Pediatric HIV/AIDS – Issues and Challenges in a resource-constrained setting

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Relationship of VL & Time to AIDS

VL correlates with reductions in MTCT of HIV

1: European Collaborative Study. *Clin Infect Dis.* 2005
5: Sax PE. *AIDS Clin Care.* 1999
8: John GC, et al. *JID.* 2001
13: Kirchner JT. *Am Fam Physic.* 1999
15: Garcia PM, et al. *NEJM.* 1999
16: Mock PA, et al. *AIDS.* 1999
Conquering MTCT of HIV in the richer nations

- Reducing maternal viral load with antiretroviral therapy (ART) radically reduced transmission
  - ACTG 076, long course ZDV, 25% → 8%
  - HIVNET 012, single dose NVP, → 13%
  - Thai-Harvard, short course ZDV + NVP → 4%
  - HAART → <2%

- HIV testing became routine in antenatal care

Estimated Number of Perinatally Acquired AIDS Cases, by Year of Diagnosis, 1985-2003—United States

Note: Data adjusted for reporting delays and for estimated proportional redistribution of cases in persons initially reported without an identified risk factor.
Spread of HIV in sub-Saharan Africa, 1984 to 1999

Estimated percentage of adults (15–49) infected with HIV

- **20.0% – 36.0%**
- **10.0% – 20.0%**
- **5.0% – 10.0%**
- **1.0% – 5.0%**
- **0.0% – 1.0%**
- **trend data unavailable outside region**
Capital city of Lusaka:
Births/year >50,000/yr
Infant mortality >100/K live births
Maternal mort. 800/100,000
Per cap income ≈$1/person/day
ANC HIV prevalence 24%

Size: Zambia ≈ Texas
pop. ≈ 10.2 M, >40% urban
People living on < US$1 a day

More Affordable Prices:
Annual cost per person for triple ART in Africa

$12,000
$10,000
$8,000
$6,000
$4,000
$2,000
$0

1991 1993 1995 1997 1999 2001 2003

Clinton Foundation
Negotiated prices
12/2004

≈US$151/yr

Ref: UNAIDS

Controversies

- Despite the relative simplicity of single dose NVP for mother and for baby to cut HIV transmission in half from mother to infant, there are many issues of controversy.
- Let us review a number of these....
Controversy 1: Was the HIVNET 012 trial valid?

- **Nevirapine (NVP) for PMTCT:** VCT & pill to HIV+ mother at the onset of labor and one dose of syrup to the baby soon after birth

- Reduced transmission by **49%** compared to very short-course zidovudine (ZDV) in Uganda

- Methods & quality of Ugandan trial exonerated by IOM in 2005

Controversy 2: Is NVP for PMTCT second class care?

- Because NVP causes viral drug resistance, there is opposition to its single dose use.

- 1997 N Engl J Med debates on efficacy

- Poor infrastructures and resource limitations suggest that coverage is enhanced by simplicity.
<table>
<thead>
<tr>
<th>Whither NVP?</th>
<th>NVP advantages</th>
<th>NVP disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effective</td>
<td>Still only protects 50% of infants</td>
</tr>
<tr>
<td></td>
<td>Safe</td>
<td>&gt;75% NVP resistance levels</td>
</tr>
<tr>
<td></td>
<td>“Simple”</td>
<td>May compromise efficacy of NNTRIs for 2nd pregnancies</td>
</tr>
<tr>
<td></td>
<td>Convenient</td>
<td>May compromise efficacy of HAART for women if NNRTI included</td>
</tr>
<tr>
<td></td>
<td>Affordable</td>
<td>Free from BI through the Axios Foundation in Ireland</td>
</tr>
</tbody>
</table>
Controversy 3: NVP coverage

Pregnant, HIV+ Women

Offered Intervention

Uptake Intervention

Adhere to Intervention

Baby gets NVP soon after delivery

i.e., women have access to ANC

i.e., have a VCT/NVP program

i.e., intervention is accepted

i.e., intervention is successful

i.e., post-partum service gives NVP

Refs (Stringer JS, Sinkala M, et al):

*JAIDS* 2000; 24: 369.
*Lancet* 2001; 358:1611.
*AIDS* 2003; 17: 1659.
*Lancet* 2003; 362:667; and 1850.
*JAIDS* 2004; 35: 60.
*AIDS* 2005; 19;1309.

Only 30% of Lusaka eligibles in 2003 → 40% by 2004
10,384 Women Gave Birth to Live Infants in Public Sector Facilities

- 66 Clotted Specimen
- 74 Insufficient Specimen Volume
- 17 Cord Avulsions
- 1 Fetal Anomaly
- 4 Retained Placentas
- 10 Unspecified Reasons

10,194 Specimens Obtained 98%

- 653 ANC Outside Lusaka
- 733 ANC at Private Facility
- 65 No ANC

8,787 Received ANC at Facility Offering PMTCT Services 86%

- 6,530 Cord Blood HIV Negative

2,257 Cord Blood HIV Positive 26%

Attrition Cascade in 8787 Surveyed Women

REF: Stringer JS et al. AIDS 2005; 19(12):130
Population NVP coverage and reasons for failed coverage among 2257 cord blood seropositive mothers and infants

- Received both mother and infant doses (n=675; 30%)
- Not offered testing (n=403; 18%)
- Refused testing (n=604; 27%)
- Infant not dosed at discharge (n=76; 3%)
- Did not ingest NVP (i.e. non-adherence; n=361; 16%)
- Given HIV negative result in ANC (seroconverters and clerical errors, n=134; 6%)
- Did not collect test result and/or NVP (n=4; <1%)

REF: Stringer J
AIDS 2005; 19(11)
Controversies 3, 4, 5, 6: Strategies for increasing coverage

- If VCT a barrier for women to accept life-saving NPV for their infants, what about universal NVP in high prevalence areas?
  - Our clinical trial showed increased uptake/decreased adherence with universal (vs. targeted) screening

- Why don’t we test in labor, offering NVP to seropositives?
  - Karen Megazzini trial in Zambia now completed
  - This is the UNICEF/NACO standard in India!

- After VCT, what about offering NVP to seropositives and to those who refused testing?

- What about VCT in ANC and universal NVP to persons with unknown status at labor?
Enrollment Scheme

Targeted

HIV counseling
↓
HIV testing
↓
HIV positive women
offered enrollment

Universal

HIV counseling
↓
HIV testing
×
All women offered enrollment
Where do we take PMTCT?

- First, global coverage is poor; population coverage must be increased

- Second, we must consider innovative strategies
  - Consider VCT even during labor with labor room NVP administration
  - Consider dosing even if status is unknown in high prevalence settings (*Lancet* 2003; 362:1850 vs. alternative view in *Bull WHO* 2005; 83:224)


- Finally, HAART, to reduce HIV drug resistance, if population coverage is not compromised.
Controversy 7: Are vertical programs the way to go with PMTCT?

- Current study of ancillary benefits of PMTCT (using syphilis as marker)
- Nurse midwife training, over 330 in Lusaka
- Upgraded infrastructure, staffing, training, supplies, labs, drug logistics
- The “numbers” game → volume vs. quality, vertical vs. horizontal
Controversy 8: What about other risk factors for perinatal transmission?

- Breastfeeding
  - Exclusive BF, rapid weaning?
  - Replacement feeding if water is contaminated and poverty blocks formula access?

- Other risk factors
  - Prematurity and chorioamnionitis
Method of Infant Feeding and HIV Transmission in Breastfeeding Children


<table>
<thead>
<tr>
<th>Infant Age</th>
<th>Never Breastfed (N=157)</th>
<th>Exclusive Breastfed (N=118)</th>
<th>Mixed Feeding (N=276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Day</td>
<td>8%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>6 Mos</td>
<td>19%</td>
<td>19%</td>
<td>26%</td>
</tr>
<tr>
<td>15 Mos</td>
<td>19%</td>
<td>25%</td>
<td>36%</td>
</tr>
</tbody>
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At 6 months:
- Exclusive vs Mixed: 0.6 (0.3-1.0)
- Exclusive vs Never: 1.2 (0.6-2.2)
HIV TRANSMISSION RATE BY GESTATIONAL AGE

European Collaborative Study
Lancet, April 25, 1992
Can simple antibiotics to reduce maternal bacterial infection during pregnancy reduce perinatal HIV transmission, and, perhaps, preterm birth?

Randomization after VCT

Active
- Metronidazole + Erythromycin
- Metronidazole + Ampicillin

Placebo
- Matched Placebo

2nd Trimester Delivery
- Matched Placebo

Background Ref: Goldenberg RL et al. Lancet 1998
Bacterial Infection and HIV Transmission

It didn’t work: Results of first ~1500 women as per Data Safety and Monitoring Committee (DSMB) report

- Antibiotics group = 19% HIV+
- Placebo group = 15% HIV+

...therefore the trial was stopped early (Feb. 2003) and declared definitive for its negative result
Controversy 9: Why save infant lives when you don’t save the parents or siblings?

- Call to Action
- MTCT-Plus
- PEPFAR and Global Fund to Fight AIDS, Tuberculosis, and Malaria
Call to Action and President’s Emergency Plan for AIDS Relief (PEPFAR)

We offer VCT/NVP to all 45,000 pregnant women in 27 Lusaka ANC and have put >22,000 patients on ART in Zambia in <2 years (2003-2005). PMTCT and ART can be done quickly, even in a resource-limited setting.

Controversy 10: Why are we not doing better with Pediatrics Care and Treatment?

- VCT opportunities for children
  - Often depend on the testing of the parents
  - Lack of family-centered care programs
- Lack of suitable drug preparations
  - Liquids more costly than pills
  - Debate regarding utility of pills vs. liquids
- Few trained practitioners expert in pediatric HIV care and treatment
Pediatric care and treatment

- In the context of family care, when possible
- Special attention to orphans
- Adolescent issues: both long-term survivors and newly acquired infection
  - Index of suspicion for VCT
  - Special care and social support needs
- Use of dual NRTI and NNRTI as first line regimen
  - 3TC, d4T, NVP or EFV
  - 3TC, ZDV, NVP or EFV
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