Treatment Recommendations for Pregnant and Breastfeeding Women: Critical Issues

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Objectives of Presentation

- Background

- Overview of Key Recommendations:
  - When to Start ART
  - Breastfeeding
  - What ART to Start

- Issues and challenges
Progress and Barriers

- Limited coverage and implementation of PMTCT and ART for pregnant women in many high burden countries
  - ~ 1.4 million HIV+ pregnant women
  - 65% PMTCT ARV coverage
  - Limited ART in those eligible for treatment
  - High loss to follow-up along PMTCT cascade
  - Low ARV coverage during breastfeeding

- Complexity of Option A
  - Different treatment and prophylaxis regimens through pregnancy and breastfeeding
  - Difficulty of long-term NVP dosing for infants
  - Requirement for CD4 to determine eligibility
  - Follow up along the PMTCT cascade is very low

- Current approach needs to be optimized to achieve universal access and elimination

Steady progress reducing infant infections

- 2009: ~430,000 infant infections
- 2012: ~290,000 infant infections
- 2015: Global Plan target <40,000
## Evolution of WHO PMTCT ARV Recommendations

<table>
<thead>
<tr>
<th>Year</th>
<th>PMTCT</th>
<th>ART</th>
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<tbody>
<tr>
<td>2001</td>
<td>4 weeks AZT; AZT+ 3TC, or SD NVP</td>
<td>No recommendation</td>
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<tr>
<td>2004</td>
<td>AZT from 28 wks + SD NVP</td>
<td>CD4 &lt;200</td>
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<tr>
<td>2006</td>
<td>AZT from 28wks + sdNVP +AZT/3TC 7days</td>
<td>CD4 &lt;200</td>
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<tr>
<td>2010</td>
<td>Option A (AZT +infant NVP)</td>
<td>CD4 ≤350</td>
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<tr>
<td></td>
<td>Option B (triple ARVs)</td>
<td></td>
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<tr>
<td></td>
<td>Option B or B+</td>
<td>CD4 ≤500</td>
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**Launch July 2013**

- **Move towards:** more effective ARV drugs, extending coverage throughout MTCT risk period, and ART for the mother’s health
When to Start ART
## Recommendations

### “Option B+”

All pregnant and breastfeeding women infected with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART.

*(strong recommendation, moderate-quality evidence)*

### “Option B”

For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women infected with HIV should initiate ART as lifelong treatment.

*(conditional recommendation, low-quality evidence)*

In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of mother-to-child transmission risk has ceased.

*(conditional recommendation, low-quality evidence)*
### Rationale: Shift from Option A to B+ or B

<table>
<thead>
<tr>
<th>Benefits for Mother and Child</th>
<th>Benefits for Program Delivery &amp; Public Health</th>
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<tbody>
<tr>
<td>Ensures all ART eligible women initiate treatment</td>
<td>Reduction in number of steps along PMTCT cascade</td>
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<tr>
<td>Prevents MTCT in future pregnancies</td>
<td>Same regimen for all adults (including pregnant women)</td>
</tr>
<tr>
<td>Potential health benefits of early ART for non-eligible women</td>
<td>Simplification of services for all adults</td>
</tr>
<tr>
<td>Reduces potential risks from treatment interruption</td>
<td>Simplification of messaging</td>
</tr>
<tr>
<td>Improves adherence with once daily, single pill regimen</td>
<td>Protects against transmission in discordant couples</td>
</tr>
<tr>
<td>Reduces sexual transmission of HIV</td>
<td>Cost effective</td>
</tr>
</tbody>
</table>

Major issue now is not “when to start” or “what to start” but “whether to stop”
• *Initiate all HIV+ pregnant and breastfeeding women on ART*

• Operational and programmatic advantages to lifelong ART for pregnant and breastfeeding women ("B+"), particularly in settings with:
  – Generalized epidemics
  – High fertility (though need to strengthen FP)
  – Long duration of breastfeeding
  – Limited access to CD4 to determine ART eligibility
  – High partner serodiscordance rates

• National programmes need to decide B or B+
ARVs and breastfeeding

2013 (no change from 2010)

<table>
<thead>
<tr>
<th>National agencies should decide between promoting mothers with HIV to either breastfeed and receive ARV interventions or to avoid all breastfeeding</th>
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</thead>
<tbody>
<tr>
<td>Where the national choice is to promote BF, mothers whose infants are HIV uninfected or of unknown HIV status should:</td>
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<tr>
<td>• exclusively breastfeed their infants for the first six months of life</td>
</tr>
<tr>
<td>• introduce appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life</td>
</tr>
<tr>
<td>• breastfeeding should then only stop once a nutritionally adequate and safe diet without breast-milk can be provided</td>
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*(strong recommendation, high-quality evidence for the first 6 months; low-quality evidence for the recommendation of 12 months)*
WHAT ART REGIMEN TO START
### Summary of Changes in Recommendations: What to Start in Adults

#### First-Line Regimens (Preferred ARV Regimens)

<table>
<thead>
<tr>
<th>Target Population</th>
<th>2010 Art Guidelines</th>
<th>2013 Art Guidelines</th>
<th>Strength &amp; Quality of Evidence</th>
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</thead>
<tbody>
<tr>
<td>HIV+ ARV-NAIVE Adults</td>
<td>AZT or TDF + 3TC (or FTC) + EFV or NVP</td>
<td>TDF + 3TC (or FTC) + EFV (as fixed-dose combination)</td>
<td>Strong, moderate-quality evidence</td>
</tr>
<tr>
<td>HIV+ ARV-NAIVE Pregnant Women</td>
<td>AZT + 3TC + NVP or EFV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV/TB Co-infection</td>
<td>AZT or TDF + 3TC (or FTC) + EFV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV/HBV Co-infection</td>
<td>TDF + 3TC (or FTC) + EFV</td>
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</table>
# Evidence Summary: Safety of EFV and TDF in Pregnancy

## EFV

- No increased risk of birth defects with EFV when compared with other ARVs

- Systematic review (including Antiretroviral Pregnancy Registry), reported outcomes for 1502 live births to women receiving EFV in the first trimester and found no increase in overall birth defects

- Excludes > 3 fold increased risk in overall birth defects

## TDF

- Potential concerns include renal toxicity, adverse birth outcomes and effects on bone density

- Systematic review assessed the toxicity of fetal exposure to TDF in pregnancy
  - In Antiretroviral Pregnancy Registry, prevalence of all birth defects with TDF exposure in 1st trimester was 2.4% (same as background)

- Limited studies showed no difference in fetal growth between exposed/unexposed

- No studies of TDF among lactating women, who normally have bone loss during breastfeeding

- Current data reassuring

- More extensive studies ongoing

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Source: Antiretroviral Pregnancy Registry Steering Committee [http://www.APRegistry.com](http://www.APRegistry.com) Siberry GK et al. AIDS, 2012
Understand the importance of implementation issues in the context of HIV treatment:

- Adequate planning for changes in guidelines
- Expansion and integration of ART into PMTCT sites
  - Supply chain for ARVs (avoidance of stock-outs)
  - Task-shifting for ART initiation
  - Adherence, retention, follow up, linkages with chronic ART
  - All MNCH sites become ART sites
- Access to ART monitoring

**Major challenge for PMTCT and MNCH settings:**
- How to expand access to VL monitoring?
- How to utilize CD4 data, especially for women with high baseline CD4?
Key research questions: Pregnant Women

**ARV toxicity surveillance:**
- Safety of early, lifelong ART for pregnant and breastfeeding women?
- Maternal toxicity, pregnancy toxicity (stillbirth, low birth weight, prematurity, birth defects) and infant toxicity?

**Mother-to-child transmission and mother and child health impact:**
- Impact on overall HIV-free survival and overall MTCT rate (at the end of breastfeeding as well as at 6-weeks)?
- Impact on maternal morbidity and mortality, sexual transmission, and the long-term success of first-line ART?

**Adherence and retention:**
- Acceptability of ART to women, especially those who initiate lifelong ART before they meet «adult eligibility» criteria
- Adherence and retention rates for women with both low and high CD4?
- Health systems and community interventions needed to achieve high levels of adherence and retention in setting of universal ART?
Transition in PMTCT Regimens in the 22 Global Plan Priority Countries

After 2010 WHO PMTCT ARV guidelines

As of June 2013
• Major paradigm shift; convergence of PMTCT and ART
• Simplified, harmonized approach for adults and pregnant women
• All pregnant and breastfeeding women with HIV should start first-line ART
• With Option B+, all pregnant women with HIV «eligible» for lifelong ART
  ➢ 1.4 million pregnant women with HIV annually
• Benefit for mother’s health, prevention of infant infections, prevention of partner infections