Achieving MDGs 4, 5 & 6 through PMTCT Interventions: Changed guidelines

Vivian Black
1 October 2010
Millennium Developmental Goals

Panel 1: Millennium Development Goals
1. Reduce extreme poverty and hunger by half relative to 1990
2. Achieve universal primary education
3. Promote gender equality and empowerment of women
4. Reduce child mortality by two-thirds relative to 1990
5. Improve maternal health, including reducing maternal mortality by three-quarters relative to 1990
6. Prevent the spread of HIV/AIDS, malaria, and other diseases
7. Ensure environmental sustainability
8. Develop a global partnership for development

Panel 2: UN Millennium Project task forces
1. Poverty and economic development
2. Hunger
3. Education and gender equality
4. Child and maternal health
5. HIV/AIDS, malaria, tuberculosis, and access to essential medicines
6. Environmental sustainability
7. Water and sanitation
8. Improving the lives of slum dwellers
9. Trade
10. Science, technology, and innovation

http://www.childsurvivalcountdown.com/
Paediatric Mortality in South Africa

Most common reason children die:
- HIV,
- Malnutrition and poverty

Paediatric mortality is linked to maternal mortality and morbidity

Saving Children 2009
MDG 5: Maternal Mortality

“with only 11% of the world’s population, Africa accounts for more than half of all maternal and child deaths”

Hogan et al; AIDS 2010
Triennium 2005-2007 there has been a 20.1% increase in the number of deaths compared to 2002-2004

Major cause of death: AIDS (44%), HT (15%), Haemorrhage (12%), Pregnancy related sepsis (9%), Pre-existing disease (6%).
Data from our own unit in Johannesburg

Facility based maternal mortality 2003-2007 was 289/100 000

For HIV positive women it was 6.2 times higher than for negative women 776 vs 124/100 000

Proportion of deaths attributable to HIV was 44%

Access to ART treatment identified as a major barrier

Mortality among HIV-positive postpartum women Zimbabwe

Mortality within 2 yrs after delivery was 54 times higher among HIV infected women with a CD4 < 200 vs. HIV negative women.

Of concern, the increased mortality among HIV infected women persists even with high CD4 cell counts (>500), although to a lesser degree.

No ART use among these women

Hargrove JW. *AIDS* 2010
Mortality and Virologic Outcomes After Access to Antiretroviral Therapy Among a Cohort of HIV-Infected Women Who Received Single-Dose Nevirapine in Lusaka, Zambia

Mortality more than halved once ART became available.

Kuhn L et al. JAIDS 2009
Benefits of ART during pregnancy

3,148 HIV+ mothers infants followed at DREAM centers in Malawi and Mozambique from 7/2005 to 12/2008

ART from 14 weeks if CD4 < 350 cells/mm³

ART from 25 weeks until weaning

Marazzi MC IAS Cape Town 2009
DREAM cohort

Maternal mortality increased with shorter duration of ART, especially with CD4 count < 200 cells/mm$^3$

Overall, 3.2% vs. 0.7% if CD4 < 200, p<0.001

<table>
<thead>
<tr>
<th>No. of days of prenatal ART</th>
<th>none</th>
<th>0-30</th>
<th>31-90</th>
<th>&gt; 90</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal mortality</td>
<td>7.4</td>
<td>2.7</td>
<td>1.2</td>
<td>0.7</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

Marazzi MC et al. 5th IAS, Cape Town 2009
HIV transmission and/or deaths between 1 to 6 months according to pre-delivery length of ART

n= 2,161 infants

| Time (days) | HIV+ | HIV+ & Death |
P|-------------|------|--------------|
| 1-30 days   | 3.6  | 5.7          |
| 31-90       | 1    | 2.9          |
| >90         | 0.3  | 2            |

p = <0.001

p = 0.011
Multivariate analysis of ART duration and Regimen on MTCT in women initiating ART (n=533)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of HAART during pregnancy</td>
<td>0.92</td>
<td>0.87-0.99</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline CD4 cell count (cells/mm(^3))</td>
<td>0.99</td>
<td>0.99-1</td>
<td>0.08</td>
</tr>
<tr>
<td>Regimen NNRTI / PI</td>
<td>0.61</td>
<td>0.28-1.35</td>
<td>0.23</td>
</tr>
</tbody>
</table>
Duration of ART on Transmission

- No maternal prophylaxis: 17.4%
- *Single dose nevirapine prophylaxis: 7.9%
- < 4 weeks of HAART during pregnancy: 9.3%
- 4-16 weeks of HAART during pregnancy: 5.5%
- > 16 to 32 weeks of HAART during pregnancy: 3.5%
- Initiated HAART prior to pregnancy: 0.7%
For Maximal Efficacy of Any Regimen, Need to Start Early in Pregnancy to Prevent *In Utero* Transmission

Even if intervention is 100% effective for IP/PP transmission, still have “residual infection” of 1.6% starting at 28 weeks

Consequences of sdNVP to reduce MTCT
OCTANE: Study Design

**Trial 1**
ART-naïve women, CD4<200, with prior SD NVP exposure ≥6mo before (n=243)

Randomise

NVP + FTC/TDF

Time to Virologic Failure / Death

LPV/RTV + FTC/TDF

**Trial 2**
ART-naïve women, CD4<200, without prior SD NVP exposure (n=502)

Randomise

NVP + FTC/TDF

Time to Virologic Failure / Death

LPV/RTV + FTC/TDF

Primary Outcome

FTC: emtricitabine; TDF: tenofovir
Kaplan Meier Plot for Time to Primary Endpoint (Virologic Failure or Death), Trial 1

<table>
<thead>
<tr>
<th></th>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPV/RTV</td>
<td>120</td>
<td>7% (8)</td>
<td>93% (112)</td>
<td>NA (NA NA NA)</td>
</tr>
<tr>
<td>NVP</td>
<td>123</td>
<td>24% (29)</td>
<td>76% (94)</td>
<td>NA (NA NA)</td>
</tr>
</tbody>
</table>
Mortality and Virologic Outcomes After Access to Antiretroviral Therapy Among a Cohort of HIV-Infected Women Who Received Single-Dose Nevirapine in Lusaka, Zambia

Kuhn L et al. JAIDS 2009
Single-dose tenofovir and emtricitabine for reduction of viral resistance to non-nucleoside reverse transcriptase inhibitor drugs in women given intrapartum nevirapine for perinatal HIV prevention: an open-label randomised trial

# Efficacy of short-course AZT + 3TC to reduce NVP resistance in PMTCT: randomized clinical trial.


<table>
<thead>
<tr>
<th>Study Arm</th>
<th>IU</th>
<th>IP</th>
<th>Cum</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD NVP</td>
<td>10%</td>
<td>1%</td>
<td>12%</td>
</tr>
<tr>
<td>(N=77)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD NVP+</td>
<td>10%</td>
<td>1%</td>
<td>11%</td>
</tr>
<tr>
<td>4d CBV</td>
<td>(N=72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD NVP+</td>
<td>8%</td>
<td>1%</td>
<td>9%</td>
</tr>
<tr>
<td>7d CBV</td>
<td>(N=79)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What about after delivery?
In Breastfeeding Settings, ~40% of All Mother to Child Transmission Can be Attributed to Breastfeeding.

Mofenson 2010
14 Week Extended ARV Prophylaxis Significantly Reduces Postnatal HIV Infection: PEPI Malawi

Kumwenda N et al., NEJM 2008:359:119-29
Ban Study

- 2369 HIV-1–positive, breast-feeding mothers, > 250 cells/mm$^3$ + and their HIV negative infants

- Randomized to maternal ART, infant nevirapine, or no extended postnatal antiretroviral regimen (control group).

- Standard PMTCT regimen sdNVP + 1 week AZT 3TC to all.

- Used Kaplan–Meier method to determine cumulative risk of HIV-1 transmission/death by 28 weeks among infants who were HIV-1– negative at 2 weeks

ARV intervention*

**Mother and Infant**

**Enhanced Control**
- ZDV/3TC sdNVP x1
- ZDV/3TC x 1 wk

**Maternal HAART**
- ZDV/3TC sdNVP x1
- ZDV/3TC x1 wk
- ZDV/3TC/NVP** x 28 wks to mother

**Infant NVP**
- ZDV/3TC sdNVP x1
- ZDV/3TC x1 wk
- NVP x 28 wks to infant

*Exclusive Breastfeeding for 24 weeks with weaning over 4 weeks.
  Weaning food “plumpy nut” provided until week 48
**NVP changed to NFV February 2005 – NFV Changed to LPV/r January 2006
A  HIV-1 Infection in HIV-1–Negative Infants at 2 Weeks

Maternal ARV vs. control, P=0.009
Infant NVP vs. control, P<0.001
Maternal ARV vs. infant NVP, P=0.10

Probability of HIV-1 Infection

Control
Maternal ARV
Infant NVP

Age (wk)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Control</th>
<th>600</th>
<th>558</th>
<th>539</th>
<th>514</th>
<th>480</th>
<th>476</th>
<th>471</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maternal ARV</td>
<td>767</td>
<td>731</td>
<td>715</td>
<td>699</td>
<td>683</td>
<td>679</td>
<td>662</td>
</tr>
<tr>
<td></td>
<td>Infant NVP</td>
<td>785</td>
<td>752</td>
<td>741</td>
<td>727</td>
<td>710</td>
<td>706</td>
<td>687</td>
</tr>
</tbody>
</table>
B  HIV-1 Infection or Death in HIV-1–Negative Infants at 2 Weeks

Maternal ARV vs. control, P=0.02
Infant NVP vs. control, P<0.001
Maternal ARV vs. infant NVP, P=0.09

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Control</th>
<th>603</th>
<th>560</th>
<th>541</th>
<th>516</th>
<th>481</th>
<th>478</th>
<th>471</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal ARV</td>
<td>768</td>
<td>732</td>
<td>716</td>
<td>699</td>
<td>683</td>
<td>680</td>
<td>662</td>
<td></td>
</tr>
<tr>
<td>Infant NVP</td>
<td>786</td>
<td>754</td>
<td>742</td>
<td>728</td>
<td>711</td>
<td>706</td>
<td>687</td>
<td></td>
</tr>
</tbody>
</table>

Ban: Infant Adverse events

Hypersensitivity ~ 2%
560 HIV-1–infected pregnant women, CD4≥200 cells/mm³ from 26 to 34/40 to 6/12

Randomized to either:
+ coformulated ABC, zAZT, and 3TC (NRTI group)
+ lopinavir–ritonavir plus zAZT, 3TC (PI group)

CONTROL:
170 women with CD4+ < 200 cells/mm³ received NVP, AZT, 3TC

Infants received sdNVP and 4 weeks of AZT.
ART Regimens in Pregnancy and Breast Feeding in Botswana

A

Women Breast-Feeding (%)

Weeks Post Partum

--- NRTI group

Protease-inhibitor group

Observational group

ART Regimens in Pregnancy and Breast Feeding in Botswana

Over all HIV transmission 1.1%

8/709 live births by 6 months (95%CI 0.5-2.2)

Including 4 in-utero infections

No difference in transmission between regimens

South African PMTCT Guidelines
2010
Up Date on WHO Guidelines
Similarity in approaches

Lifelong ART for HIV-infected women in need of treatment for their own health, which is also safe and effective in reducing MTCT.

ARV prophylaxis to prevent MTCT during pregnancy, delivery and breastfeeding for HIV-infected women not in need of treatment.

Unified approach to preventing MTCT throughout pregnancy, labour and delivery, postpartum, and the breastfeeding period.

Post natal prophylaxis to allow for safer breast feeding.
<table>
<thead>
<tr>
<th>SA</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women CD4≤350 and or Clinical stage 3 or 4 qualify for life long ART to be initiated ASAP (different for pregnant and non pregnant women)</td>
<td>Pregnant women CD4≤350 and or Clinical stage 3 or 4 qualify for life long ART to be initiated ASAP (same for pregnant and non pregnant women)</td>
</tr>
</tbody>
</table>

**Regimen:**
- **TDF, 3TC, NVP**

**Preferred Regimen:**
- **AZT , 3TC, NNRTI**
  - (alt to AZT=TDF; delay EFV)
<table>
<thead>
<tr>
<th>Women CD4&gt;350 WHO 1 or 2</th>
<th>SA</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT twice daily from 14 weeks gestation</td>
<td>AZT twice daily from 14 weeks gestation</td>
<td></td>
</tr>
<tr>
<td>sdNVP in labour + Truvada</td>
<td>or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + PI/EFV/ABC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sdNVP in labour + AZT 3TC *7d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(AZT &gt; 4 weeks, don’t need NVP/AZT/3TC)</td>
<td></td>
</tr>
</tbody>
</table>
### HIV exposed infants

**SA**

- All to commence on daily NVP from birth to 6 weeks
- If infant is being breast fed and mother not on ART, NVP to continue until 1 week after BF cessation

**WHO**

- All infants being breast fed whose mothers are not on ART should commence NVP from birth until 1 week post BF cessation (minimum 4-6 weeks)
- All other infants either NVP daily for 4/6 weeks
  - OR
  - sdNVP + AZT twice daily 4/6 weeks
Simplified dosing schedule

- Birth Weight < 2,500 gram 10mg/daily
- Birth Weight ≥ 2,500 gram 15mg/daily
- > 6 weeks to 6 months 20mg/daily
- > 6 to 9 months 30mg/daily
- > 9 months to end of BF 40mg/daily
Summary of What is New

Qualification criteria

Timing of initiation

Regimen

Introduction of tail to reduce NVP resistance

Infant PEP duration has increased

Introduction of strategies to reduce HIV transmission through breast feeding
New Policies in SA to improve implementation

**Urgent cases**
- CD4<100
- Stage 4
- Pregnancy

**Decentralization to PHC**

Accreditation of facilities no longer policy but readiness assessment using a new tool.

**Nurse initiated Rx**

**Task Sharing**

**HCT (HIV testing & counselling)**
Praise for revised II PMTCT guidelines

Note that it is only half the key.

The other half lies in service coverage.

Even the most potent interventions will not protect those infants who do not receive them

(Stringer et al. AIDS Conference, Vienna July 2020)
PMTCT Cascade: Most Critical Thing for PMTCT is Number of Women Completing Cascade

P. Barker, WHO Mtg Nov 2008

100 HIV+ mothers

- Attend ANC clinic 92%
- Counseled and tested for HIV, CD4 95%
- Get ARVs (pre- and perinatal) 95%

Enter into program

- 92
- 87
- 82

Missed - no PMTCT

- 8
- 13
- 18

Overall Program Effectiveness (early MTCT)

- sdNVP: 11% tx
- AZT/sdNVP: 7% tx
- HAART: 6.1% tx

sdNVP (8% MTCT): 6.5 infected
AZT/sdNVP (3% MTCT): 2.5 infected
HAART (2% MTCT): 1.6 infected

No ARV (25% MTCT): 4.5 infected
Towards eradicating paediatric HIV