for d4T and phase out process in the profile " **Stavudine (d4T) phase-out management: Guiding principles**", at page 38].

Risks/Benefits

Benefits

- Reduced rates of long term d4T-associated mitochondrial toxicities (particularly lipoatrophy and neuropathy) and potential better long term adherence
- Potential for one pill once daily FDCs (TDF+3TC or FTC+EFV)
- TDF+3TC or FTC is the preferred NRTI backbone in presence of HBV co-infection (both drugs with anti-HIV and anti-HBV activity)
- AZT+3TC is the preferred NRTI backbone in pregnant woman
- Opportunity to reduce the apparent disparity between high and low middle income country (LMIC) ART recommendations

Risks

- May need more laboratory monitoring for specific toxicities: haematological (AZT) and renal (TDF)
- TDF not approved in individuals <18 years old
- Uncertainty whether TDF requires renal screening (all patients or those at higher risk) prior to initiation and monitoring on TDF treatment
- Initial GI side effects are common with AZT
- Some concerns about virological efficacy of TDF+3TC or FTC+NVP
- Significant change in procurement requirements
- Not all options are available as full FDC (AZT+3TC+EFV, TDF+3TC or FTC+NVP)

Benefits outweigh risks

Values and acceptability

PLHIV consultations suggest phasing out of d4T is a high priority.

The panel placed high value on avoiding unpleasant, disfiguring and disabling side-effects of d4T.

Health-care providers place high value on critical patient outcomes and the use of safer ARVs.

Uncertainty No

Cost

Initial increase in costs is expected, but potentially will be offset in the long term by reduced toxicity management costs.

Uncertainty Yes

Feasibility

As with new recommendations on when to start ART, these recommendations for less toxic but currently more expensive first-line ARTs need to be phased-in as they may not be currently feasible in many high burden settings with low coverage, less developed health systems, limited lab capacity, finite budgets and competing health priorities. In countries with high coverage, transition to new treatment regimens may occur sooner.

Current evidence suggests that these regimens are comparable in terms of efficacy. In terms of feasibility, countries should select the preferred regimen(s) with the objective of covering the majority patients initiating ART based on following factors:

- Numbers of new patients needing to start ART according 2010 and 2015 targets
- Predicted expenditure per person needing ART (based on selected national start criteria)
- Availability in country of a fixed dose combination formulation
- In country cost of the drug regimens
- Laboratory requirements to monitor toxicities
- Number of patients starting ART who have/are
 - TB co-infection
 - Hepatitis B co-infection
 - Anaemia (due to malaria or other recognized causes)
 - Women on reproductive age
- Training required to phase-in and manage these regimens
- Use in children

Countries may need to use modeling and other analysis to assist in decision making.

Uncertainty Yes

Gaps, research needs, comments

- Estimates of discontinuation and toxicity rates of specific drugs
- National/sub national program reporting on regimen specific discontinuation and toxicity rates
- Lab requirements for toxicity monitoring
- Update on the safety of EFV in pregnancy
- The need for renal screening and monitoring for TDF toxicity. The ASSERT study (Europe) is comparing ABC+3TC+EFV and TDF+FTC+EFV with a primary endpoint is renal function
- Data on safety of NVP considering CD4 levels and gender
- The need for lead-in dosing of NVP in the presence of rifampicin
- The use of NVP in once daily or twice daily dosing schedules
- Safety of d4T using lower doses

Final comment

Strong recommendations

In developing these recommendations, the panel placed high value on avoiding the disfiguring and unpleasant toxicity of d4T, and the suitability of the preferred regimens for most patient groups. The panel was reassured by GRADE-profile evidence from RCTs, non-randomized trials and observational studies from LMIC that indicate no clear superiority of AZT over TDF or NVP over EFV, as part of combination ART for treatment-naïve individuals. It is recommended that programs select

What to start

AZT+3TC+EFV option

Recommendation

It is recommended that AZT+3TC+EFV is one of the preferred regimens for ART-naïve patients initiating ART. (Strong recommendation, moderate quality of evidence)

Domains and considerations

Quality of evidence

Low (AZT) to moderate (EFV) evidence on critical patient outcomes (mortality, clinical progression and SAEs) supports the recommendation. AZT toxicity review suggests that the toxicity is more commonly observed in patients with low BMI and low CD4 cell count. EFV toxicity review shows consistent reports of self-limiting or tolerable CNS side effects. There are uncertainties about teratogenic risk in humans. EFV may be superior to NVP in the non-critical outcome of resistance, which has been reported to be more common in the case of NVP.

On the question of **EFV teratogenicity**, retrospective data and prospective registries currently are too limited to provide an assessment of neural tube defect risk with first trimester exposure, except to rule out a large increase in risk. The overall rate of birth defects with EFV exposure does not appear to be significantly greater than that with exposure to NVP, LPV/r, TDF, or to that of the general population (comparison is with the population of Atlanta, USA). Given that closure of the neural tube is complete by 25 days after conception, EFV exposure in the remainder of the first trimester may pose little risk. Until further evidence is available, continued surveillance of the risks of first trimester EFV and other ARV exposure are crucial and the benefits of EFV use must be weighed against the potential risks. Evidence for the use of high-dose folate to reduce neural tube defects is being reviewed.

No uncertainty about the quality of evidence

Risks/Benefits

Benefits

- Relatively low pill burden (AZT+3TC [as FDC] +EFV)
- No lead-in dosing required
- EFV-based regimens are preferred in TB co-infection

Risks

- Use in anaemia: Background rates vary considerably; malaria, pregnancy, malnutrition and advanced HIV disease are well recognized risk factors for anaemia
- EFV associated with CNS side effects
- Other potentially troublesome AZT toxicities such as GI intolerance, skin hyperpigmentation, lipodystrophy are not uncommon
- EFV not approved in children less than 3 years of age
- EFV not recommended in 1st trimester of pregnancy
- Recent (<12 months) single dose NVP (SDN) or AZT+SDN (without tail) for PMCT may compromise response to EFV because of cross resistance

Benefits outweigh risks

Values and acceptability

- PLHIV have concerns about EFV use during reproductive age
- Side effects of AZT and EFV unacceptable to some PLHIV

<ul style="list-style-type: none"> • Most clinicians highly value AZT+EFV-based regimens • AZT requires twice daily dosing • Clinicians find the risks of potentially severe adverse events such as anaemia of concern <p>Uncertainty Yes</p>
<p>Cost</p> <ul style="list-style-type: none"> • Incremental drug cost comparisons: <ul style="list-style-type: none"> ○ d4T <AZT≈TDF ○ NVP <EFV • Increase costs <ul style="list-style-type: none"> ○ If laboratory monitoring (Hb) is required for management of toxicity ○ If an alternate regimen is required in the 1st trimester (or 25 days) of pregnancy or women seeking to become pregnant <p>Uncertainty Yes</p>
<p>Feasibility</p> <ul style="list-style-type: none"> • Currently no full FDC • EFV not approved in children less than 3 years of age <p>No major uncertainties</p>
<p>Gaps, research needs, comments</p> <ul style="list-style-type: none"> • Safety of EFV in pregnancy • Reduced AZT and EFV dosing
<p>Final comment</p> <p>Strong recommendation</p> <p>In developing this recommendation, the panel placed high value on the optimal treatment of HIV/TB co-infection. The panel were reassured about low rates of EFV adverse events but asked for additional information on potential for high-dose folate to decrease neural tube defects in pregnant women using EFV.</p>

What to start

AZT+3TC+NVP option

Recommendation

It is recommended that AZT+3TC+NVP is one the preferred regimens for ART-naïve patients initiating ART. (Strong recommendation, moderate quality of evidence)

Domains and considerations

Quality of evidence

Low (AZT) to moderate (NVP) evidence on critical patient-important outcomes (mortality, clinical progression and SAEs) supports the recommendation.

On the question of the **safety of NVP in those with higher or unknown CD4 counts**, increased rates of hepatotoxicity and hypersensitivity were reported in some studies (van Leth, Mocroft, Lyons, Jamisse, Hitti, Ananworanich, Kiertiburanakul, Taiwo) and not in others [Knobel, Bonjoch, De Lazzari Kondo, Torti, Phanuphak, Manfredi (two trials; one in treatment naïve and pre-treated patients and another in pregnant women) Marazzi (also pregnant women)]. Other studies [De Lazzari (meta analysis of 4 trials) Kumarasamy and Wit] reported no difference in adverse events between those with low and high CD4 cell counts in virologically suppressed patients switching to NVP. The available evidence is based largely on retrospective reviews or open-label studies, with one RCT (Hitti) and two post hoc analyses within a RCT (2NN study) providing evidence. While there is a good representation of studies in RLS, the key recommendation regarding cautious use of NVP and high CD4 cell counts is from high-middle income settings (2NN study, van Leth 2005)

See profile of AZT+3TC+EFV (page 11) for discussion on AZT

Uncertainty about the quality of evidence

Risks/Benefits

Benefits

- Triple FDC formulations available for adults and children
- Applicable to adults, adolescents and children
- Has been extensively used in pregnancy and is a preferred option
- Large programmatic experience

Risks

- Conflicting data on the safety of NVP in those with higher or unknown CD4 cell counts
- NVP associated hepatotoxicity/skin rash can be life threatening (but unclear relationship with CD4 and gender)
- Rifampicin and NVP drug-drug interactions
- Recent (<12 months) single dose NVP (sdNVP) use for PMTCT may compromise response

Benefits outweigh risks

Values and acceptability

- PLHIV value low pill burden and FDC options but AZT and NVP side-effects may cause concern
- Clinicians value the extensive experience with this regimen

Uncertainty Yes

Cost

- Incremental drug cost comparisons:
 - d4T < AZT≈TDF
 - NVP < EFV
- Increase costs
 - If laboratory monitoring (LFTs and Hb) is required for management of toxicity
 - If EFV is substituted for NVP following toxicity

Uncertainty No**Feasibility**

- Regimens with extensive programmatic experience
- Drugs widely available
- FDCs available
- Applicable to adults, adolescents and children
- NVP lead-in dose adds complexity

Uncertainty No**Gaps, research needs, comments**

- Under what circumstances can NVP be recommended as once daily? Is lead-in dosing needed?
- NVP toxicity at high CD4 counts

Final comment

Strong recommendation

In developing this recommendation, the panel placed high value on this regimen being the preferred option in pregnancy, widely available, with extensive experience in its use, and lower cost compared to an EFV-containing regimen.

What to start

TDF+(3TC or FTC)+NVP option

Recommendation

It is recommended that TDF+(3TC or FTC)+NVP is one of the preferred regimens for ART-naïve patients initiating ART. (Strong recommendation, moderate quality of evidence)

Domains and considerations

Quality of evidence

See (TDF+3TC+EFV) profile for discussion on TDF
 See (AZT+3TC+NVP) profile for discussion on NVP

No uncertainty about the quality of evidence

Risks/Benefits

Benefits

- Two active drugs against HBV
- Low pill burden
- Potential once daily regimen

Risks

- Potential drug interactions between TDF and NVP
- Small trials with this combination have reported higher rates of virological failure when compared to TDF+3TC or FTC+EFV
- TDF not approved in children and adolescents <16 years old
- Some concerns about its use in pregnancy (risk of bone toxicity to fetus)
- NVP associated hepatotoxicity/skin rash can be life threatening (but unclear relationship with CD4 and gender)
- Rifampicin and NVP drug-drug interactions
- Limited programmatic experience with this combination
- Recent (<12 months) single dose NVP (sdNVP) use for PMTCT may compromise treatment response

Benefits outweigh risks

Values and acceptability

- TDF-based regimens are very well accepted by patients
- Patients can find some TDF and NVP side effects may cause concern
- Clinicians find the risks of potentially severe adverse events of concern
- Clinicians have concerns about TDF use without renal screening

Acceptable

Cost

Incremental drug cost comparisons:

- d4T < AZT ≈ TDF
- NVP < EFV
- Increase in costs if laboratory monitoring (creatinine, hepatotoxicity) is required to manage toxicity

No uncertainty

Feasibility

- NVP lead-in dose adds complexity
- Only feasible where renal screening is available or when it is not a prerequisite

Uncertainty Yes
Gaps, research needs, comments <ul style="list-style-type: none">• Rates of renal disease/dysfunction in unscreened populations, particularly in Africa• Under what circumstances can NVP be recommended as once daily?• Safety of TDF in children and adolescents• Develop a triple FDC for once daily use
Final comment <p>Strong recommendation In developing this recommendation, the panel placed high value on the need for a regimen suitable for the treatment of HIV/HBV co-infection.</p>

What to start

TDF+(3TC or FTC)+EFV option

Recommendation

1. It is recommended that TDF+(3TC or FTC)+EFV is one the preferred regimens for ART-naïve patients initiating ART.
(Strong recommendation, moderate quality of evidence)

Domains and considerations

Quality of evidence

Low (TDF) to moderate (EFV) evidence on critical patient-important outcomes (mortality, clinical progression and SAEs) supports the recommendation. Existing TDF toxicity data suggest low rates of renal toxicity in pre-screened patients. However, baseline rates of renal disease in African patients seem to be higher than in non-African populations

On the question of the **renal safety/toxicity of TDF**, the cumulative incidence of nephrotoxicity has been reported as 1-4% and the rate of Fanconi's syndrome 0.5 to 2% with no association demonstrated between gender, age or race. (Sax 2007, Rolling 2006) One study (open label, 86 participants) from a RLS (Brazil, Argentina and the Dominican Republic) reported no discontinuations due to renal adverse events. (Cassetti 2007) Risk factors for increased serum creatinine were concomitant nephrotoxic medications, elevated serum creatinine, low body weight, advanced age and lower CD4 cell count. One study of 15 pregnant women with limited treatment options reported creatinine clearance >90 mL/min/1.73 m² in all but one woman who had a transient decline. (Nurutdinova et al. 2008). The GRADE profile demonstrated no difference in the occurrence of adverse events (changes in creatinine, proteinuria, all grade 3/4 adverse events or treatment discontinuation) in patients using TDF-containing regimens compared to other regimens. Imprecision (one pharmacokinetic study) and limitations (small sample size) were reported in the GRADE profile.

The systematic review on this topic did not find RCTs which addressed critical HIV outcomes, and the GRADE profile reported only outcomes related to HBV (HBV viral load and HBV drug resistance)

On the question of **when and what ART to start in HIV/HBV co-infection**, there were no trials which address critical HIV outcomes. However, data from one RCT and observational studies report a reduction in liver related disease, improved HBV viral load response and less development of HBV drug resistance with early initiation of ART, which includes at least two agents with activity against HBV.

See profile of AZT+3TC+EFV (page 11) for discussion on EFV

No uncertainty about the quality of evidence

Risks/Benefits

Benefits

- Triple FDC available
- Low pill burden (one pill once daily)
- Two active drugs against HBV
- No lead-in dosing required
- Can be used in TB co-infection

Risks

- Limited data on the use of TDF without renal screening and/or monitoring in RLS
- TDF not approved in children and adolescents

<ul style="list-style-type: none"> Limited data on the safety of TDF in pregnancy <p>Benefits outweigh risks</p>
<p>Values and acceptability</p> <ul style="list-style-type: none"> Once daily TDF-based regimens very are well accepted by PLHIV Clinicians have concerns about TDF use without renal screening <p>Acceptable</p>
<p>Cost</p> <p>Incremental drug cost comparisons</p> <ul style="list-style-type: none"> d4T < AZT ≈ TDF NVP < EFV <p>Increase in costs</p> <ul style="list-style-type: none"> If laboratory monitoring (creatinine) is required to manage toxicity If an alternative regime is required in the context of 1st trimester of pregnancy or women seeking to become pregnant <p>Uncertainty No</p>
<p>Feasibility</p> <p>Only feasible where renal screening is available or when it is not a prerequisite</p> <p>Uncertainty Yes</p>
<p>Gaps, research needs, comments</p> <ul style="list-style-type: none"> Rates of renal disease/dysfunction in unscreened populations, particularly in Africa
<p>Final comment</p> <p>Strong recommendation</p> <p>In developing this recommendation, the panel placed high value on the need for regimens with simplicity of use (potential for one pill, once daily) and the treatment of HIV/HBV co-infection.</p>

ART for HIV/TB co-infection

Recommendations

1. It is recommended that ART should be commenced in all HIV-infected individuals with active tuberculosis irrespective of CD4 cell count. (Strong recommendation, low quality of evidence)
2. It is recommended that TB treatment should be commenced first and ART commenced subsequently, as soon as possible and within the first 8 weeks of starting TB treatment. (Strong recommendation, moderate quality of evidence)
3. The recommended preferred 1st-line ART regimen in patients on TB treatment is AZT+3TC+EFV or TDF+3TC or FTC+EFV. (Strong recommendation, high quality of evidence)
4. For those who are unable to tolerate or who have contraindications to an EFV-based regimen, AZT+3TC+NVP or TDF+3TC or FTC+NVP or a triple NRTI regimen (AZT+3TC+ABC or AZT+3TC+TDF) are recommended with the choice based on the available regimen within countries. In the presence of rifampicin, the lead-in dose of NVP is not necessary. (Conditional recommendation, moderate quality of evidence)
5. If ART is changed for the duration of TB treatment, switching back to the original regimen following the completion of TB treatment is a country decision given that an EFV based regimen may be preferred in some countries. (Conditional recommendation, low quality of evidence)

In individuals who need TB treatment who require ART containing a boosted PI (bPI), it is recommended to give rifabutin-based TB treatment and standard bPI regimens. If rifabutin is not available, it is recommended to use rifampicin and a LPV- or SQV-containing ART with additional RTV-boosting and close monitoring. (Conditional recommendation, moderate quality of evidence)

Domains and considerations

Quality of evidence

On the question of **when to initiate ART after TB treatment**, the SAPIT trial, (Abdool Karim, CROI 2009) an RCT in South Africa, examined early ART (initiation during intensive or continuation phase of TB therapy) versus sequential (ART initiated after TB therapy completed). The mortality rate was 55% lower in the early treatment groups compared to the sequential group, which was stopped by the IRB. In the GRADE table, data from one RCT provides moderate evidence for early initiation of ART for the critical outcomes of all-cause mortality, successful TB treatment and incidence of immune reconstitution inflammatory syndrome (IRIS). Imprecision (one RCT which was stopped early) was reported in the GRADE profile.

On the question of **when to initiate ART in the context of active TB**, another RCT (the CIPRA HT-001 trial, Fitzgerald, IAS, 2009) reported a decreased risk of TB in the early ART treatment group (ART starting at CD4 200 to 350 cells/mm³) compared to the deferred ART group (ART started at CD4 <200 cells/mm³). GRADE analysis of RCTs on when to start ART in adults supports that early treatment at higher CD4 counts has impact on the occurrence of TB (moderate quality). There are limited data on the need to initiate ART in patients with TB and CD4 >350 cells/mm³. Data from observational studies also support early initiation of ART for the critical outcome of mortality (Velasco 2009, Varma 2009, Westreich 2009, Tabarsi 2009).

On the question of **initiating ART for all individuals with HIV/TB co-infection**, observational studies from resource-limited settings and resourced settings (Jones 2000, Girardi 2000, Santoro-Lopes 2002, Badri 2002, Golub 2007 and 2009, Miranda 2007, Muga 2007, Moreno 2008) reported high mortality rates among HIV-infected TB patients and significant reductions in mortality risk of up to 95% with the use of ART. The long-term risk of people living with HIV for developing active TB was also found to be correlated to the time that patients spend at a CD4 count below 500 cells/mm³, (Lawn 2009) with the incidence of TB

doubling each time the CD4 count falls by 150 cells/mm³ (Antonucci 1995; Badri 2002).

On the question of the impact on **TB transmission and incidence**, ART has been reported to reduce TB incidence rates by up to 90% at the individual level (Lawn 2009), by 60% at population level (Middelkoop, IAS 2009) and to reduce TB recurrence rates by 50% (Golub 2008). Additionally, modeling suggests that the use of ART, even earlier than a CD4 count of 350 cells/mm³, can reduce the number of TB cases, TB mortality rates and TB transmission at a population level. Modeling also suggests that early initiation of ART in the course of HIV infection, high population coverage with ART (75% or higher) and high compliance levels would be needed to effectively reduce the number of TB cases and TB mortality rates (Abdool Karim 2009, Atun 2007). Further modeling suggests that starting ART less than five years after initial HIV infection could cut the incidence of TB by about 60-70% (Williams, submitted).

On the question of **what ART to initiate**, previous observational studies provided conflicting results about the efficacy of EFV and NVP administered with and without rifampicin. One RCT comparing standard doses of EFV- and NVP-based ART in HIV-infected TB patients receiving rifampicin demonstrated that 600 mg EFV once daily was adequate for suppression of HIV viral load despite inter-patient variability in serum drug concentrations (Manosuthi 2009).

Nevirapine at the standard dose of 200 mg BID was effective in achieving viral load suppression although EFV was superior. A cohort study in Botswana showed no difference in immunological and virological outcomes throughout the first year of EFV and nevirapine-based ART co-administered with or without rifampicin (Shipton 2009). In South Africa, less favourable virological outcomes were reported in individuals starting NVP while already receiving rifampicin-based TB treatment compared to those who had started EFV after rifampicin (Boulle 2008). Similar poorer virological outcomes were reported for those who initiated TB treatment while already receiving NVP- or EFV -based ART. GRADE analysis of one RCT (Manosuthi 2009) and 6 observational studies (Boulle 2008, Manosuthi 2008, Sathia 2008, Shipton 2008, Varma 2009, Sungkanuparph 2006) found low evidence of better virological response when using EFV compared to NVP.

Reports of safety and tolerability of these therapeutic regimens varied across observational studies: while there was no difference in adverse events between NVP and EFV when given with rifampicin in some studies (Shipton 2009, Boulle 2008), higher rates of hepatotoxicity due to nevirapine were observed in others (Manosuthi 2008).

Data from pharmacokinetic cohorts support that concomitant use of rifampicin leads to short-term sub-therapeutic NVP plasma concentrations (Boulle 2008, van Oosterhout 2007, Manosuthi 2006, Avihingsanon 2008, Cohen 2008). Some studies reported a negative impact on VL suppressions and some did not (Manosuthi 2008, Boulle 2008).

Data are limited on the use of triple NRTIs for first-line HIV therapy to avoid the interaction between NNRTIs and rifampicin, with VL suppression of 76% in one observational study (Srikantiah 2008).

On the question of the use of **rifabutin** in individuals receiving a bPI-containing ART regimen, rifabutin was recently added to EML and seems safe and effective for the treatment of TB infection in HIV-infected individuals, easier to use and cost-effective. A daily dose of 75 mg has been considered and supported by pharmacokinetic modeling. However, the majority of safety and efficacy data on rifabutin was generated by studies in HIV-negative individuals. No difference in efficacy is evident between rifabutin and rifampicin in 5 RCTs in developed and resource constrained settings (Gonzales 1994, McGregor 1996, Schwander 1995, Rowinska 1992, HKCS 1992).

Uncertainty about the current quality of evidence

<p>Risks/Benefits</p> <p>Benefits</p> <ul style="list-style-type: none"> • Reduced HIV and TB mortality • Reduced TB transmission and recurrence • Use of rifabutin permits standard bPI dosing regimens and simplifies management <p>Risks</p> <ul style="list-style-type: none"> • More IRIS if ART and TB treatment are commenced close to each other • Reduced adherence due to high pill burden (TB and ART regimens) • Increased risk of drug-drug interactions and drug toxicity • TB diagnosis is uncertain in situations where TB is diagnosed clinically (or smear negative TB) • Different TB regimens according to the ART regimen used (i.e., rifampicin if using 2 NRTIs+NNRTI or 3 NRTIs, and rifabutin if using bPIs) can increase program management complexity and can cause confusion in the field • Rifabutin is still not available in FDC and daily dose still not approved. (Currently, rifabutin should be used 3 times a week, but other TB drugs are usually recommended daily.) <p>Benefits outweigh risks</p>
<p>Values and acceptability</p> <ul style="list-style-type: none"> • PLHIV and clinicians value highly reduced rates of TB in the HIV-infected population • Physician concern about IRIS and toxicity risks on concomitant use of ART and TB regimens • HCW and families value likely reduced risk of TB transmission <p>Uncertainty No</p>
<p>Cost</p> <ul style="list-style-type: none"> • In break-even analysis, the overall cost is comparable • Net cost may be favourable given reduced TB transmission • Rifabutin costs more than rifampicin, but overall cost may be offset against the cost of extra doses of RTV needed for a PI-boosting strategy. <p>Uncertainty No</p>
<p>Feasibility</p> <ul style="list-style-type: none"> • Will require better integration of TB and HIV services • The use of rifabutin in patients using bPIs still poses significant operational challenges <p>Uncertainty Yes</p>
<p>Gaps, research needs, comments</p> <ul style="list-style-type: none"> • Are individuals with HIV/TB and with CD4 >350 in urgent need of ART? Can it be delayed? If so, until when? • Establishment of FDC formulations that permit the use of rifabutin once daily • More on use of NVP with rifampicin, results awaited from studies • Poor bPI adherence will result in suboptimal rifabutin exposure • The optimal dosing of rifabutin with bPI is under discussion
<p>Final comment</p> <p>Strong recommendation</p> <p>In developing these recommendations, the panel placed high value on the reduction of early mortality from HIV/TB co-infection, the reduction of TB transmission when ART is initiated in all individuals with TB and improved management of TB in the context of 2nd-line PI-based ART</p>

ART for HIV/HBV co infection

Recommendations

1. HBsAg testing is recommended for all individuals before initiate ART. (Conditional recommendation, moderate quality of evidence)
2. In HIV/HBV co-infected individuals who require treatment for HBV infection, ART should be initiated irrespective of CD4 cell count or WHO clinical stage. (Strong recommendation, low quality of evidence)
3. In HIV/HBV co-infected individuals eligible for treatment, 1st-line ART regimen should include TDF and 3TC or FTC. (Strong recommendation, moderate quality of evidence)
4. In HIV/HBV co-infected individuals who are failing therapy, second and subsequent ART regimens should include TDF+3TC or FTC, both should be continued in the 2nd-line regimen for anti-HBV activity and to reduce the risk of hepatic flares, irrespective of the selected 2nd-line ART regimen. (Conditional recommendation, moderate quality of evidence)
5. In patients who are already being treated with 3TC without TDF and are subsequently found to be HBsAg positive, treatment should be changed to include two drugs that target HBV (TDF+3TC or FTC). (Conditional recommendation, moderate quality of evidence)

Domains and considerations

Quality of evidence

The systematic review on this topic did not find RCTs which addressed critical HIV outcomes, and the GRADE profile reported only outcomes related to HBV (HBV viral load and HBV drug resistance).

On the question of **when to start ART in HIV/HBV co-infection**, there are no trials comparing early versus late initiation of ART. However, observational data support that those with HIV/HBV co-infection have an increased risk of fibrosis and cirrhosis (Marra 2007). Some studies found 3- to 6-fold risk of developing chronic HBV (Bodsworth,1991, Hadler 1991, Gatanaga 2000) and a 17-fold increase risk of death (Thio 2002) in HIV/HBV co-infected patients when compared with HIV-negative individuals. Three observational studies also showed a reduction in liver related disease (LRD) in HIV/HBV co-infected individuals with earlier and HBV active combination ART (Thio 2002, Hoffman 2009, Jain 2009).

On the question of **what ART to start in HIV/HBV co-infection**, data supporting the use of at least 2 agents with activity against HBV in an ART regimen come from one RCT (Matthews 2008) with better HBV viral load response and less development of HBV drug resistance. However, severe limitations (small sample size and short duration of follow up) were reported in the GRADE profile of this study.

On the question of **adding TDF** to those with HIV/HBV co-infection already taking 3TC, 3 observational studies found no significant differences in HBV response between the 3TC-naïve and 3TC-experienced patients. (Alvarez 2009, Matthews 2009, Schmutz 2006)

On the question of **retaining TDF+(3TC or FTC)** in 2nd line or subsequent ART regimens, 1 study reported better HBV VL response and no TDF mutations (Benhamou 2006).

No uncertainty

While HBV has minimal effect on the progression of HIV, those with HIV/HBV co-infection have an increased risk of fibrosis and cirrhosis (Marra 2007). Some studies found **three to six** fold risk of developing chronic HBV (Bodsworth, 1991;Hadler, 1991,Gatanaga, 2000) and a 17 fold increase risk

of death (Thio, 2002) in HIV/HBV co-infected patients when compared with HIV negative individuals. Three observational studies also showed a reduction in liver related disease (LRD) in HIV/HBV co-infected individuals with earlier and HBV active combination ART. (Thio 2002, Hoffman 2009, Jain 2009). TDF, 3TC and FTC treat both infections.

On the question of **when to start ART in HIV/HBV co-infection**, there are no trials comparing early versus late initiation of ART. Observational data support the reduction in the development of chronic hepatitis in HIV/HBV co-infected individuals with earlier and HBV-active combination ART (Thio 2002, Hoffman 2009, Jain 2009).

On the question of **what ART to start in HIV/HBV co-infection**, data supporting the use of at least 2 agents with activity against HBV in an ART regimen come from observational studies and one RCT (Matthews 2008) with non-critical outcomes of HBV viral load response and development of HBV drug resistance. Limitations (small sample size and short duration of follow-up) were reported in the GRADE profile.

On the question of **adding TDF** to those with HIV/HBV co-infection already taking 3TC, observational studies found no significant differences in HBV response between the 3TC-naïve and 3TC-experienced patients (Alvarez 2009, Matthews 2009, Schmutz 2006).

On the question of **retaining TDF+(3TC or FTC)** in 2nd-line or subsequent ART regimens, one study reports better HIV response (Benhamou 2006).

Some uncertainty about the quality of evidence

Risks/Benefits

Benefits

- Reduced morbidity and mortality associated with chronic HBV
- Reduction of HBV transmission
- Reduction of HBV resistance
- Reduced incidence of hepatic flares

Risks

- TDF not approved in < 18 years old and limited data on its use in pregnancy
- HBV monotherapy results in HBV resistance (90% of HIV/HBV co-infected individuals treated with 3TC as the only anti-HBV drug are resistant to 3TC after 4 years of treatment)
- Increase in ART-related hepatotoxicity in HIV/HBV co-infection (3- to 5-fold)

Benefits outweigh risks

Values and acceptability

- It is not acceptable to PLHIV to treat HIV and not to optimally treat HBV
- HIV/HBV co-infection is common (from 5% to more than 20%) and treatment should be directed to both infections
- Improved management of HIV-HBV is likely to be acceptable to physicians and to PLHIV

Uncertainty No

Cost

- Increased costs from TDF use in first-line
- There will be increased costs for laboratory tests for HBV screening and evaluation of disease activity

Uncertainty No

Feasibility

- Management is complicated by limited availability of HBV testing and other markers of disease activity (HBV DNA, HbeAg) in RLS
- More laboratory needs for adequate HBV screening, evaluation of disease activity
- These components can be implemented in areas where HIV programmes are already in place.
- HbsAg is available as a ELISA test and can use the same platform of HIV testing
- HBV DNA can use the same lab platform of HIV viral load
- Liver biopsy, commonly used in developed settings for evaluation of liver fibrosis, is mostly unavailable in RLS and a major challenge in diagnosis and management
- Common drugs used to treat HIV and HBV, and some common epidemiological aspects of management of both diseases, suggest an integrated, programmatic approach as the best strategy

Gaps, research needs, comments

- Access to HBV lab tests for this population in RLS is an important challenge.
- Establishment of adequate treatment algorithms using non-invasive tests is needed, particularly for evaluation of liver fibrosis

Final comment

Strong recommendation

In developing these recommendations, the panel placed high value on promoting HBV diagnosis and more effective treatment of HIV/HBV co-infection in RLS

ART for pregnant women

Recommendations

When to start

1. It is recommended to treat all pregnant women with CD4 count <350, irrespective of WHO stage. (Strong recommendation, moderate quality of evidence)
2. It is recommended that all pregnant women with WHO Clinical Stage 1 and 2 should have access to CD4 testing to decide when to initiate treatment (Strong recommendation, low quality of evidence)
3. It is recommended to treat all pregnant women with WHO HIV clinical stage 3 and 4, irrespective of CD4 count. (Strong recommendation, moderate quality of evidence)

What to start

1. It is recommended that one the following regimens be used for ART-naïve pregnant women initiating ART (Strong recommendation, moderate quality of evidence)

AZT+3TC+EFV (preferred)

AZT+3TC+NVP (preferred)

TDF+3TC or FTC+EFV

TDF+3TC or FTC+NVP

2. It is recommended that an EFV-based 1st-line regimen should not be initiated during the 1st trimester of pregnancy. (Strong recommendation, low quality of evidence)

Domains and considerations

Quality of evidence

When to Start: [See also *When to Start* summary of recommendations for the general population., at page 5]

No studies were identified specific to the population of pregnant women. The consensus panel felt strongly that treatment recommendations for pregnant women should be aligned with those for the general population, with one additional recommendation not to start EFV-containing regimens in the first trimester. Overall evidence supports strong recommendations considering reduction in risk of death, disease progression, occurrence of severe adverse events, risk of TB and sexual transmission in all populations, in addition to the reduction in vertical transmission from mother to child.

Considering the uncertain prognostic value of WHO clinical stage 2 and some modelling and observational data suggesting that more than 50% of HIV-infected patients with this clinical stage have a CD4 count of <350 cells/mm³, the panel recommended all pregnant women infected with HIV should have access to CD4 testing.

CD4 counts have been observed to decline during the 1st trimester of pregnancy, increasing during the 3rd trimester into the postpartum period. Whether this is due to physiological haemodilution or not remains to be clarified, although the opinion is that it is likely to be not significant.

What to Start: See *What to Start* summary of recommendations for the general population.

No GRADE profile as no RCTs were identified for the use of AZT+3TC+NVP specifically in pregnant women. Cohort studies report reduction of HIV transmission or death. When compared with short course regimens, AZT+3TC+NVP starting at 34 weeks was shown to reduce HIV transmission or death at 7 months (Hwan-Bae 2008). There is no evidence for this regimen that evaluates maternal severe

adverse events or maternal response to ART.

There is no evidence to suggest an increase in maternal serious adverse events and no evidence evaluating maternal response to ART. Pregnancy registry data on the use of TDF in pregnancy show no concerning signals and there is no evidence to suggest that TDF+3TC or FTC is not an acceptable alternative to AZT+3TC. One observational study (Nurutdinova 2008) found that TDF was well-tolerated in a very small population (n=15) of pregnant women. The results may not apply to a wider population.

There is low quality of evidence to suggest that EFV is associated with a potential risk of neural tube defects. Since neural tube closure occurs in the first 28 days by the time many pregnancies have been recognised, the at-risk exposure has occurred. According to a systematic review including data from the Antiretroviral Pregnancy Registry, the overall rate of birth defects associated with EFV exposure appears consistent with the rates for those with NVP, LPV/r or TDF exposure, and consistent with other congenital defects registries from general populations.

Data on toxicity of NVP in pregnancy, including risk of hypersensitivity reaction to NVP with unknown or CD4 >250 cells/mm³, are mixed and of poor quality. Studies are needed to understand the real magnitude of this problem, particularly in RLS where NVP is the major NNRTI in use.

A systematic review of NVP safety and toxicity in pregnant woman prepared for this revision noted that the available evidence on the occurrence of adverse events based on gender and CD4 cell count is based largely on retrospective reviews or open-label studies, with very few randomised controlled trials. The review didn't confirm an increased risk of serious adverse events associated with NVP in pregnant women with CD4 cell count between 250-350.

There is extensive program experience for the use of AZT in pregnant women and for the reduction of MTCT. However, when compared with short-course regimens at 28 to 32 weeks, AZT+3TC+NVP at 24 weeks resulted in more maternal SAE requiring treatment modification (Tonwe-Gold 2007)

NNRTI-resistance mutations have been identified subsequent to the use of sdNVP for PMTCT due to the long half-life of NVP (Musoke 1999) (Kunz 2009), as detected in a plasma virus and in breast milk.

[See the *special comments on what to start for MCTC-exposed women*]

No uncertainty about the quality of evidence

Risks/Benefits

Benefits

- Key benefits are reduction of mortality and morbidity in women/mothers and reduction of mother to child transmission of HIV
- Compared with short-course regimens, AZT+3TC+NVP starting at 34 weeks reduced transmission or death at 7 months (Hwan-Bae 2008)
- When compared with AZT + sdNVP in a RCT, AZT+3TC+NVP starting at 34 weeks significantly decreased maternal resistance (Lehman 2009)
- When compared with short course regimens, AZT+3TC+NVP significantly decreased MTCT at 1 month (Hwan-Bae 2008), 7 months (Hwan-Bae 2008), and 12 months (Ekouevi 2008)
- EFV is indicated in treatment of TB in pregnant women
- The same regimens are recommended for pregnant women and the general population of adults and adolescents

Risks

- There are limited data on the use of TDF in pregnancy
- TDF not approved for <18 years of age

- Possible bone toxicity for the fetus and for breastfeeding women with use of TDF

Benefits outweigh risks

Values and acceptability

In favour

- The panel placed high value on the long-standing experience with AZT-based regimens for the treatment of pregnant women and on the use of AZT and NVP in the prevention of mother to child transmission of HIV
- The use of EFV in the 1st trimester is not acceptable PLHIV or to physicians
- The panel placed high value on the need for CD4 testing in pregnant women

Against

- The limited data and studies specific to pregnant women and the potential for toxicity, which may affect acceptability
- Teratogenicity is a concern

No Uncertainty

Cost

When to Start:

- If 2006 guidelines have been followed, the recommendation is cost-neutral. If higher thresholds are used, there will be cost increases.

What to Start:

- Incremental drug cost comparisons: NVP < EFV
- Increased costs if EFV is substituted for NVP
- Overall, a cost saving may be realized in reducing costs for HIV care and services

No Uncertainty

Feasibility

- There are major problems with assessing eligibility in ANC and MCH clinics
- CD4 testing is essential for implementation of these recommendations
- ART is currently not started in most ANC/MCH
- Timing and regimens are consistent with those recommended for other adults/adolescents and comprise drugs with extensive programmatic experience.
- ANC and MCH need to be linked with ART programme
- Prioritize pregnant women for treatment

No Uncertainty

Gaps, research needs, comments

- Successful programmes that put ART in MCH clinics and integrate MCH clinics into ART services with CD4 testing
- Improved data on hepatotoxicity and hypersensitivity to NVP with unknown or CD4 >250 cells/mm³ are needed to understand the real magnitude of this problem, particularly in a RLS context where NVP is the major NNRTI in use
- Better information on safety related to TDF and the teratogenicity of EFV use during pregnancy

Final comment

In developing these recommendations, the ART and PMCT panels placed high value on early and CD4-guided initiation of ART for eligible women, the reduction of mother to child transmission and improved maternal and child-health outcomes

When to switch ART

Recommendations

1. Where viral load (VL) is available for routine use, it is recommended to use it every 6 months to detect viral replication. (Conditional recommendation, low quality of evidence)
2. When VL is available, it is recommended to use it in a targeted approach to confirm clinical and/or immunological failure. (Strong recommendation, low quality of evidence)
3. The VL threshold for detection of treatment failure should be persistent > 5,000 copies/ml. (Conditional recommendation, low quality of evidence)
4. When VL is not available, it is recommended that immunological criteria for failure be used to confirm clinical failure. (Strong recommendation, moderate quality of evidence)

Domains and considerations

Quality of evidence

This review focused on improving the sensitivity and specificity of the current WHO clinical, immunological and virological definitions of failure by combining the criteria as follows.

1. Clinical versus immunological and clinical monitoring
2. Clinical versus virological, immunological, and clinical monitoring
3. Immunological and clinical versus virological, immunological, and clinical monitoring

The GRADE profiles of the two major RCTs (HBAC and DART) confirmed the low quality of the current evidence, but the pooled analysis of the size effects suggests a trend towards a higher risk of disease progression or death when clinical monitoring is used compared with clinical-immunological monitoring (moderate quality) and also less chance to switch to 2nd-line ART in patients that used clinical monitoring only (low quality). The same trend was observed when clinical or clinical-immunological monitoring was compared to clinical-immunological-virological monitoring (low to very low quality).

Clinical vs. immunological and clinical monitoring. Based upon two randomized trials (HBAC 2008, DART 2009), clinical monitoring alone resulted in increased mortality (low-quality evidence), increased AIDS-defining illnesses and mortality as a composite endpoint (moderate), no difference in serious adverse events (low), and increased numbers of unnecessary switches (low) compared to immunological and clinical monitoring.

Clinical vs. virological, immunological, and clinical monitoring. Based on a single randomized trial, (HBAC 2008) clinical monitoring alone resulted in increased mortality (low), increased AIDS-defining illnesses and mortality as a composite endpoint (low), increased unnecessary switches (low), and no difference in virological treatment failures (low) compared to virological, immunological, and clinical monitoring.

Immunological and clinical vs. virological, immunological, and clinical monitoring. Based on a single randomized trial (HBAC 2008) immunological and clinical monitoring resulted in no difference in mortality (low), no difference in AIDS-defining illnesses and mortality as a composite endpoint (low), no difference in unnecessary switches (very low), and no difference in virological treatment failures (low) compared to virological, immunological, and clinical monitoring.

On the question of **VL threshold**, there is evidence to support a threshold of 5,000 copies/ml to define failure in an adherent patient with no other reasons for an elevated VL (e.g., drug-drug

interactions, poor absorption, and intercurrent illness), as this value is associated with clinical and immunological deterioration in some cohort studies (e.g., PLATO, ICONA). Data from observational studies demonstrated that programs with virological, immunological, and clinical monitoring switch therapy more frequently (very low), and earlier (very low), and at higher CD4 counts (very low) compared to programs with only immunological and clinical monitoring (ARTLINC 2006, 2008).

Systematic reviews on studies on ART switching strategies and treatment failure definitions have shown low quality of evidence, with high variability on studies, no long term data and are usually not focused on a public health approach, which makes it difficult to establish definitive recommendations on this topic for RLS.

Other Key Points

- Clinical, immunological and virological criteria are frequently dissociated in clinical practice
- It is uncertain if viral load monitoring affects critical outcomes
- Immunological failure, as a stand alone criterion, is not a good predictor of virological failure
- Virological monitoring strategies are associated with earlier and more frequent switching
- Treatment switching has occurred at lower than expected rates in RLS

Uncertainty about the quality of evidence

Benefits

- More accurate assessment of treatment failure
- Reduction in the delay in switching to 2nd-line regimen
- Targeted use of VL can reduce the possibility of unnecessary switching based on immunological/clinical criteria when patient has VL suppression
- Regular use of VL can reduce the risk of resistance and protect susceptibility to 2nd-line drugs and may also have impact on HIV transmission
- Improved failure diagnostic criteria will save the cost of expensive 2nd-line drugs by confirming that they are needed or not by VL testing

Risks

- The optimum threshold for defining VL failure in a public health approach is unknown
- There are limited data on diagnostic accuracy of VL in RLS
- Modelling data suggest no difference in critical outcomes in VL versus no VL scenarios

Benefits outweigh risks

Values and acceptability

- Physicians and PLHIV consider clinical and immunological monitoring insufficient to promote a timely switch and want VL monitoring.
- ART switching has occurred at lower than expected rates in RLS, and the limited use of virological monitoring has been identified as an important factor.
- Many countries are considering employing VL to optimize the use of expensive 2nd-line drugs. The same rationale applies if/when 3rd-line drugs are available.

Acceptable

Cost

- The initial and ongoing cost is high. Use of VL to confirm clinical-immunological switch (targeted approach) probably will cost less than routine use of VL monitoring.
- Quality assurance programs need to be implemented at VL facilities irrespective of the VL strategy adopted
- Unclear cost-effectiveness of different monitoring strategies

Uncertainty Yes

Feasibility

- Central VL facilities with adequate specimen transportation from clinic to laboratory are feasible
- Point of care VL capacity in urban settings is feasible
- Point of care VL capacity in rural settings is likely to remain unfeasible with current technologies
- Targeted use of VL seems to be more feasible

Feasibility with targeted use of VL more feasible than routine VL

Gaps, research needs, comments

- New and simplified CD4 and VL techniques (point of care, dipstick) will become more available in the next 3 to 4 years
- Feasibility of dried blood spot (DBS) for VL
- What is the optimal viral load threshold for ART switch?
- What is the best VL monitoring strategy: targeted or routine approach?
- What is the long-term impact of drug resistance development on critical patient outcomes?
- Need to simplify immunological criteria
- Is 30% drop from the peak CD4 count any better than 50% drop?
- Does CD4 <100 after many months in an adherent patient who is clinically well an indication of failure?
- List of OIs that define clinical failure should be revised. Should pulmonary TB be considered as a criterion for ART switching?
- Role of Centers of Excellence/Switch Committees

Final comment

Strong recommendation

In developing these recommendations, the panel placed high value on the significant limitations of clinical and immunological monitoring for diagnosing treatment failure, the need to optimize virological monitoring, and ensure adherence

Second-line ART

Recommendations

1. A boosted PI + 2 NRTIs are recommended for 2nd-line ART. (Strong recommendation, moderate quality of evidence)
2. ATV/r and LPV/r are the preferred boosted PI options for 2nd-line ART. (Strong recommendation, moderate quality of evidence)
3. TDF+3TC or FTC and AZT+3TC as the preferred NRTI backbone options for 2nd-line ART. (Strong recommendation, moderate quality of evidence)
4. Heat stable, fixed-dose combinations or co-packaged formulations are recommended wherever possible. (Strong recommendation, high quality of evidence)

Domains and considerations

Quality of evidence

On the question of whether **3TC should be maintained** in second-line regimens, five trials (3 RCTs) have addressed the impact of retaining 3TC in 2nd-line regimens (Castagna, Eron, Campbell, Fox and Hull). In the GRADE profile, the quality of evidence is low for 4 of the 5 trials (Hull is not included in the profile) and the effect size is moderate for the non-critical outcomes of the proportion of patients achieving VL suppression and the mean reduction in HIV RNA from baseline, supporting conditional recommendation to retain 3TC in 2nd-line regimens for its impact on viral fitness. If the recommended sequencing of NRTIs is followed (AZT+3TC in 1st line is followed by TDF +3TC in 2nd-line and TDF+3TC is followed by AZT+3TC in 2nd-line), then 3TC is maintained by default.

On the question of whether **PI monotherapy** be used as second-line ART, there is moderate quality of evidence from 9 RCTs showing less virological suppression (<50 copies/ml) for PI monotherapy compared to standard triple ART regimens. There were no other significant differences in critical or important outcomes (very low to moderate quality evidence), although non-critical outcomes, such as grade 2 adverse events and lipoatrophy, were not captured in the GRADE table. Further, there is evidence from individual trial reports of higher rates of viral rebound in patients on monotherapy compared to combination ART. All but two studies (Cameron 2008 and Delfraisy 2008) enrolled ART-naïve patients and/or patients with VL suppression. Hence, the GRADE profiles were downgraded for serious imprecision and indirectness. Current PI monotherapy data are insufficient to suggest that NRTIs should not be retained in the regimen.

On the question of **which boosted PI (bPI)** should be used in second-line therapy, there is moderate quality of evidence that ATV/r is non-inferior to LPV/r (in combination with TDF and an optimized second NRTI) in treatment experienced patients, (Johnson 2005, Johnson 2006). Imprecision and indirectness were reported in the GRADE table with patients being two-regimen experienced. There is low-moderate quality evidence that FPV/r, ATV/r and DRV/r are non-inferior to LPV/r in ART naïve patients (Castle, Klean and Artemis studies). Non-serious adverse events varied by boosted PI with no significant difference in serious adverse events (very low quality evidence). All unboosted PIs (including NFV and ATV) are considered inferior to bPIs.

On the question of which **NRTI backbone** to use in 2nd-line therapy, very few studies of relevance were identified. The recommended NRTI sequencing is based on likely resistance mutations and potential for retained antiviral activity in the two scenarios of early and late diagnosis of failure and switching (Elliot 2008). If AZT+3TC is used in 1st-line with sensitive monitoring and a low switch threshold, (M184V mutation common, TAMS less common), the NRTIs with remaining activity are TDF and ddI, (both very likely), ABC (likely), with likely benefit from 3TC. In the scenario of intensive monitoring and high switch threshold, (M184V, TAMS common, K65R rare but possible), TDF and ddI

activity are less likely, AZT and ABC unlikely, with benefit from 3TC less likely.

If TDF +3TC are use in 1st line, with sensitive monitoring and a low switch threshold, (M184V common, K65R possible), the NRTIs with remaining activity are AZT and d4T (very likely), ddl, ABC, TDF (possible) with likely benefit from 3TC. In the scenario of intensive monitoring and high switch threshold, (M184V, K65R common), activity of AZT and d4T is very likely, activity of ddl, ABC and TDF unlikely with likely benefit from 3TC.

No uncertainty about the current quality of evidence on the efficacy of bPIs

Uncertainty about the current quality of evidence about which NRTIs should be used but studies are ongoing

Risks/Benefits

Benefits

- Simplification of therapeutic options
- Simple procurement as the preferred NRTIs are included as 1st-line regimens
- Reduction of pill burden (some combinations can be used once daily)
- Possible benefit in patients with HBV infection, especially if combined with TDF in 2nd-line
- Reduced chance of hepatic flare associated with stopping 3TC in patients with HIV/HBV co-infection
- 3TC has good safety profile and few side effects
- Limiting use of ABC and ddl as second line NRTIs will reduce complexity and cost

Risks

- Some countries have chosen alternate bPIs already (IDV/r, SQV/r, FPV/r)
- Confusion may arise because 3TC is recommended in 1st-line and 2nd-line

Benefits outweigh risks

Values and acceptability

- PLHIV want simpler, better and more user-friendly 2nd-line options
- Program managers want simpler and clearer 2nd-line choices
- Physicians are comfortable with the evidence of some benefit and the safety profiles of 3TC
- PLHIV are comfortable with 3TC
- Clinicians may not be comfortable with not replacing all drugs (not feel comfortable recycling NRTIs)

Cost

- Cost containment by limiting choices and promoting use of FDC
- Generic heat stable LPV/r in the market already
- Co-blistered generic heat stable ATV and RTV in the market already
- Generic heat stable FDC of ATV/r in the pipeline and expected 2010 (co-blisters with TDF+3TC)

Feasibility

- Feasible with drugs readily availability in ART programs
- Generic formulations widely available
- Preferred bPIs are available in most countries
- A majority of country guidelines recommend 2nd-line ART be available
- Simplified procurement: the NRTIs recommended in 2nd-line are also used in 1st-line (in different combinations) and should be purchased by all national HIV/AIDS programs
- Other alternative bPIs (SQV, IDV, FPV and DRV) not available as FDC and more expensive than preferred options. SQV has a high pill burden, IDV has a high toxicity risk and FPV has a high cost

Gaps, research needs, comments

Ongoing studies

SECOND-LINE (48 sites: LPV/r+2 NRTIs vs. LPV/r+RAL), **2LADY** trial (Burkina Faso, Cameroon, Senegal- LPV/r+TDF+FTC vs. LPV/r+ABC+ddi vs. DRV/r+TDF+FTC, **EARNEST** trial (Malawi, Uganda, Zimbabwe: LPV/r vs. LPV/r+RAL vs. LPV/r+ 2 NRTIs, **SARA** trial (Uganda, Zimbabwe: LPV/r vs. LPV/r-based ART, **HIVSTAR** (Thailand: LPV/r vs. LPV/r+TDF+3TC or FTC)

Final comment

Strong recommendation

In developing these recommendations, the panel placed high value on simple 2nd-line regimens and availability of heat stable FDCs.

Third-line regimens

Recommendations

1. It is recommended that National programs should develop policies for third-line therapy that address funding, sustainability and the provision of equitable access to ART. (Conditional recommendation, low quality of evidence)
2. Third line regimens should include ideally two new drugs with predicted activity such as boosted DRV, raltegravir and etravirine. (Conditional recommendation, low quality of evidence)
3. If patients are on a failing regimen without further therapeutic options, a tolerated regimen should be continued. (Conditional recommendation, very low quality of evidence)

Domains and considerations

Quality of evidence

The quality of evidence was not based on a systematic but a targeted literature review for relevant studies. Indirectness was noted among these trials. With the optimized background regimen based on genotypic or phenotypic testing and study populations which were generally not in low- and middle-income countries. Strong recommendations not possible until more information is available on the role of etravirine, darunavir and raltegravir in 3rd-line in the context of a RLS.

Data from RCTs in developed and developing country settings are available for boosted darunavir (DRV/r), etravirine (ETR) and raltegravir (RAL). Taken together, these data support the success of these newer agents in ART experienced patients. DRV/r has been demonstrated to be non-inferior and well tolerated compared to LPV/r.

DRV/r (TITAN Power 1-2-3)

RAL (BENCHMARK 1-2, EASIER)

ETR (Duet 1, 2, TMC-125 C223, Cohen, Montaner)

Combination of all three (TRIO)

Uncertainty about the current quality of evidence but many studies are ongoing

Risks/Benefits

Benefits

- Avoid death and disease progression in patients failing second-line therapy
- Third-line/salvage studies conducted in developed/high-middle income countries showed benefit using non-critical outcomes (viral load suppression)

Risks

- Information about long-term safety is limited
- Potential drug-drug interactions with TB, malaria, hepatitis and opioid substitution therapy (OST) drugs
- New evidence on higher rates of hypersensitivity to etravirine than previously reported (recent warning informing about etravirine hypersensitivity risk published in Aug 09)
- Raltegravir is not approved for use in individuals <16 years old
- Limited data on use of these drugs in pregnancy
- Limited resources diverted from scale-up of ART coverage
- Equity of access may be compromised

Benefits outweigh risks

Values and acceptability

- Physicians and PLHIV want to have a 3rd-line regimens available but the panel also valued

<p>maintaining access to 1st-line ART</p> <p>No uncertainty</p>
<p>Cost</p> <ul style="list-style-type: none"> • Expensive and costly to national programmes • In studies conducted in developed countries and in modeled cost-effectiveness analyses, DRV/r has been demonstrated to be cost effective compared other boosted PIs in heavily pretreated patients • The acquisition cost for etravirine is 1 to 2 times that of EFV and NVP • The acquisition cost of DRV and raltegravir is not well established in RLS but is expected to be high • Provision of 3rd-line will be costly and it is unclear if price reductions are likely <p>No uncertainty</p>
<p>Feasibility</p> <ul style="list-style-type: none"> • Availability of these drugs in RLS now and in the near future is uncertain • Availability of generic formulations and FDCs in the near future is uncertain <p>Uncertainty Yes</p>
<p>Gaps, research needs, comments</p> <ul style="list-style-type: none"> • More information on critical patient outcomes on patients on 2nd-line ART • Current and near-future licensing and availability of these new drugs in RLS • Coming availability of generics and FDCs (UNITAID and patent pool initiative) • Ongoing studies with once daily dosing for DRV/r and raltegravir • Pilot studies on 3rd-line implementation and pharmacovigilance studies on monitoring long-term adverse events and other potential drug-drug interactions in RLS are necessary • Toxicity monitoring of patients on 2nd-line and 3rd-line regimens • "Green Light Committee" assesses suspected MDR TB cases and establishes mechanisms for countries to access the needed drugs. Could a GLC for 3rd-line ART be an option? • GLC might be able to attract separate funding and negotiate lower prices for 3rd-line drugs than if countries do this independently and could be a mechanism to avoid countries having to balance the need to scale up vs. the need to fund 3rd-line regimens
<p>Final comment</p> <p>Conditional recommendation</p> <p>In developing these recommendations, the panel placed high value on balancing the need to develop policies for 3rd-line therapy while maintaining increased access to 1st-line therapy. It was recognized that countries are financially constrained.</p>

Stavudine (d4T) phase-out management: Guiding principles

1. It is recommended that in settings where d4T regimens are used as the preferred option for ART initiation, a phase-out plan towards using AZT- or TDF-based 1st-line regimens should be developed.
2. The d4T phase-out plan should be based on an assessment of the cost and feasibility of phasing out d4T use.
3. All countries continuing to use d4T as part of a preferred 1st-line regimen should undertake a risk assessment for continuing to use d4T at lower doses.
4. It is recommended that programs implement systems to monitor and manage toxicities for all ongoing use of d4T-containing regimens.

Domains and considerations

Summary of evidence

- Some experts advocate for the complete removal of d4T (already a delisted option in the majority of ART guidelines from industrialized countries)
- Phasing out d4T is ongoing at global level but still the preferred 1st-line ARV in 56% of LMIC/LIC programs
- Most adverse events are related to mitochondrial toxicity and due to cumulative exposure (usually after 6 to 12 months of therapy)
- There are limited data on the toxicities of reduced doses (studies suggest that efficacy is maintained)
- Reduced dose d4T may be valid initial option in settings with limited N(t)RTI options, limited laboratory capabilities and/or as a backup option for treatment-limiting toxicity to AZT or TDF
- Option exists to initiate d4T-based ART and switch after 6 to 12 months before or immediately at detection of mitochondrial toxicities, but relative data is sparse.
- Close monitoring of its long-term toxicities is required
- Higher risk patients for lipoatrophy are those >35 years old, women with high BMI and/or pregnant
- Higher risk patients for lactic acidosis are women with high BMI and/or pregnant
- Higher risk patients for neuropathy are those receiving concomitant use of d4T and INH (seven-fold increase in the risk of peripheral neuropathy)

Risks/Benefits

Benefits

- Phase-out of a drug associated with significant adverse events
- Reduction in stigma caused by lipoatrophy, disability caused by peripheral neuropathy and mortality due lactic acidosis
- Potential positive impact on adherence if disfiguring and unpleasant side-effects are avoided

Risks

- Current cheap, good and readily available generic FDCs for adults and children, well tolerated in the short-term, will need to be replaced
- Loss of a drug which is well tolerated in the short-term but has unacceptable complications in the long-term
- Potential for wasted stock of d4T FDCs
- Potential for reduced coverage due to increased cost of new regimens
- Uncertainty about the impact of AZT-induced anaemia and TDF renal toxicity as programs transition away from d4T to AZT or TDF

Benefits outweigh risks
<p>Values and acceptability</p> <ul style="list-style-type: none"> • PLHIV place high value on avoiding d4T-related side-effects • Physicians' concerns about long term toxicities such as lipoatrophy, peripheral neuropathy and lactic acidosis • Countries place high value on cheap and easily available regimens <p>No uncertainty</p>
<p>Cost</p> <ul style="list-style-type: none"> • Initial increased cost (TDF > AZT) which may be offset by reduced costs of d4T toxicity management in long term • Prices of TDF and AZT combinations are significantly higher than d4T combinations but are progressively reducing (generic versions as dual and triple FDCs more available) • Costs of lab monitoring and HCW training on AZT and TDF toxicity management <p>Uncertainty about cost savings of d4T phase-out</p>
<p>Feasibility</p> <ul style="list-style-type: none"> • Cost is a major limitation and moves away from easily available and affordably fixed-dose combinations • TDF substitution may be more feasible if no renal monitoring is required • Favours phased, planned replacement of d4T by AZT or TDF, with speed and completeness determined by health system structure, disease burden, ART coverage, lab capacity and funding • Countries which have transitioned away from d4T suggest that it is feasible <p>Uncertainty Yes</p>
<p>Gaps, research needs, comments</p> <ul style="list-style-type: none"> • Further evaluation of safety and prevalence of major d4T toxicities at doses ≤ 30 mg BID in RLS is necessary • Further evaluations of the cost of phase out d4T use • Tools for risk assessment on continuing d4T use • Tools for pharmacovigilance, detection and monitoring of major d4T toxicities
<p>Final comment</p> <p>Strong recommendation</p> <p>In developing these recommendations, the panel placed high value on the disfiguring and unpleasant side effects of d4T and unacceptability to PLHIV over and above the cost and programmatic implications of moving to alternative safer, but more expensive drugs.</p>

ART laboratory monitoring: Guiding principles

1. Laboratory monitoring in patients who do not yet need to initiated ART

- With most patients still presenting for the first time with CD4 counts <200 cells/mm³ (in both resource limited and developed country settings), earlier identification of HIV status though expanding VCT and PITC is critical
- Patients who are not yet eligible for ART should have CD4 count measurement (if available) every 6 months and more frequently as they approach the threshold to initiate ART.

2. Laboratory monitoring for ART efficacy

- Laboratory monitoring is not a pre-requisite to the initiation of ART
- Viral load is not necessary in deciding when to start ART
- For patients receiving ART, monitoring of CD4 cell counts (if available) is recommended every 6 months, or more frequently if clinically indicated
- If resources permit, viral load may be used in patients receiving ART in a targeted approach to confirm suspected treatment failure based on immunological and/or clinical criteria
- If resources permit, viral load may be used routinely every 6 months, with the objective of detecting failure earlier than would be the case if immunological and/or clinical criteria were used to define failure
- VL testing may be introduced for specific target groups first, including those at high risk for failure, such as pregnant women with a past history of ARV exposure, those with prior ARV exposure who have discontinued due to loss to follow-up, those co-infected with HIV/TB, HIV/HBV and IDUs.

3. Laboratory monitoring for ART toxicity

- As a general principle, symptom-directed laboratory toxicity monitoring is recommended
- The inability to perform renal monitoring is not a barrier to TDF use
- Renal monitoring (calculated creatinine clearance, eGFR) is recommended in patients receiving TDF, especially in patients with underlying renal disease, older age group, small body weight or other renal risk facts such as diabetes or hypertension. There is evidence that patients taking TDF and a bPI may experience greater median decline in eGFR than those taking TDF and a non-NRTI. eGFR should be monitored more closely when TDF is used with a bPI.
- For patients receiving AZT-containing regimens, haemoglobin should be measured before initiation and then as directed by signs/symptoms. Patients receiving AZT-containing regimens and with low body weight and/or low CD4 cell counts are at greater risk for anaemia. Such patients should have routine Hb one month after initiating AZT and then at least 3 months of monitoring.
- In patients with HIV/HCV co-infection, regular monitoring of hepatic enzymes after initiation is recommended if available

Domains and considerations

Summary of evidence

Monitoring for efficacy:

Low CD4 counts, even with undetectable viral load, are associated with increased morbidity and mortality (AIDS-related complications and deaths, cardiovascular, liver and kidney disease and non-AIDS cancers) and complications (including IRIS on initiation or ART) providing impetus for earlier initiation of ART.

In the **FIRST** study, regardless of viral load, incremental CD4 increases lowered the risk of AIDS-related diseases by 44% for each 100 CD4 cell increase and the risk of non-AIDS diseases by 14% for each 100 CD4 cell increase (Baker 2008). Limited data exist to support frequency of CD4 count

monitoring.

While viral load is not a major factor in deciding when to begin treatment, it has value when monitoring patients on ART to detect early treatment failure and reduce the chances of resistance.

Monitoring for toxicity:

1. NVP toxicity in patients with higher or unknown CD4

There is conflicting evidence on the safety of NVP in people with higher CD4 counts. The available evidence is largely based on retrospective reviews or open-label studies, with very few randomized controlled trials providing evidence and results should be interpreted with caution. While there is a good representation of studies in RLS, key recommendations regarding use of NVP and CD4 cell count are based on trials in a resource unlimited settings. Initiation of NVP in patients with higher CD4 counts and undetectable VL may be a safer option. HIV/hepatitis C co infection is associated with higher incidences of hepatic toxicity, NVP discontinuation and mortality.

2. d4T in HIV+ pregnant women, particularly regarding the risk of lactic acidosis

In a systemic review, 14 articles were identified on d4T-related lactic acidosis all were non-comparative single-arm studies and provided no data suitable for creating GRADE profiles. Four articles and 3 case reports were from RLS. One of the articles (Wade) and 2 of the case reports focused on pregnant women and no conclusions could be drawn regarding the occurrence of lactic acidosis in pregnant women using d4T.

In a systematic review of the efficacy and toxicity of standard d4T dose (30 mg BID weight unadjusted following the addendum to the 2006 guidelines) and reduced d4T dose (weight adjusted 30 mg BID >60 kg, 20 mg BID <60 kg), appears to support equivalent efficacy and better tolerability for 20 mg BID in patients <60 kg. Two retrospective studies with small numbers of patients assessed 20 mg BID irrespective of body weight but no clear conclusions can be made from these data.

3. AZT-related anaemia and neutropoenia

Lower body mass and CD4 cell count appear to be factors related to risk of developing anaemia (Ssali, Isaakidis). No conclusions can be drawn regarding the use of AZT in pregnant women and risk of anaemia or neutropoenia, given the lack of data.

4. Tenofovir (TDF) renal toxicity (glomerular and tubular dysfunction) and osteopoenia

In a systematic review, 16 articles were identified on TDF-related renal toxicity, two of which came from RLS. Three of the studies were suitable for entry into GRADE tables, see below following the overall summary. In summary, the cumulative incidence rate of nephrotoxicity was 1% to 4%, with an estimated rate of Fanconi syndrome of 0.5% to 2%. Gender, age and race have not been demonstrated to be associated with TDF-induced nephrotoxicity. A 2007 report of all post marketing adverse drug reactions up to April 2005 for 10,343 patients in developed countries (Nelson) using TDF reported that serious adverse renal events were observed in 0.5% of patients and graded elevations of serum creatinine were observed in 2.2% of patients. Risk factors for increased serum creatinine were concomitant nephrotoxic medications, elevated serum creatinine, low body weight, advanced age and lower CD4 cell count. The authors conclude that risk factors for nephrotoxicity can be identified and may be useful in managing patients at risk. Gallant and Moore 2009 reported no differences in renal outcomes in patients who initiated treatment with TDF or an alternate NRTI. The studies used in the TDF GRADE analysis (with the exception of Squires) are either open-label or observational studies.

5. EFV teratogenicity, hepatotoxicity and CNS adverse effects

No consensus was reached on whether any change can be made to the recommendation that EFV **NOT** be used in the 1st trimester. Pregnancy should be excluded in women of child-bearing potential before initiating EFV. EFV appears to be safe in the 2nd and 3rd trimester with no increase in birth

defects above background levels reported to pregnancy registers. In RLS, EFV-related hypersensitivity, rash and liver toxicity appear to be low and self-limiting. Symptom-directed laboratory monitoring of liver enzymes is recommended in patients receiving EFV.
<p>Risks/Benefits</p> <p>Benefits</p> <ul style="list-style-type: none"> • VL will result in more accurate and earlier diagnosis of treatment failure • Regular pre-ART CD4 monitoring will reduce losses to follow-up with PLHIV waiting for ART and facilitate earlier ART initiation • Will facilitate scale up of TDF as preferred 1st-line ARV • Reduce unnecessary HB testing in patients on AZT with no clinical anaemia <p>Risks</p> <ul style="list-style-type: none"> • Uncertainty about the safety of TDF in some populations without renal screening and monitoring • Benefits outweigh risks for recommendations on VL, HB and pre-ART CD4 • Need more information on TDF use without renal monitoring, to decide if benefits outweigh risks <p>Benefits outweigh risks</p>
<p>Values and acceptability</p> <ul style="list-style-type: none"> • Some physicians may be uncomfortable with recommendations on renal monitoring. • Recommendations on VL, HB and pre-ART CD4 acceptable. • Need more information on TDF use without renal monitoring. <p>Uncertainty: Yes</p>
<p>Cost</p> <ul style="list-style-type: none"> • Increased costs for VL, pre-ART CD4. • Potential for cost saving with Hb (minor) and no renal monitoring. <p>No uncertainty</p>
<p>Feasibility</p> <ul style="list-style-type: none"> • Widespread use of TDF may only be feasible if renal screening and monitoring is either available or not a prerequisite. • VL and CD4 feasible with adequate investment in infrastructure and training. • Broadly feasible for VL, pre-ART CD4 and Hb. <p>Uncertainty: Yes</p>
<p>Gaps, research needs, comments</p> <ul style="list-style-type: none"> • Need more information on TDF use without renal screening and monitoring.
<p>Final comment</p> <p>Strong recommendation</p> <p>In developing these recommendations, the panel placed high value on improving access to and monitoring of safer ARVs.</p>

Comments on what ART to start for women with prior exposure to MTCT regimens

NNRTI-resistance mutations can be selected following the use of single-dose nevirapine (sdNVP) used for prevention of perinatal transmission in women, and in infants who become infected despite prophylaxis. The long half-life of NVP means that detectable drug levels may persist for some time in the face of active viral replication following a single maternal dose. Administration of NRTIs for a period of time following sdNVP (a "tail") can reduce the development of resistance to very low levels.

Data from one RCT and 7 observational studies suggest that women starting NNRTI-based therapy within 6-24 months of sdNVP exposure have higher rates of viral failure than those without sdNVP exposure (Coovadia 2009, Lockman 2007, Chi 2007, Lockman 2009, Coffie 2008, Kuhn 2009). Though the studies are not directly comparable, a few observations can be made.

- If viral failure occurs in women with prior sdNVP exposure, it generally occurs within the first 6 months after initiating treatment.
- Viral failure appears to occur preferentially (although not solely) among the small proportion of women with NNRTI resistance mutations following sdNVP exposure (varied between 11-32% of women with sdNVP exposure).
- A definite relationship between time from sdNVP exposure to starting NNRTI-based therapy was observed but varied between studies from 6 months to 24 months, with definite improvement in response if >12 months since sdNVP exposure and start of therapy.

The risk of resistance is affected by maternal CD4 count and viral load at the time of exposure (Eshleman 2001). Women at greatest risk of NNRTI resistance post-sdNVP have low CD4 count and high viral load, and who are eligible for initiation on cART.

While detection of resistance is frequent in the first few weeks following exposure, the likelihood of detection decreases over time. In most women, resistant virus can no longer be detected 6 to 12 months after exposure using standard population genotyping methods. However, low levels of viral resistance can persist for longer periods and in some cases can remain present in latently infected cells (Flys 2007, Wind-Rotolo 2009). Though resistance at virological failure to NNRTI at 48 weeks is high (between 61% and 88.3%), the rate of virological failure at 6 months is expected to be very low (<5%).

Where women who have been exposed to PMTCT-prophylaxis are to be started on ART for their own health, consideration should be given to the prophylactic regimen and amount of time passed since she had taken it in order to reduce resistance, virological failure, and subsequent disease progression and mortality.

- Initiate a non-NNRTI based ART regimen for women who have taken sdNVP (alone or with short course AZT) with *no AZT/3TC tail* within the last 12 months. A protease inhibitor-based regimen is preferred over 3 NRTI's.

When an NNRTI-based regimen has been initiated for women who have taken sdNVP (alone or with short course AZT) with no AZT/3TC tail, if possible, check viral load at 6 months and if >5,000 copies/ml, switch to second line ART with protease inhibitors.¹

- Initiate an NNRTI-based ART regimen for women who have taken sdNVP (alone or with short course AZT) *with an AZT/3TC tail* within last 12 months. If possible, check viral load at 6 months and if >5,000 copies/ml, switch to second line ART with protease inhibitors.¹
- Initiate an NNRTI-based ART regimen for women who have taken sdNVP (alone or with short course AZT) with or without an AZT/3TC tail more than 12 months prior to starting ART. If possible, check viral load at 6 months and if >5,000 copies/ml, switch to second line ART with protease inhibitors.¹
- Initiate a standard NNRTI-based ART regimen for women who have taken any other NNRTI-based regimen with a tail, or PI-based ART regimen, regardless of duration of exposure and time since exposure.

References

Chi BH, Sinkala M, Stringer EM, et al. Early clinical and immune response to NNRTI-based antiretroviral therapy among women with prior exposure to single-dose nevirapine. *AIDS*. 2007 May 11;21(8):957-64.

Coffie PA, Ekouevi DK, Chaix ML et al. Maternal 12-month response to antiretroviral therapy following prevention of mother-to-child transmission of HIV type 1, Ivory Coast, 2003-2006. *Clin Infect Dis*. 2008 Feb 15;46(4):611-21.

Coovadia A, Hunt G, Abrams EJ, et al. Persistent Minority K103N Mutations among Women Exposed to Single-Dose Nevirapine and Virologic Response to Nonnucleoside Reverse-Transcriptase Inhibitor-Based Therapy. *Clin Infect Dis*. 2009;48:462-72.

¹ Where VL not available, immunological (CD4) criteria for failure should be used to confirm failure prior to switching regimens.

Eshleman SH, Mracna M, Guay L, et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). *AIDS* 2001;15:1951-7

Flys TS, Donnell D, Mwatha A, et al. Persistence of K103N-containing HIV-1 variants after single-dose nevirapine for prevention of HIV-1 mother-to-child transmission. *J Infect Dis.* 2007;195:711-5.

Kuhn L, Semrau K, Ramachandran S, et al. Mortality and virologic outcomes after access to antiretroviral therapy among a cohort of HIV-infected women who received single-dose nevirapine in Lusaka, Zambia. *JAIDS.* 2009 Sep 1;52(1):132-6.

Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med.* 2007 Jan 11;356(2):135-47.

Lockman S and A5208/OCTANE Study Team. Lopinavir/ritonavir + tenofovir/emtricitabine is superior to nevirapine + tenofovir/emtricitabine for women with prior exposure to single-dose nevirapine: A5208 (“Octane”). 16th Conference on Retroviruses and Opportunistic Infections, Montreal, Canada, February 8-11 2009, abstract 94LB.

Wind-Rotolo M, Durand C, Cranmer L, et al. Identification of nevirapine resistant HIV-1 in the latent reservoir after single-dose nevirapine to prevent mother-to-child transmission of HIV-1. *J Infect Dis* 2009;199:1301-9.

Special Note on HIV-Hepatitis C co-infection

There is no clinical trial that specifically evaluated when ART should be initiated and what the best regimen to be used in HIV-HCV co-infected patients. However, observational data showed that Hepatitis C co-infection is significantly associated with risk of death and advanced liver disease in HIV-positive individuals. It has been strongly suggested that HIV infection accelerates HCV-related disease progression and mortality (Mohsen 2003; Smit, 2008; Benhamou, 1999), but the reciprocal effect of HCV on the rate of HIV disease progression remains difficult to distinguish due to the heterogeneity of study results. A recent meta-analysis confirmed the increase in the overall risk of mortality, but did not demonstrate an increased risk of AIDS-defining events among coinfecting patients (Chen, 2009).

A major observational cohort study has examined the level of toxicities of specific ART regimens used for HIV/HCV co-infection and did not find significant differences (Mocroft, 2005). However, the systematic review on drug-drug interactions prepared for this guidelines review found important pharmacological interactions of ribavirin with ABC, ATV, AZT, d4T and ddI that can increase the toxicity risk if these drugs are used concomitantly.

Many studies also suggest that the sustained viral response rates of HCV therapy in HIV co-infected individuals are significantly lower than in HCV mono-infected patients (Carrat, 2004; Laguno, 2004; Torriani 2004; Chung 2004), but others have achieved higher rates in this population (Laguno, 2009).

Considering the significant level of uncertainty on these topics and the importance of Hepatitis C management in the context of HIV co-infection (an important gap highlighted by the guidelines panel group, particularly the representatives from the people living with HIV community), WHO is planning to revise the recommendations for the prevention and treatment of major HIV-related opportunistic infections and co-morbidities, including Hepatitis C. Furthermore, it is expected that the 2010 World Health Assembly will establish clear recommendations for the management and care of viral hepatitis, which will increase support for an integrated approach to the prevention, treatment and care of HCV/HIV coinfection.

Meanwhile, the panel recommends that the **initiation of ART in HIV/HCV co infected people follows the same principles and recommendations as for its initiation in HIV monoinfected individuals. However, patients should be closely monitored due to the increased risk of drug toxicities and drug interactions between some ARVs and anti-HCV drugs. (strong recommendation, low quality of evidence).**