

## ART for pregnant women

### Recommendations

#### When to Start:

1. Start ART in all pregnant women with HIV and CD4 count  $\leq 350$  cells/mm<sup>3</sup>, irrespective of clinical symptoms. **(Strong recommendation, moderate quality of evidence)**
2. CD4 testing is required to identify if pregnant women with HIV and WHO clinical stage 1 or 2 disease need to start antiretroviral treatment or prophylaxis. **(Strong recommendation, low quality of evidence)**
3. Start ART in all pregnant women with HIV and WHO clinical stage 3 or 4, irrespective of CD4 count. **(Strong recommendation, low quality of evidence)**

#### What to Start:

4. Start one the following regimens in ART-naïve pregnant women eligible for treatment. **(Strong recommendation, moderate quality of evidence)**
  - AZT + 3TC + EFV
  - AZT + 3TC + NVP
  - TDF + 3TC or FTC + EFV
  - TDF + 3TC or FTC + NVP
5. Do not start EFV during the first-trimester of pregnancy. **(Strong recommendation, low quality of evidence)**

### Domains and considerations

#### Quality of evidence

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

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/mm<sup>3</sup>, the panel recommended all pregnant women infected with HIV should have access to CD4 testing.

CD4 counts have been observed to decline during the 1<sup>st</sup> trimester of pregnancy, increasing during the 3<sup>rd</sup> 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.

The use of EFV is contraindicated in the 1<sup>st</sup> trimester of pregnancy. Although early animal studies detected a high incidence of neural tube defects, incidence in human studies has not corroborated this evidence. Additionally, neural tube closure is complete by 28 days after conception, and the use of EFV after that time is unlikely to contribute to defects. Commonly, pregnancy may not be confirmed by 25 days post-conception. If a woman is already on EFV at the time she is determined to be pregnant, she may continue on EFV if past the time of neural tube closure.

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/mm<sup>3</sup>, 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 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. No consistent patterns were identified.

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 MTCT-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.

<p><b>Risks</b></p> <ul style="list-style-type: none"> <li>• There are limited data on the use of TDF in pregnancy</li> <li>• TDF not approved for &lt;18 years of age</li> <li>• Possible bone toxicity for the fetus and for breastfeeding women with use of TDF</li> </ul> <p><b>Benefits outweigh risks</b></p>
<p><b>Values and acceptability</b></p> <p><i>In favour</i></p> <ul style="list-style-type: none"> <li>• 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</li> <li>• The use of EFV in the 1<sup>st</sup> trimester is not acceptable PLHIV or to physicians</li> <li>• The panel placed high value on the need for CD4 testing in pregnant women</li> </ul> <p><i>Against</i></p> <ul style="list-style-type: none"> <li>• The limited data and studies specific to pregnant women and the potential for toxicity, which may affect acceptability</li> <li>• Teratogenicity is a concern</li> </ul> <p><b>No Uncertainty</b></p>
<p><b>Cost</b></p> <p><i>When to Start:</i></p> <ul style="list-style-type: none"> <li>• If 2006 guidelines have been followed, the recommendation is cost-neutral. If higher thresholds are used, there will be cost increases.</li> </ul> <p><i>What to Start:</i></p> <ul style="list-style-type: none"> <li>• Incremental drug cost comparisons: NVP &lt;EFV.</li> <li>• Increased costs if EFV is substituted for NVP.</li> <li>• Overall, a cost saving may be realized in reducing costs for HIV care and services.</li> </ul> <p><b>No Uncertainty</b></p>
<p><b>Feasibility</b></p> <ul style="list-style-type: none"> <li>• There are major problems with assessing eligibility in ANC and MCH clinics.</li> <li>• CD4 testing is essential for implementation of these recommendations.</li> <li>• ART is currently not started in most ANC/MCH.</li> <li>• Timing and regimens are consistent with those recommended for other adults/adolescents and comprise drugs with extensive programmatic experience.</li> <li>• ANC and MCH need to be linked with ART programme.</li> <li>• Prioritize pregnant women for treatment.</li> </ul> <p><b>No Uncertainty</b></p>
<p><b>Gaps, research needs, comments</b></p> <ul style="list-style-type: none"> <li>• Successful programmes that put ART in MCH clinics and integrate MCH clinics into ART services with CD4 testing.</li> <li>• Improved data on hepatotoxicity and hypersensitivity to NVP with unknown or CD4 &gt;250. cells/mm<sup>3</sup> are needed to understand the real magnitude of this problem, particularly in a RLS context where NVP is the major NNRTI in use.</li> <li>• Better information on safety related to TDF and the teratogenicity of EFV use during pregnancy.</li> </ul>

**Final comment**

In developing these recommendations, the ART and PMTCT panels placed high value on early and CD4-guided initiation of ART for eligible women, as ways to improve maternal and child-health outcomes and reduce vertical transmission.