Prevention of Mother-To-Child Transmission of HIV

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Outline

• Timing of HIV transmission to infant
• Factors to consider when selecting ARV for PMTCT
• Intrapartum management and mode of delivery
• Management of infants exposed to HIV
Timing of transmission to infant: Non-breastfeeding population

Figure 2: Estimation of timing of mother-to-child HIV-1 transmission in a non-breastfeeding population. Estimates are based on a hypothetical cohort of 100 children born to HIV-infected women without any interventions. Upper line numbers indicate number of children at risk for infection. Adapted from reference 6.

Timing of transmission to infant: Breastfeeding population

Figure 3: Estimation of timing of mother-to-child HIV-1 transmission in a population that practises prolonged breastfeeding of 18–24 months. Estimates are based on a hypothetical cohort of 100 children born to HIV-infected women without any interventions. Upper line numbers indicate number of children at risk for infection.

Risk factors for perinatal HIV transmission

- High maternal viral load
- Low maternal CD4 count
- Vaginal delivery
- Premature rupture of membrane
- Preterm delivery, low birth weight


PMTCT during the antepartum period

Antepartum ARV for pregnant women
To reduce maternal HIV RNA level to the lowest level as soon as possible
To increase maternal CD4 count to the highest level
To improve maternal health and reduce pre-term and low birth weight delivery
PMTCT during the intrapartum and delivery period

Elective Caesarian Section
Avoid invasive procedure and prolonged rupture of membrane

Intrapartum ARV or ARV before delivery
To prepare adequate plasma ARV level in the infant for “pre-exposure prophylaxis”
PMTCT after delivery

ARV for infant after delivery
As post-exposure prophylaxis for the infant

Formula feeding
To prevent HIV acquisition through breast feeding
ARV to reduce perinatal HIV transmission

• Antiretroviral drugs reduce perinatal transmission by
  – lowering maternal antepartum viral load and
  – acting as pre- and post-exposure prophylaxis of the infant

• Therefore, antiretroviral drugs need to be delivered at every period including
  – Antepartum to the mother
  – Intrapartum to the mother (for the infant) and
  – Postpartum to the infant
Factors to consider when selecting ARV for PMTCT

- **Efficacy** in reducing perinatal HIV transmission

- Development of **NVP resistance** in mothers after delivery and in HIV-infected infants

- **Safety** of 3-drug antiretroviral regimens
  - NVP in women with CD4 >250: hepatitis, rash
  - EFV: teratogenicity if used during the 1st trimester
  - PI: hyperglycemia, preterm delivery

- **Convenience** when drugs need to be discontinued after delivery in women with high CD4 count
Perinatal HIV transmission in the UK and Ireland when HAART is recommended for all pregnant women, Year 2000-2006 (N = 5131)

- Overall transmission rate = 1.2%
- TR reduced 1% for every additional week of HAART
- TR 0.1% if HAART and VL < 50

Efficacy in reducing perinatal HIV transmission

- AZT from 28 wk GA plus single-dose NVP (when maternal therapy is not indicated)
  - 2% from PHPT-2
  - 5.8% from Dept. of Health report 2007 (Thailand)

- HAART for PMTCT
  - <1-2% in developed and developing countries
  - 2.4% from Thai Red Cross cohort

Thailand must aim to reduce “new pediatric HIV cases” from 500 (5.8%) to <100 cases/year (1%)
= 80% reduction in the whole country’s pediatric HIV burden.


NVP resistance after sd-NVP

- NVP has long half-life and has low genetic barrier
- NVP resistance after exposure to sd-NVP has varied from 15% to 75%
- Exposure to NVP when viral is not fully suppressible, e.g. AZT monotherapy + intrapartum sd-NVP, poses certain risk
- NVP resistance in plasma and cellular provirus can still be detected at 12 months after exposure
- Resistance to NVP can also cause cross-resistance to other NNRTI

NVP resistance after sd-NVP

- 1-week AZT/3TC to women exposed to sd-NVP after delivery decreased NVP resistance (from 60% to 10%) but did not eliminate the risk

- Efforts made to prevent NVP resistance in middle-income countries when possible are crucial as NNRTI-based regimen is still the preferred first-line regimen in these countries

McIntyre JA, et al. Addition of short course Combivir to single-dose Viramune for the prevention of mother to child transmission of HIV-1 can significantly decrease the subsequent development of maternal and paediatric NNRTI resistant virus. Presented at: 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment.
NVP toxicities in pregnant women

- Hepatotoxicity and cutaneous rash are the most common toxicities
- More common in women who are started on NVP-based ART when CD4 >250
- Fatal case reported in pregnant women, not known if pregnancy further predisposes women to NVP toxicities
- Risk does not seem to increase in pregnant women with CD4 <250
- Risks among pregnant women with CD4 250-350 are inconclusive


Safety of EFV use in pregnant women

- Hepatitis and rash can occur
- 5 retrospective cases and 1 prospective case of neural tube defects in human exposed to EFV during the first trimester
- Antiretroviral Pregnancy Registry (through Jan 2007): 2.5% birth defects from 281 first trimester exposure (2.7% in general population), none were neural tube defects >> Use only after the first trimester
- Discontinue EFV before the other drugs in the regimen (due to long half-life similar to NVP) to avoid NNRTI resistance
Safety of PI use in pregnant women

- Use in pregnant women with high CD4 count (>250 or >350) to avoid serious hepatotoxicity from NVP-based regimen
- LPV/rtv is the most recommended PI
- Overall side effects: dyslipidemia, nausea, vomiting, loose stools, hyperglycemia and hepatitis
- No concern regarding drug resistance if discontinue after delivery


“When HAART is indicated”
When HAART is indicated

- AIDS-defining illness, irrespective of CD4 count
- CD4 count <350 with any symptoms
- CD4 count <200, irrespective of symptoms

WHO

OR

- All with CD4 count <350

BHIVA and DHHS


For Thailand

“HAART is indicated” if CD4<250 or 250-350 with symptoms*

- **3-drug is recommended**
- **When to start?**
  - As soon as possible even during the first trimester
- **What to start?**
  - AZT/3TC/NVP if CD4<250
  - (EFV or LPV/r if CD4 250-350 with symptoms)
- **Discontinue after delivery?** → **No**

*oral candidiasis, oral hairy leukoplakia (OHL), herpes zoster, pruritic papular eruptions (PPE)
Opportunistic Infection Prophylaxis During Pregnancy

- Cotrimoxazole for PCP prophylaxis can be given (recommended with folic acid during the first trimester)

- Fluconazole 400-800mg/d caused fetal malformation when use daily: not recommended for prophylaxis use

“When HAART is not yet indicated”
When HAART is not yet indicated

| Mother | Antepartum | AZT from 28 weeks or as soon as feasible thereafter  
|        | Intrapartum | Sd-NVP + AZT/3TC  
|        | Postpartum  | AZT/3TC x 7 days  
| Infant |            | Sd-NVP + AZT x 7 days (or 4 weeks if maternal AZT < 4 weeks)  

WHO 2006
When HAART is not yet indicated

<table>
<thead>
<tr>
<th>DHHS 2008</th>
<th>BHIVA 2008</th>
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</thead>
<tbody>
<tr>
<td><strong>When to start?</strong></td>
<td><strong>When to start?</strong></td>
</tr>
<tr>
<td>– after 10-12 weeks</td>
<td>– 20-28 weeks</td>
</tr>
<tr>
<td><strong>Which drugs?</strong></td>
<td><strong>Which drugs?</strong></td>
</tr>
<tr>
<td>– AZT/3TC/LPV/rtv</td>
<td>– PI-based ART</td>
</tr>
<tr>
<td>– AZT monotherapy “controversial”, may consider if VL&lt;1000</td>
<td>– AZT monotherapy + PLCS if VL&lt;6-10K</td>
</tr>
<tr>
<td><strong>When to stop?</strong></td>
<td><strong>When to stop?</strong></td>
</tr>
<tr>
<td>– Discontinue after delivery</td>
<td>– Discontinue after delivery</td>
</tr>
<tr>
<td>– 6-week AZT to infant</td>
<td>– 4-week AZT to infant</td>
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</table>
For Thailand

“HAART is not yet indicated” if CD4≥250 without symptoms

- National policy will incorporate the use of **HAART for all pregnant women** very soon
- When to start?
  - **At 24 weeks GA**
- What to start?
  - **AZT/3TC/LPV/r or EFV**
- Discontinue after delivery? → Yes (give AZT/3TC for 1 week after delivery if HAART contains EFV)

Generic LPV/r (GPO) tablet can be given at the dosage of 400/100 BID throughout pregnancy
“Pregnant while on HAART”
Pregnant while on HAART

- Continue ART +/- AZT substitution
- If on EFV and pregnancy recognized in the first trimester → switch to other drug, otherwise can continue EFV-based ART
- Discontinuation of therapy could lead to increase in viral load, decline in immune status and disease progression
- Check if ART is still effective
“Intrapartum management and mode of delivery”
Intrapartum ARV for Thailand

- Continue antepartum ARV regimen on schedule as much as possible
- Add oral AZT 300mg every 3 hrs (even if mother has AZT resistance) to prepare for adequate drug level in the infant (pre-exposure prophylaxis)
- Do not give single-dose NVP if mother receives 3 drugs (increased NVP resistance without additional efficacy)
- Drugs can be taken with a sip of water during pre-operational period
- If scheduled caesarean section is planned, give at least 2 doses of AZT 300mg every 3 hrs before surgery
Mode of delivery

• Pre-labour caesarean section (PLCS)
  – Reduce TR especially if mother does not receive 3 drugs or receives short duration of ARV or VL >1000 copies/ml before delivery (uncertain benefit if VL <1000)
  – PLCS at 38 wk (or 39 wk if mother receives 3 drugs with undetectable VL)
  – Pre-operative antibiotic is generally recommended

• Vaginal delivery
  – Avoid invasive fetal monitoring and artificial rupture of membrane
  – Terminate pregnancy as quickly as possible if >4 hrs of membrane rupture
“Management of infants exposed to HIV”
ARV given to HIV-exposed infants in Thailand

- AZT syrup 4mg/kg every 12 hrs for 4-6 weeks (as post-exposure prophylaxis), start as soon as possible after delivery
- Do not give single-dose NVP except high risk mother (does not receive 3 drugs or no ANC)
- Start cotrimoxazole syrup (after discontinue AZT) 10mg/kg/d, divided into 2 doses, 3 days/wk until 6 months of age or earlier if HIV-negative status can be assured from blood tests
- Breast feeding is not recommended, do not use mixed feeding
- Vaccination can be given for healthy infants
Laboratory tests to determine infant’s HIV status

• **DNA-PCR x 2**
  First DNA-PCR at 1-2 months of age
  – If 1\textsuperscript{st} DNA-PCR is positive, repeat immediately, if 2\textsuperscript{nd} DNA-PCR is positive \rightarrow “HIV-positive”
  – If 1\textsuperscript{st} DNA-PCR is negative, repeat at 4 months of age, if 2\textsuperscript{nd} DNA-PCR is negative \rightarrow “HIV-negative”, can discontinue cotrimoxazole syrup
  – If 2 DNA-PCR give inconsistent results, repeat 3\textsuperscript{rd} DNA-PCR immediately and interpret the result according to the 3\textsuperscript{rd} test result
<table>
<thead>
<tr>
<th>Age</th>
<th>Percent positive if HIV-infected</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 3 days</td>
<td>30%</td>
<td>Only positive if infection occurs in-utero</td>
</tr>
<tr>
<td>14 days</td>
<td>60%</td>
<td>Could be in-utero infection or intrapartum infection but may still be negative for intrapartum infection</td>
</tr>
<tr>
<td>1 month</td>
<td>95%</td>
<td>Could be in-utero infection or intrapartum infection but almost all of the intrapartum infection should be positive</td>
</tr>
<tr>
<td>4 months</td>
<td>98%</td>
<td>Could be in-utero infection or intrapartum infection</td>
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Laboratory tests to determine infant’s HIV status

- **Anti-HIV** at 12 months of age
  - If anti-HIV negative → “HIV-negative”
  - If anti-HIV positive, could still be maternal antibody → repeat anti-HIV at 18 months of age
  - If anti-HIV positive at 18 months and does not go along with 2 DNA-PCR test results → repeat anti-HIV using non-Ag-Ab test or repeat at 24 months of age
<table>
<thead>
<tr>
<th>Age</th>
<th>Percent negative if HIV-uninfected</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 months</td>
<td>74%</td>
<td>26% not infected but still have maternal antibody</td>
</tr>
<tr>
<td>12 months</td>
<td>96%</td>
<td>4% not infected but still have maternal antibody</td>
</tr>
<tr>
<td>18 months</td>
<td>100%</td>
<td>All HIV-uninfected children should have negative result (reported cases of positive 4th generation ELISA or Ag-Ab test in HIV-uninfected children)</td>
</tr>
<tr>
<td>24 months</td>
<td>100%</td>
<td>All HIV-uninfected children should have negative result</td>
</tr>
</tbody>
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Maternal and infant ARV when there is no ANC

- Pregnant woman
  - AZT 300mg every 3 hrs with single-dose NVP (if delivery is not expected within 2 hrs)
  - AZT/3TC 1 wks after delivery (or give AZT/3TC/LPV/rtv until getting CD4 result)

- Infant
  - AZT syrup 6 wks with single-dose NVP
  - AZT/3TC syrup 4 wks with NVP 2mg/kg/d x 1 wk then 4mg/kg/d x 1 wk
Summary

• All HIV-positive pregnant women should receive 3 drugs antiretroviral regimens
• Regimen selection depends on gestational age, CD4 count, HIV-related symptoms (and probably viral load)
• HIV-exposed infants should receive AZT syrup and cotrimoxazole syrup
• DNA-PCR and anti-HIV testing should be done for all HIV-exposed infants to determine HIV status
• National policy will incorporate the use of HAART for all pregnant women very soon
แนวทางการดูแลหญิงตั้งครรภ์
เพื่อป้องกันการต่ำแหน่งหรือเอ็กซีเวียร์จากแม่สุข
ของสภากาชาดไทย ปี พ.ศ. 2551

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