PMTCT: Risk-based Neonatal Prophylaxis

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Talk Outline

• Introduction
• When is VT risk increased?
• Boosted infant PEP reduces IP risk?
• Which ARV combination?
• Managing increased risk in breastfeeding.....
• Conclusion
PMTCT Evolution In RSA

The National Antenatal Sentinel HIV and Syphilis Prevalence Survey, South Africa 2010
### Perinatal Infant HIV-Exposure and MTCT: Weighted Results by Province and National % (95% CI)

<table>
<thead>
<tr>
<th>Province</th>
<th>Infant HIV-Exposed (95% CI)</th>
<th>MTCT % (95% CI)</th>
<th>Infant HIV-Exposed (95% CI)</th>
<th>MTCT % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Cape</td>
<td>30.0 (26.3-33.7)</td>
<td>4.7 (2.4-7.0)*</td>
<td>32.0 (29.6-35.5)</td>
<td>3.82 (2.1-5.54)</td>
</tr>
<tr>
<td>Free State</td>
<td>31.1 (28.9-33.3)</td>
<td>5.9 (3.8-8.0)</td>
<td>30.9 (28.6-33.3)</td>
<td>3.80 (2.29-5.3)</td>
</tr>
<tr>
<td>Gauteng</td>
<td>30.2 (27.7-32.8)</td>
<td>2.5 (1.5-3.6)</td>
<td>33.1 (29.8-36.4)</td>
<td>2.13 (0.91-3.36)</td>
</tr>
<tr>
<td>KwaZulu Natal</td>
<td>43.9 (39.7-48.0)</td>
<td>2.9 (1.7-4.0)</td>
<td>44.4 (39.8-48.9)</td>
<td>2.10 (0.94-3.26)</td>
</tr>
<tr>
<td>Limpopo</td>
<td>22.6 (20.4-24.8)</td>
<td>3.6 (1.4-5.8)</td>
<td>23.0 (19.9-26.2)</td>
<td>3.06 (1.21-4.91)</td>
</tr>
<tr>
<td>Mpumalanga</td>
<td>36.2 (33.6-38.9)</td>
<td>5.7 (4.1-7.3)</td>
<td>35.6 (33.3-37.8)</td>
<td>3.32 (2.17-4.48)</td>
</tr>
<tr>
<td>Northern Cape</td>
<td>15.6 (13.0-18.3)</td>
<td>1.4 (0.1-3.4)*</td>
<td>15.1 (12.7-17.5)</td>
<td>6.06 (2.48-9.63)*</td>
</tr>
<tr>
<td>Northwest</td>
<td>30.9 (28.6-33.1)</td>
<td>4.4 (2.9-5.9)</td>
<td>30.8 (28.5-33.1)</td>
<td>2.57 (1.13-4.00)</td>
</tr>
<tr>
<td>Western Cape</td>
<td>20.8 (16.8-24.9)</td>
<td>3.9 (1.9-5.8)</td>
<td>17.8 (14.8-20.8)</td>
<td>1.98 (0.65-3.31)</td>
</tr>
<tr>
<td><strong>National</strong></td>
<td><strong>31.4% (30.1-32.6%)</strong></td>
<td><strong>3.5 (2.9-4.1)</strong></td>
<td><strong>32.2% (30.7-33.6%)</strong></td>
<td><strong>2.67 (2.13-3.21)</strong></td>
</tr>
</tbody>
</table>

*Note unstable estimates due to smaller sample size realisation precision is low*
Figure 31: Trends in under-five mortality rates in South Africa since 1998 and the 2015 MDG target

Source: Demographic and Health Survey 1998, Department of Health; Mortality and Causes of Death, Mid-year Population Estimates, Statistics South Africa
Fig. 3.4. Number and percentage of pregnant women living with HIV receiving ARV medicines for PMTCT of HIV in the 21 Global Plan priority countries in the WHO African Region, 2013

- **South Africa**: 200,000 (50%)
- **Nigeria**: 150,000 (77%)
- **Uganda**: 100,000 (75%)
- **United Republic of Tanzania**: 60,000 (73%)
- **Mozambique**: 50,000 (84%)
- **Kenya**: 40,000 (63%)
- **Zambia**: 30,000 (70%)
- **Zimbabwe**: 30,000 (78%)
- **Malawi**: 20,000 (79%)
- **Cameroon**: 15,000 (63%)
- **Ethiopia**: 15,000 (55%)
- **Democratic Republic of Congo**: 12,000 (33%)
- **Côte d’Ivoire**: 12,000 (55%)
- **Angola**: 10,000 (30%)
- **Lesotho**: 10,000 (57%)
- **Ghana**: 10,000 (67%)
- **Chad**: 10,000 (19%)
- **Botswana**: 5,000 (65%)
- **Namibia**: 5,000 (90%)
- **Swaziland**: 5,000 (95%)
- **Burundi**: 5,000 (58%)

- **Total number of pregnant women living with HIV (all needing PMTCT ARVs)**
- **Number of pregnant women living with HIV receiving ARV medicines for PMTCT (options A, B and B+)**

Adapted from WCP DOH

Transmission Rate: W Cape

Better program, coverage and uptake
Reduced MTCT, better mother/infant health and survival
But.....
Sub optimal PMTCT not uncommon
and.....
NVP resistance on the rise

2000: NVP Monotherapy
From 34wk to 28 wk AZT
+Targeted ART (CD4<200).
Infant sdNVP.

2008: Infant sdNVP + AZT
2010: Targeted ART if
CD4<350 or 14 wk AZT.
Infant extended NVP.

2013: Lifelong ART for all.
Infant eNVP.
# METRO WEST Jan-June 2013

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013 Jan-June</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caesarean Section Rate</td>
<td>24.2%</td>
<td>25.3%</td>
<td>27.8%</td>
<td>28%</td>
</tr>
<tr>
<td>Births Before Arrival</td>
<td>3.6%</td>
<td>3.5%</td>
<td>3.2%</td>
<td>2.9%</td>
</tr>
<tr>
<td>No Antenatal care “UNBOOKED”</td>
<td>5.8%</td>
<td>5.9%</td>
<td>5.1%</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

- Thanks to Metro West PPIP Team
- Dr C Nelson, Dr L Dietrich, Dr D Nage and Dr L Jacobs
• 24 unbooked/ no or minimal prelabour ARVs
• 1 Substance abuse (unbooked)
• 2 Substance abuse (one with congenital syphilis; both unbooked)
• 1 Congenital CMV (despite AZT)
• 2 Rebound viraemia (twins NNRTI resistance) – ART many years but alcoholic defaulter
• 1 Maternal TB (pre initiation of ART at 12wks before delivery)
Talk Outline

• Introduction
• **When is VT risk increased?**
  • Boosted infant PEP reduces IP risk?
  • Which ARV combination?
• Managing increased risk in breastfeeding.....
• Conclusion
Low Risk

- Adequate maternal ART
- Good adherence, no resistance
- Good viral control early in pregnancy
- Good viral control by labour and delivery
- No obstetric complications or co-morbidities
- FF or maternal VL control in breastfeeding
- Infant mono-ARV PEP 4-6 weeks only
Timing of HIV Transmission (pre ARVs and non-Breastfeeding)

- Transmission risk is small prior to 28 weeks gestation, rises towards term and peaks during labour and delivery.
- Maternal IP Rx + infant PEP reduce IP risk but not IU risk.
- Infant PEP reduces IP proportion and some early PP risk.
- Boosted infant PEP targets brief period of intense IP risk.

**Figure 2.** Estimated distribution of the dates of transmission.

**Am J Epidemiol 1995; 142:1330-7.**

- sdNVP
- Dual Rx/HAART
- Late IU infection: Birth PCR
- Early ART = early disease control
Timing of HIV Transmission – pre ARV era

Boosted infant PEP decreases IP transmission

4% Transmission of HIV for every 6 months of breast-feeding

Adapted with permission M Besser and G Theron
Increased Risk & Timing

- CD4 < 350c/mL = > 80% of MTCT (IU +IP)
- Inadequate maternal ART (IU +IP)
- VL > 1000cps/mL (IU +IP) or lower if no ART
- Primary HIV in pregnancy (IU)
- Rebound viraemia (IU)
- Comorbidity (syphilis, tuberculosis) (IU)
- PTL + PROM, chorioamnionitis (IP)
- ARV resistance
Risk assessment considerations

• “Non-low risk” vs “high risk”
  – BHIVA: maternal VL > 50cps/mL
  – NIH: minimal prelabour ART, IP ART only, no ART

• Timing of risk (IU, IP, PP?)
  – IP risk may be low if > 4 wks ART suppresses VL by labour
  – VL at time of delivery important

• Resistance (NNRTI, ? others)
“Risk” Precedents in SA Guidelines

• National:
  – 2008 sdNVP + 4 weeks AZT if mother < 4 wks ARVs
  – 2010 National: No concession to risk
  – 2013 STG/PEDL: Birth PCR if BWt <2500g or symptomatic; extend NVP for BF prophylaxis if high risk.

• WCP:
  – 2010 Preterm guideline – risk based early PCR
  – 2013 Risk-based birth PCR (resistance/no prelabour ARVs) and boosted infant PEP (AZT + NVP) clinician discretion.
  – 2014 Birth PCR and AZT/NVP for increased risk

• WHO
  – 2013 – no concession
MMH Protocol (Oct 2013)

• **Maternal factors:**
  – Maternal antiretroviral therapy < 8 weeks
  – Maternal viral load > 1000 copies/ml
  – Maternal viral rebound
  – Maternal comorbidity
  – Maternal substance abuse
  – Incident/recent infection (initial HIV test negative, subsequent tests positive)
  – Adolescent pregnancy (possible perinatally acquired HIV infection, more likely to have problems with follow up)
  – Likely NNRTI resistance

• **Infant factors:**
  – Symptomatic
  – PT delivery regardless of cause and/or LBW infants
  – Abandoned infants (if Alere Determine test or HIV ELISA test positive)
MMH Results: Early HIV PCR Tests

117 neonates had HIV PCR test within 48 hours of birth

9 were confirmed positive (7.7%)
108 were negative (92.3%)

In utero HIV transmission rate = 7.7%
Intra-partum Risk

• Very early PCR test cannot detect transmission during labour and delivery
• PCR negative at <48 hrs/positive after 7 days means IP transmission likely
• Relatively brief IP exposure lends itself to PEP
• Boosted infant PEP further reduces IP MTCT
MMH Results: 6-week HIV PCR tests in infants with negative early HIV PCR test and AZT/NVP PEP

Birth PCR negative: 108

6 week PCR: 75 results found (69%)
- 2 positive (2.7%)
- 73 negative (68%)

6 week PCR: 33 results not found (31%)

S Pillay. SAPA 2014
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Evidence for infant multi-ARV PEP

  – 6wk AZT vs 6wk AZT + 3 doses NVP
  – AZT-alone: 24 IP infections (4.8%)
  – AZT + NVP: 11 IP infections (2.2%; P=0.046)

  – sdNVP vs sdNVP + 1 wk AZT: 12,1% vs 7,7% (p=0,03)

• PEPI Malawi 2008 – 1 wk AZT not enough

• Thai sdNVP add on. Lallemant et al. NEJM 2004
HPTN 040

Proportion with HIV transmission

Zidovudine alone
Zidovudine plus nelfinavir and lamivudine
Zidovudine plus nevirapine

Nielsen Saines NEJM 2012;366: 2368-79
At 14 weeks: sdNVP1wk AZT = 8.4%
Extended 2.8%
When to consider multi-ARV PEP

General Considerations for Choice of Infant Prophylaxis

All HIV-exposed infants should receive postpartum antiretroviral (ARV) drugs to reduce perinatal transmission of HIV. The 6-week neonatal zidovudine chemoprophylaxis regimen is recommended for all HIV-exposed infants.\(^1,2\) Table 9 shows recommended zidovudine dosing based on the status of maternal antepartum ARV regimens. Infants born to mothers who have received standard antepartum and intrapartum ARV prophylaxis and have undetectable viral loads are at very low risk of HIV transmission and should receive the 6-week zidovudine regimen alone.

The risk of transmission is increased when maternal viral load at delivery is high or maternal antepartum and/or intrapartum prophylaxis was not received. Most experts feel that the potential benefit of combining zidovudine infant prophylaxis with additional ARV drugs may exceed the risk of multiple drug exposure to infants born to:

- mothers who received antepartum and intrapartum ARV drugs but who had suboptimal viral suppression at delivery, particularly if delivery was vaginal;
- mothers who received only intrapartum ARV drugs;
- mothers who received neither antepartum nor intrapartum ARV drugs; and
- mothers with known ARV drug-resistant virus.
BHIVA 2012 INFANT PEP

8.1 Infant post-exposure prophylaxis

8.1.1 Zidovudine monotherapy is recommended if maternal VL is <50 HIV RNA copies/mL at 36 weeks’ gestation or thereafter before delivery (or mother delivered by PLCS while on zidovudine monotherapy). Grading: 1C

8.1.2 Infants <72 h old, born to untreated HIV-positive mothers, should immediately initiate three-drug therapy for 4 weeks. Grading: 1C

8.1.3 Three-drug infant therapy is recommended for all circumstances other than Section 8.1.1 where maternal VL at 36 weeks’ gestation/delivery is not <50 HIV RNA copies/mL. Grading: 2C

8.1.4 Neonatal post-exposure prophylaxis (PEP) should be commenced very soon after birth, certainly within 4 h. Grading: 1C

8.1.5 Neonatal PEP should be continued for 4 weeks. Grading: 1C
Neonatal PEP Anomaly

• Standard PEP is for 4 weeks
• Occupational: Risk = 0.3% - multi ARV PEP
• Sexual assault: Risk = ?% - multi ARV PEP
• Intrapartum exposure is relatively brief and comparable to scenarios in which PEP used
• Intrapartum (no ARVs): Risk = 15% - NVP or AZT monotherapy PEP!!!!
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Which ARV Combo?

- BHIVA (AZT, 3TC for 4 wks + NVP for 2 wks)
- NIH (AZT for 6 wks, NVP 3 doses in 1st week)
- SA 2008 (sdNVP+ AZT as per Lallemant 2004)
- Need to consider BF prophylaxis
- Role of genotyping if resistance likely?
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12 hours of labour has the same risk of transmission as 18 months of breastfeeding!!!
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Conclusion

• Significant gains from PMTCT program
• Sub optimal PMTCT still not uncommon
• Address by
  – systems strengthening
  – Improve early maternal ART uptake
• Further improve outcomes by
  – recognition of high risk newborns
  – Boosted infant PEP to reduce IP risk
  – Very early diagnosis
  – Early treatment of IU infection
• Prevention is better than cure
HIV-EXPOSED INFANT

BIRTH/DISCHARGE

Low risk
Infant NVP for 6 weeks irrespective of feeding choice

High risk
Do birth PCR & Give intensified PEP from birth

Do birth PCR
Negative
Continue PEP

Positive
Transition from PEP to ART

If breastfed:
NVP for at least 12 weeks. AZT for 4 weeks.
During BF, continue NVP until maternal VL <1000.

If formula fed:
NVP for 6 weeks. AZT for 4 weeks.

Routine HIV PCR test at 6 weeks

6 WEEKS

Positive
Fast track for ART and continue CPT

Negative

HIV test if clinically indicated

Initiate CPT at 6 weeks

9 MONTHS

If positive
Confirm positive result with HIV PCR test.

Determine® rapid HIV test at 9 months
Also test infants with unknown HIV status

Negative

HIV test 6 weeks after the final breastfeed

18 MONTHS

Rapid HIV test at 18 months

Stop CPT if negative

Infant testing

<9 months:
HIV PCR test

9-17 months:
Determine® rapid HIV test and confirm positive result with HIV PCR test

≥18 months:
Test as per adult testing algorithm

Stop CPT if formula feeding
Continue CPT if breastfeeding

WCP PMTCT Guidelines June 2014