

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

<p>Benefits outweigh risks</p>
<p>Values and acceptability</p> <ul style="list-style-type: none"> • PLHIV have concerns about EFV use during reproductive age • Side effects of AZT and EFV unacceptable to some PLHIV • 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 naive 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

<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 (LFTs and Hb) is required for management of toxicity ○ If EFV is substituted for NVP following toxicity <p>Uncertainty No</p>
<p>Feasibility</p> <ul style="list-style-type: none"> • Regimens with extensive programmatic experience • Drugs widely available • FDCs available • Applicable to adults, adolescents and children • NVP lead-in dose adds complexity <p>Uncertainty No</p>
<p>Gaps, research needs, comments</p> <ul style="list-style-type: none"> • Under what circumstances can NVP be recommended as once daily? Is lead-in dosing needed? • NVP toxicity at high CD4 counts
<p>Final comment</p> <p>Strong recommendation</p> <p>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.</p>

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
<p>Feasibility</p> <ul style="list-style-type: none"> • NVP lead-in dose adds complexity • Only feasible where renal screening is available or when it is not a prerequisite <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 • 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
<p>Final comment</p> <p>Strong recommendation</p> <p>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

<ul style="list-style-type: none"> • No lead-in dosing required • Can be used in TB co-infection <p>Risks</p> <ul style="list-style-type: none"> • Limited data on the use of TDF without renal screening and/or monitoring in RLS • TDF not approved in children and adolescents • 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>