

What to start

Recommendations

1. It is recommended that one of 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 to 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