Maternal Health and HIV

Vivian Black
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/
Saving Mother’s Report

• Triennium 2005-2007 there has been a 20.1% increase in the number of deaths compared to 2002-2004

• Major cause of death: AIDS (43.7%), HT (15%), Haemorrhage (12.4%) Pregnancy related sepsis (9%), Pre-existing disease (6%)

4th Report on Confidential Enquiries into Maternal Death in South Africa; 2009
Table 7. Comparison of institutional Maternal Mortality Ratios per disease category

<table>
<thead>
<tr>
<th>Primary Obstetric Cause</th>
<th>2002-2004</th>
<th>2005-2007</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct</td>
<td>77.99</td>
<td>69.95</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>27.72</td>
<td>23.92</td>
<td>&lt;0.01; OR 0.86</td>
</tr>
<tr>
<td>Postpartum haemorrhage</td>
<td>13.82</td>
<td>14.73</td>
<td>NS</td>
</tr>
<tr>
<td>Antepartum haemorrhage</td>
<td>5.69</td>
<td>4.15</td>
<td>NS</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>2.07</td>
<td>2.12</td>
<td>NS</td>
</tr>
<tr>
<td>Abortion</td>
<td>5.03</td>
<td>5.23</td>
<td>NS</td>
</tr>
<tr>
<td>Pregnancy Related Sepsis</td>
<td>12.09</td>
<td>8.58</td>
<td>&lt;0.0001; OR 0.80</td>
</tr>
<tr>
<td>Anaesthetic related</td>
<td>4.02</td>
<td>4.11</td>
<td>NS</td>
</tr>
<tr>
<td>Embolism</td>
<td>2.82</td>
<td>2.19</td>
<td>NS</td>
</tr>
<tr>
<td>Acute collapse</td>
<td>4.72</td>
<td>4.92</td>
<td>NS</td>
</tr>
<tr>
<td>Indirect</td>
<td>63.12</td>
<td>75.61</td>
<td></td>
</tr>
<tr>
<td>Non pregnancy related Infections</td>
<td>55.00</td>
<td>66.49</td>
<td>&lt;0.000; OR 1.21</td>
</tr>
<tr>
<td>AIDS</td>
<td>29.22</td>
<td>35.19</td>
<td></td>
</tr>
<tr>
<td>Pre-existing Maternal Disease</td>
<td>8.12</td>
<td>9.11</td>
<td>NS</td>
</tr>
<tr>
<td>Unknown</td>
<td>4.37</td>
<td>6.69</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>145.48</td>
<td>152.25</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table 10. Distribution of causes of non pregnancy related infections in relation to their HIV status

<table>
<thead>
<tr>
<th>Sub categories</th>
<th>HIV +</th>
<th>HIV -</th>
<th>Unk</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>224</td>
<td>21</td>
<td>148</td>
<td>393</td>
</tr>
<tr>
<td>AIDS</td>
<td>891</td>
<td>1</td>
<td>23</td>
<td>915</td>
</tr>
<tr>
<td>TB</td>
<td>138</td>
<td>20</td>
<td>71</td>
<td>229</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>UTI</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Malaria</td>
<td>3</td>
<td>2</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Meningitis</td>
<td>56</td>
<td>6</td>
<td>44</td>
<td>106</td>
</tr>
<tr>
<td>Other</td>
<td>34</td>
<td>5</td>
<td>27</td>
<td>66</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1347</td>
<td>55</td>
<td>327</td>
<td>1729</td>
</tr>
</tbody>
</table>
Scale of the problem
Antenatal HIV prevalence surveys
South Africa 1990-2007

www.doh.gov.za/docs/reports/hivreport.html
Antenatal HIV prevalence surveys
South Africa 1990-2007

>1 million pregnancies in 2006

Actuarial Society of SA, UNAIDS,
National DoH
Question of Scale
Number of HIV infected pregnant women / year

- United States: < 7000
- Namibia: 7600
- Botswana: 14000
- Europe: 15000
- Kenya: 100000
- South Africa: 300000

Adapted from McIntyre
HIV Epidemic

- 5.5/47 million HIV infected
- Majority in reproductive age group.
- >50% women.
- Most unaware they are HIV positive!
- Only test when sick
- Treatment gap
Opportunity of Antenatal Services
Using ANC to fight against HIV

- 94% of pregnant women attend ANC care
- Find healthy HIV infected women
  - stage HIV infected pregnant women;
  - *initiate them on HAART*
  - Improve Referral systems
  - Find partners, other children infected with HIV
HIV-infected pregnant women receiving antiretroviral prophylaxis, 2004–2007

Number of HIV-positive pregnant women receiving antiretrovirals

% of HIV-positive pregnant women receiving antiretrovirals
Managing Pregnant Women on HAART

• What CD4 cell count should we initiate pregnant women onto HAART?
• What regimen should we use?
• What strategy for initiation is best?
• What are the effects of HAART on pregnancy?
• What are the effects on transmission?
• What impacts transmission when HAART is used?
• Does this have an impact on infant / maternal mortality?
• If HAART is used for PMTCT is there a risk to mother?
What CD4 cell count should we initiate women on HAART?
Numerous guidelines advocate HAART for all pregnant women regardless of the CD4 cell count.

**However:** Over 80% of maternal deaths, and over 80% of perinatal transmissions in pregnant women with CD4 counts < 350 cell/mm$^3$

Over 50% of maternal deaths in women with CD4 counts < 200 cells/mm$^3$
What regimen should we use?
Don’t use single dose Nevirapine

Octane Study

• 7 African countries

• 241 HIV+ women, history of sdNVP at least 6 months earlier randomized to receive either:

  NVP+TDF+FTC (n = 121) or LPV/r+TDF+FTC (n = 120)

• Primary endpoint virologic failure or death:

(Lockman S et al. 16th CROI, Montreal, 2009. Abs 94LB )
### OCTANE cont...

#### Virologic failure:

<table>
<thead>
<tr>
<th>Time since sdNVP</th>
<th>NVP arm</th>
<th>LPV/r arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 to &lt; 12 months</td>
<td>37%</td>
<td>3%</td>
</tr>
<tr>
<td>12 to &lt; 24 months</td>
<td>26%</td>
<td>12%</td>
</tr>
<tr>
<td>&gt; 24 months</td>
<td>12%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Difference between the 2 arms decreased with time since last sdNVP*

(Lockman S et al. 16th CROI, Montreal, 2009)
Risk of Congenital Abnormality

- Evidence from trials, cohorts and surveillance studies of ART use in pregnancy – estimated 2-3% prevalence of birth defects
- Similar to that seen in the general population
- No pattern of birth defects suggestive of a common aetiology seen

Antiretroviral Registry Update

- 10,405 pregnancies evaluated
- No increase in the prevalence of birth defects following **first trimester** ARV exposure compared to general population
- Sufficient numbers of first trimester exposure to confirm no increased birth defects from the following drugs:
  - Lamivudine, Zidovudine, Abacavir, Stavudine, Tenofavir Emtricitabine
  - Nevirapine, Efavirenz
  - Lopinavir/ritonavir, Ritonavir,
  - Nelfinavir Indinavir Atazanavir

http://www.apregistry.
Antiretroviral Registry Update

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  - Nevirapine, Efavirenz
  - Lopinavir/ritonavir, Ritonavir, Nelfinavir, Indinavir, Atazanavir

http://www.apregistry.
What strategy for initiation is best?
Access to HAART among pregnant women

3 service models evaluated

- ANC + ARV services >1 km apart
- ANC + ARV same premise – different building
- Same facility, dedicated day

Stinson, K et al. 2008
Access to HAART among pregnant women

Among 516 HAART-eligible pregnant women,

- 51% successfully initiated treatment before delivery.
- 27% received PMTCT prophylaxis.
- 22% of women who were HAART-eligible had no record of receiving any antenatal intervention.

- No difference between referral models.

Stinson, K et al. 2008
Integrating HAART into Antenatal Clinics

Established a HAART clinic in an antenatal clinic (ANC ARV) in late 2004.

Expanded programme to Secondary and Primary Health Care Facilities

Rapid initiation of pregnant women with AIDS/advanced HIV onto ART including close monitoring & support.

Black V, R Hoffman et al. JAIDS 2008
Number of Women Accessing HAART in Antenatal Clinics in the Inner City and Proportion of Known HIV Status at Delivery

Estimated need: 807 women /yr

Number initiated onto ART at Charlotte Maxeke Johannesburg Hospital
Number initiated onto ART at Primary Health Clinics
Percent women of known HIV status

Black et al Jour Obs & Gyn. 2009
Outcome of integrated services

- Within the ANC ARV programme, initiating pregnant women on HAART was feasible, safe, and effective.
- Advanced gestational stage at treatment initiation, and loss to follow-up emerge as important challenges in this population.
- Strategies are needed to facilitate earlier treatment of HIV-infected pregnant women with advanced disease.
What are the effects of HAART on pregnancy?
Reassuring data

- 400 HIV infected women receiving antiretroviral therapy, adverse events are uncommon (<5%)
  Am J Obstet Gynecol 2004 Feb;190(2):506-16

ANC ARV, treated over 1200 pregnant women with ARVs. Feasible, safe & effective

CROI 2008
Pregnancy outcomes on ART

European multicentered study HAART
Prematurity increased (OR 2.6) with PIs (OR 1.8) with non PIs
AIDS 2000;14:2913

American WITS
Small increase maternal complications including:
- anaemia
- gestational diabetes
- preterm deliver
J Aquir Immune Defic Syndr 2005;38:449

American multicentered study with HAART
Increased LBW with PIs (OR 3.6)
No increase in prematurity
N Eng J Med 2002;346:1863
Meta-analysis was performed

14 studies were included (1998-2006)
ART during pregnancy did not increase the risk of premature delivery overall.
Treatment initiated prior to conception or in the 1\textsuperscript{st} trimester were associated with a slightly increased risk of prematurity.

But....
- Study done in Brazil; 1996 to 2006
- N = 696 HIV+ pregnant women

<table>
<thead>
<tr>
<th></th>
<th>Preconception HAART</th>
<th>Post conception HAART</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBW</td>
<td>33.3%</td>
<td>16.5%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>PTD</td>
<td>26.3%</td>
<td>17.7%</td>
<td>p=0.09</td>
</tr>
</tbody>
</table>

(Machado ES, Sex Transm Infect. 2009;85(2):82-87)
Infant outcomes in women with advanced HIV disease exposed and unexposed to HAART Johannesburg

1397 on HAART vs. 233 no HAART

HAART exposure to any regimen was associated with **pre term birth** (34-37 weeks)
More marked for HAART-exposure before 28 weeks gestation.

Low Birth Weight was not associated with HAART-exposure

Van der Merwe K et al IAS 2009
What are the effects on transmission?
Transmission among women on / not on HAART

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>Transmission rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conceived on ART</td>
<td>1/140</td>
<td>0.7%</td>
</tr>
<tr>
<td>ART initiated in Pregnancy</td>
<td>42/734</td>
<td>5.7%</td>
</tr>
<tr>
<td>CD4 &gt;250 with sdNVP</td>
<td>121/1534</td>
<td>7.4%</td>
</tr>
<tr>
<td>No ART</td>
<td>4/23</td>
<td>17.4%</td>
</tr>
</tbody>
</table>

Hoffman, Black et al IAS 2009
Maternal HAART Duration is Predictive of Infant HIV Infection N= 734

Hoffman, Black et al IAS 2009
HIV transmission and/or deaths between 1 to 6 months according to pre-delivery length of HAART

n= 2,161 infants

<table>
<thead>
<tr>
<th></th>
<th>1-30 days</th>
<th>31-90</th>
<th>&gt;90</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+</td>
<td>3.6</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>HIV+ &amp; Death</td>
<td>5.7</td>
<td>2.9</td>
<td>2</td>
</tr>
</tbody>
</table>

p = <0.001
p = 0.011

Dream cohort. IAS Cape Town 2009
## Rates of MTCT

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Conceived on ART</th>
<th>ART initiated in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lop/Rit (401)</td>
<td>4% (1/25)</td>
<td>5.3% (20/376)</td>
</tr>
<tr>
<td>NVP (356)</td>
<td>0% (0/40)</td>
<td>6.3% (20/316)</td>
</tr>
<tr>
<td>EFV (117)</td>
<td>0% (0/75)</td>
<td>4.8% (2/42)</td>
</tr>
<tr>
<td>Total MTCT (874)</td>
<td>0.7% (1/140)</td>
<td>5.7% (42/734)</td>
</tr>
</tbody>
</table>

CI: 0.02-3.8, 4.2-7.7

Hoffman, Black et al IAS 2009
Influence of HAART on risk factors for vertical HIV transmission

A Garcia-Tejedor 2009 Acta Obs et Gynec
Male partner

Kenya study, 1999 – 2003
465 HIV+ pregnant women, and infants followed up until 12 months postpartum

After adjusting for maternal VL and breast milk exposure, male partner attendance also associated with:

~ 50% reduction in HIV transmission risk at 1yr postpartum
~ 60% greater infant HIV-free survival, and
2.5-fold higher survival in HIV-uninfected children

(Aluisio A et al. IAS, Cape Town 2009, Abs TUAC105)
Does HAART in pregnancy have an impact on maternal/infant mortality?
DREAM cohort

- Malawi and Mozambique; July 2005 to December 2008
- 3,273 HIV+ pregnant women initiated on HAART
- NVP-based HAART from 14 weeks if eligible for own health - CD4 < 350
- Or from 25 weeks until 6 months postpartum if CD4 > 350

Assessed infant HIV transmission and death at 1 month, and maternal mortality based on duration of prenatal HAART

(Marazzi MC et al. 5th IAS, Cape Town July 2009)
DREAM cohort results

- Infant HIV infection and death at 1 month:

<table>
<thead>
<tr>
<th>Baseline CD4</th>
<th>Pre delivery HAART</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 350</td>
<td>&lt;= 30 days</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>&gt; 30 days</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>1.7</td>
</tr>
<tr>
<td>&gt;= 350</td>
<td>&lt;= 30 days</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>&gt; 30 days</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0.7</td>
</tr>
</tbody>
</table>

(Marazzi MC et al. 5th IAS, Cape Town July 2009)
DREAM cohort results

- Maternal mortality increased with shorter duration of HAART, especially with CD4 count < 200 cells/mm³
- Overall, 3.2% vs. 0.7% if CD4 < 200, p<0.001

<table>
<thead>
<tr>
<th>No. of days of prenatal HAART</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 July 2009)
Facility based Maternal Mortality
CMJAH 2003-2007

There were 106 maternal deaths (excl 2 incidental)
No change in maternal mortality over time
Among 76 (72%) women tested, 78% were HIV infected.
The median CD4 cell count was 72cells/mm3 (IQR=29-194 cells/mm3)

BUT

Only 60% of HIV positive women (30/50)
Only two women with AIDS had initiated HAART.
If HAART is used for PMTCT is there a risk to the mother?
HAART for PMTCT

• HAART for PMTCT standard in resource-rich countries
• Practice is to stop Rx post-delivery – concern expressed about viral rebound syndrome
• Rx restarted when indicated for own health – concern about later response to Rx reinitiation
HAART for PMTCT

- Brazil, 2000 to 2005
- N = 75
- Median baseline CD4 count 573
- Prophylaxis started after 26.6 weeks of gestation in 75% of cases
- 24.5% CD4 increase over baseline with prophylaxis

HAART for PMTCT

• Postnatal withdrawal of Rx not associated with immediate significant viral rebound or drop in CD4 count
• Mean time for CD4 count to drop below 300 was 3.5 yrs
• Reinitiation of HAART not associated with an increased risk of virologic failure

Challenges in managing pregnant women with HAART
The PEARL study

• To assess PMTCT coverage
• April 2007 to October 2008
• 43 sites in Cameroon, Cote d’Ivoire, South Africa and Zambia
• All site used sdNVP, with or without ZDV, or NVP-based HAART
• N (cord blood specimens) = 29 095
• 1° outcome – PMTCT coverage = detectable NVP in HIV+ specimens, and recorded infant NVP ingestion

(Coetze D et al. IAS, Cape Town, July 2009)
The PEARL study

- 448 seropositive deliveries in the Western Cape
- 26% had no drugs detected

Reasons for no coverage

<table>
<thead>
<tr>
<th>HIV test not offered</th>
<th>Testing declined</th>
<th>HIV+ results not given</th>
<th>NVP not dispensed</th>
<th>Mother non adherent</th>
<th>Infant not dosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>16%</td>
<td>6%</td>
<td>13%</td>
<td>7%</td>
<td>27%</td>
<td>15%</td>
</tr>
</tbody>
</table>

(Coetzee D et al. IAS, Cape Town, July 2009)
Number and proportion of new pregnant women who had an HIV test in relation to counsellor remuneration in three antenatal clinics March 2007 - February 2008

Woolman S et al. SAJHR 2009
## Rapid HIV test performance

<table>
<thead>
<tr>
<th>Category</th>
<th>First Response</th>
<th>Standard diagnostic</th>
<th>Pareekshak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>271</td>
<td>42</td>
<td>313</td>
</tr>
<tr>
<td>Positive</td>
<td>69</td>
<td>7</td>
<td>74</td>
</tr>
<tr>
<td>False negative</td>
<td>4</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>94.5 (CI:85.8-98.2)</td>
<td>87.5 (CI:46.7-99.3)</td>
<td>90.2 (CI:81.2-95.4)</td>
</tr>
<tr>
<td>Specificity</td>
<td>100 (CI:97.6-100)</td>
<td>100 (CI:87.7-100)</td>
<td>100 (CI:98-100)</td>
</tr>
</tbody>
</table>

Black, von Mollendorf et al IAS 2009
Something else to consider...
Fertility and HIV: HIV infected women are getting pregnant

• Survey reported that 80% of HIV affected couples (US) who had previously conceived had engaged in unprotected intercourse to achieve pregnancy
• Three studies of unintended pregnancies in HIV infected women in sSA
  – 84% among PMTCT clients in South Africa
  – 51% among women in Cote d’Ivoire
  – 99% among women in an ART program in Uganda

Klein J Obstet Gynecol 2003
Rochat et al; JAMA2006
Desgrées-du-Lou et al., Int J STD AIDS 2002
Smart, T. Aidsmap. 2006.
HIV infected “couples” want children

- Studies above show benefit of early HAART
- Low risk of transmission to infant
- High risk of transmission if they do not engage with health sector…
Women’s vulnerability to infection: Pregnancy

Pregnancy and HIV acquisition

- Rakai: 2188 HIV–ve pregnant women, compared to 8473 non-pregnant women. Adjusted incidence rate ratio of HIV acquisition 2·16 (95%CI 1·39–3·37) during pregnancy. Gray R 2005


- Johannesburg: 25% reported multiple partners during pregnancy. Macphail C personal communication 2007

- Universally, condom use decreases in pregnancy.
Acknowledgements

- PEPFAR
- USAID
- Department of Obstetrics and Gynaecology, University of Witwatersrand
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- ECHO
- Louise Kuhn and Coceka Manyani for slides
- National and Gauteng Department of Health
- Risa Hoffman, Helen Rees, Karin van der Merwe, Francois Venter and Matthew Chersich