Updated Prevention of Mother-to-Child Transmission of HIV: A Global Challenge

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The first cases of unusual immune deficiency are identified among gay men in the USA.

In Africa, a heterosexual AIDS epidemic is revealed.

The Human Immunodeficiency Virus (HIV) is identified as the cause of AIDS.

Acquired Immunodeficiency Syndrome (AIDS) is defined for the first time.

Rock Hudson becomes the first public figure to disclose he has AIDS.

At least one case of HIV/AIDS has been reported from each region of the world.

In the USA, the first HIV antibody test is approved by the Food and Drug Administration and HIV screening of blood donations starts.

The first therapy for AIDS - azidothymidine (AZT) - is approved for use in the USA.

In 1991-1993, HIV prevalence in young pregnant women in Uganda begins to decrease, the first major downturn in a developing country.

The World Health Organization (WHO) launches the Special Programme on AIDS.

Highly Active Antiretroviral Therapy (HAART) is discussed for the first time.

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UNAIDS is created.

The UN Security Council discusses HIV/AIDS for the first time.

The UN Secretary-General Kofi Annan maps a plan of action, and calls for the creation of a global fund on AIDS and health.

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PERINATAL HIV TRANSMISSION

- **Major advances**
- Increased knowledge of risk factors associated with transmission
- Reduction of perinatal transmission by 67% by use of ZDV mother / infant (ACTG 076)
- Shorten course ZDV in mother. Thai study 50% reduction.
- Simple cheap regimens NEV in mother /infant IP & PP HIVNET 012 reduce transmission by 50%
- Multi drug regimens reduce transmission to < 2%
- Recent efficacy of 6 week NVP prophylaxis in infants reduces BFT
- World wide implications
Perinatal HIV-1 Infection

- The majority of pediatric HIV infection occurs from maternal-fetal transmission
- Transmission rates vary by population and geographic area
  - 13% Europe
  - 40% Africa
  - 25%-30% USA overall without treatment
- Heterosexual transmission to women is now the most common route
- As number of women HIV-infected increases perinatal infection will also increase
Global Challenges

- Perinatal HIV transmission - major problem worldwide.
- Approaches must be feasible, effective, and affordable.
- Approaches may differ by country and population.
- Development of an effective HIV vaccine is still the major hope and goal for the future.
- Interim plans are focused on reduction of breast feeding transmission and childhood mortality in infants who are weaned.
This is a story about AIDS in Africa.
Look at the pictures.
Read the words.
And then try not to care.

Number of Cases (thousands)

Quarter-Year

Number of Cases

Heterosexual contact
IDU
Pediatric cases
Perinatal HIV-1: What Do We Know Now?

**In Utero**
- HIV in fetal tissues
- Early fetal loss

**Intrapartum**
- Virus/immunological patterns
- Discordant twin
- C-section/blood exposure
- Ruptured membranes

**Breast Feeding**
- HIV in milk
- Seroconverting mothers
- Established inf. 14%

**Infected Live Born Infants**
- 30 - 50% positive virus birth
- 50 - 70% negative virus birth - presumed intrapartum
HIV-1 DNA PCR
Relative Contribution of Intrauterine and Intrapartum Transmission
Dunn et al., AIDS ‘95

• Analysis of 271 HIV-infected infants
  - HIV DNA PCR
    *38% (90% CI 29-46) < 48 hrs
    93% (90% CI 76-97) 14 days
    96% (90% CI 89-98) 28 days

*In utero
Plasma HIV-1 RNA Levels at Birth in Infants of Infected Mothers

![Graph showing plasma HIV-1 RNA levels at birth in infants of infected mothers. The graph displays the levels in logarithmic scale, with categories for in utero, intrapartum, and uninfected. The labels for in utero, intrapartum, and uninfected are represented by different symbols: ○ for rapid, ◦ for intermediate, and ● for slow.]
### Potential Factors Influencing Perinatal Transmission of HIV

<table>
<thead>
<tr>
<th><strong>Viral</strong></th>
<th><strong>Maternal</strong></th>
<th><strong>Fetal/Placental</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Virus load (cell ass./cell free)</td>
<td>- Clinical advanced disease</td>
<td>- Prematurity</td>
</tr>
<tr>
<td>- Phenotype (SI, tropism)</td>
<td>- Primary HIV infection</td>
<td>- Chorioamnionitis</td>
</tr>
<tr>
<td>- Genotype</td>
<td>- Co-infection</td>
<td>- Infant host-immune response</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Immune</strong></th>
<th><strong>Obstetrical Events</strong></th>
<th><strong>Timing of Infection</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Decreased CD4 count</td>
<td>- Twins-first born</td>
<td>- Twins-first born</td>
</tr>
<tr>
<td>- Humoral (NAb, ADCC/ gp120 V3 loop Ab, other)</td>
<td>- Obstetrical Events</td>
<td>- Obstetrical Events</td>
</tr>
<tr>
<td>- Cell mediated (CTL, CD8 supression)</td>
<td></td>
<td>- Timing of Infection</td>
</tr>
</tbody>
</table>

- Mucosal immunity
What Do We Know Now?

- Risk factors - Maternal
  - Clinical disease status
  - Primary Infection
  - Immune suppression - CD4 / CD8 cell counts
  - Humoral immunity - Auto-Neutralizing AB
  - Virus load critical factor
  - Virus phenotype – (SI / NSI ) CXCR4/CCR5
  - OB factors - C-section - Prolonged ruptured membranes - infant exposure to blood - Chorioamnionitis
  - Maternal drug us
  - Duration of breast feeding, mixed feeding mastitis
In Utero Transmission

- Maternal virus load cell-associated, cell-free
- Neutralizing antibody
- CD4 count / cell-mediated immunity
- Virus phenotype / tropism

- Placental breaks
- Maternal-fetal transfusion
- HIV or other infection of placenta
- Fetal loss
Intrapartum Transmission

- Maternal virus load
  - blood (cell-associated, cell-free)
  - cervicovaginal secretions
- Duration of ruptured membranes
- Infant exposure to blood
  - mucous membranes, swallowing

- Delivery mode-vaginal vs. c-section
- Trauma
- Maternal-fetal transfusion
- Placenta - abruption
  - chorioamnionitis
  - co-infections
Breastfeeding Transmission

- Breakdown of skin barrier
- Intercurrent infections (mastitis)
- Maternal plasma/milk viral load
- Primary infection in mother
- Mixed feedings
- Early introduction of solids
- Duration of breastfeeding
Important Concepts

- Analysis of factors related to perinatal HIV transmission
  - May differ according to timing of transmission
    - viral load (plasma - cervical)
    - neutralizing AB
- Analysis of interventions
  - Efficacy may differ with:
    - Timing of transmission
    - Timing of Initiation of antiretrovirals
      - 14 to 26 weeks gestation or later
      - at delivery
      - C-section - not expected to effect infants infected in utero
      - Post partum breast feeding
HIV RNA levels in the plasma of transmitting and non-transmitting mothers at delivery (Dickover et al.)

![Graph showing HIV RNA levels in the plasma of transmitting and non-transmitting mothers at delivery. The graph compares median HIV RNA levels in the plasma of transmitting and non-transmitting mothers, with data points indicating different levels of HIV RNA copies per milliliter. The graph includes data for ZDV and No ZDV treated groups.]
HIV-1 PLASMA RNA & PERINATAL TRANSMISSION
(Mofenson et al., ACTG 185 NEJM 8/5/99)

• HIV-1 RNA (per log increment)
  Odds Ratio P Value
  (CI 95%)
  AT BASELINE 2.4(1.2-4.7) .02
  AT DELIVERY 3.4(1.7-6.8) .001

• NO PERINATAL TRANSMISSION
  (N=84) UNDETECTABLE HIV RNA AT BASELINE(<500 HIV RNA)
  (N=107) UNDETECTABLE HIV RNA AT DELIVERY p<.006
Maternal Plasma HIV-1 RNA Levels at Delivery and Antiretroviral use during Pregnancy: Impact on Perinatal Transmission

Maternal Plasma HIV-1 RNA Levels at Delivery

- None
- ZDV Mono (<4/94)
- ZDV Mono (>4/94)
- Multi-ART
- HAART

Rates per 100
Interruption of perinatal HIV transmission

Intrauterine
- vaccines
- antiretroviral therapy
- immune modulation

Intrapartum
- vaccines
- antiretroviral therapy
- immune modulation
- C-section
- vaginal washing

Post-partum
- breast feeding

Gestation 3 6 months
Labour and Delivery
2 years
Potential Approaches to Intervention of Vertical HIV-1 Transmission

**Antiretrovirals**
- during gestation
- intrapartum
- postpartum - infant
  BF mother (HAART)

**Local Approaches**
- vaginal washing
- topical or oral
  treatment of infant
- mode of delivery

**Immune Based Therapy**
- Specific HIV immunoglobulin
- HIVIG, monoclonals (Combinations)
- Other - immune modulators
- HIV-1 Vaccine
  - Maternal immunization
  - infant
- Combinations of above
076 Protocol

**Infusion**

**Zidovudine or placebo**

- **Oral**
  - **Zidovudine or placebo**
    - **Mother**
      - **16 weeks**
  
- **Oral**
  - **Zidovudine or placebo**
    - **Infant**
      - **6 weeks**

**Infection outcome**

**Gestation**

**Labour**

**Post delivery**
# RESULTS PACTG 076

<table>
<thead>
<tr>
<th>Placebo</th>
<th>ZDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>8%</td>
</tr>
</tbody>
</table>

- **PERINATAL HIV TRANSMISSION**

P < 0.0001

(Conner et al, NEJM ‘94)
DURATION OF RUPTURED MEMBRANES AND VERTICAL TRANSMISSION
META-ANALYSIS 1999

• 4721 VAGINAL DELIVERIES

• RISK OF VERTICAL TRANSMISSION INCREASED LINEARLY FOR EACH ONE HOUR INCREMENT (ADJUSTED ODDS RATIO=1.02 (95%) CI 1.01,1.04)

• WOMEN WITH AIDS-- HIGHER RISK
  - 8% 2 HR DRM
  - 31% 24 HRS DRM

P<0.01
MODE OF DELIVERY AND RISK OF VERTICAL HIV-1 TRANSMISSION META-ANALYSIS OF 15 PROSPECTIVE COHORTS
(THE INTERNATIONAL PERINATAL GROUP NEJM APRIL ‘99)

- 8,533 MOTHER/INFANT PAIRS
- OVERALL

<table>
<thead>
<tr>
<th>MODE OF DELIVERY</th>
<th>N</th>
<th>% TRANSMISSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELECTIVE C-SECTION</td>
<td>809</td>
<td>8.2%</td>
</tr>
<tr>
<td>OTHER MODES</td>
<td>7,031</td>
<td>16.7%</td>
</tr>
</tbody>
</table>

P < 0.001
<table>
<thead>
<tr>
<th>MODE DEL/ZDV</th>
<th>% TRANSMISSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTHER MODES NO ZDV</td>
<td>19%</td>
</tr>
<tr>
<td>ELECTIVE C-SECTION NO ZDV</td>
<td>10.4%</td>
</tr>
<tr>
<td>OTHER MODES + ZDV</td>
<td>7.3%</td>
</tr>
<tr>
<td>ELECTIVE C-SECTION + ZDV</td>
<td>2%</td>
</tr>
</tbody>
</table>
IMPORTANT CONSIDERATIONS
C-SECTION

• NO EFFECT OF C-SECTION ON IN UTERO INFECTION

• COMBINATION ANTIVIRALS
  - NO TRANSMISSION WHEN <500 HIV RNAcp/ml
  - USE OF ANTIVIRALS DURING LABOR DELIVERY-NEV

• DISCUSS WITH WOMEN- OPTIONS FOR WOMEN WITH HIGH VIRUS LOAD DESPITE RX >1000 RNA

• MORBIDITY TO MOTHER
## Design of Select Completed Perinatal Trials

<table>
<thead>
<tr>
<th>076</th>
<th>Thai (Harvard)</th>
<th>Thai (Harvard)</th>
<th>Thai (Harvard), BMS</th>
<th>IvC (ANRS), PETRA, Thai (Harvard)</th>
<th>Thai (CDC), IvC (CDC)</th>
<th>PETRA, 012, SAINT</th>
<th>PETRA</th>
<th>Wade (observational)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 wks</td>
<td>28 wks</td>
<td>36 wks</td>
<td>3d-1 wk</td>
<td>6 wks</td>
<td></td>
<td></td>
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</tr>
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</table>
# HIVNET 012 STUDY

<table>
<thead>
<tr>
<th>%PERINATAL TRANSMISSION</th>
<th>INFANT AGE DX</th>
<th>ZDV</th>
<th>NEV</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT BIRTH</td>
<td>10.4</td>
<td>8.2</td>
<td></td>
<td>.35</td>
</tr>
<tr>
<td>6-8 WEEKS</td>
<td>21.3</td>
<td>11.9</td>
<td></td>
<td>.0027</td>
</tr>
<tr>
<td>14-16 WEEKS</td>
<td>25.1</td>
<td>13.1</td>
<td></td>
<td>.0006</td>
</tr>
</tbody>
</table>

- EFFICACY OF NEV vs ZDV WAS 47% UP TO 16 WEEKS OF AGE
HIVNET 012-Intrapartum/Postpartum Nevirapine vs ZDV: HIV Transmission

Owen M. XIII AIDS Conf, July 2000, Durban S Africa (LbOr01)

Risk Difference:  6 Wks:  8.2%
                 12 Mos:  8.4%

P = 0.003
Does the Addition of Single Dose NVP to Short-Course AZT Improve Efficacy in Formula-Fed Infants?

Lallemant M et al. 11th Retrovirus Conf, Feb 2004 Abs 40LB

### 28 wk oral 1 wk

**AZT Backbone**

**Plus:**

<table>
<thead>
<tr>
<th>Arm 1 -</th>
<th>Arm 2 -</th>
<th>Arm 3 -</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVP</td>
<td>NVP</td>
<td>PL</td>
</tr>
<tr>
<td>NVP</td>
<td>PL</td>
<td></td>
</tr>
<tr>
<td>PL</td>
<td>PL</td>
<td></td>
</tr>
</tbody>
</table>

**Does SD NVP provide added efficacy?**

Does infant NVP dose needed?

Interim analysis April 2002 after ~50% enrollment:

- PL/PL arm discontinued; continued enrollment into NVP arms
- D/C’d 04/02
Comparing Combination Single-Dose NVP + AZT Arms to Short-Course AZT Alone

Lallemant M et al. 11th Retrovirus Conf, Feb 2004 Abs 40LB

28 wk | oral | 1 wk

AZT Backbone

Plus:

Arm 1 - NVP NVP
{+}

Arm 2 - NVP PL

N=686

Arm 3 - PL PL

N=349

Does SD NVP provide added efficacy to SD AZT?
Phase III Randomized Trial of the Safety and Efficacy of Three Neonatal Antiretroviral Regimens for the Prevention of *Intrapartum* HIV-1 Transmission

**NICHD HPTN 040/ PACTG 1043**

Karin Nielsen-Saines*, D. Heather Watts, Valdilea G. Veloso, Yvonne J. Bryson, Esau C. Joao, Jose Henrique Pilotto, Glenda Gray, Gerhard Theron, James Bethel, Lynne Mofenson for the NICHD/HPTN 040 Study Group

**CROI 2011**

**Boston**

**March, 2011**
Study Design

Arm 1: No Maternal AP ARV
- n=5
- ZDV x 6 wk

Arm 2:
- n=5
- ZDV x 6 wk
- NVP

Arm 3:
- n=5
- 3TC + ZDV x 6 wk
- Nelfinavir x 2

Target: 1731

End 6 mo f/up
In Utero and Intrapartum HIV Transmission

Statistical comparisons between single and multiple ARV arms:
Hochberg’s modified Bonferroni approach

HIV-1 PMTCT rates at 3 months (n = 1684)

% based on KM curves

ZDV (11.1%)
ZDV/NVP (7.1%)
ZDV/3TC/NFV (7.4%)

ZDV vs. ZDV/NVP: Intrapartum: p = 0.045; Overall transmission: p = 0.034
ZDV vs. ZDV/3TC/NFV: Intrapartum: p = 0.045; Overall transmission: p = 0.034
Summary

- The risk of *intrapartum* HIV transmission was significantly reduced in the 2 and 3-drug arms as compared to ZDV alone (2.2%, 2.5%, 4.9%, $p = 0.045$).

- The overall HIV transmission rate (*in utero* + *intrapartum*) was also significantly lower in the 2 and 3 drug arms as compared to ZDV alone (7.1%, 7.4%, 11.1%, $p = 0.034$).

- Parameters independently associated with transmission on multivariate analysis were treatment arm and maternal viral load.

- Adherence was 97% or higher in all treatment arms and retention was 96% at 3 months of age.
Summary/ Conclusions

- 43 infant deaths occurred in the study. None were related to study drug. 6 mo IMR were lower than 12 mo country-specific statistics. Majority of deaths were due to respiratory infections.

- Infants at high risk of HIV-infection, i.e., born to mothers who received no ARV during pregnancy should receive a 2 or 3-drug ARV regimen within 48 hours of life to reduce the risk of HIV infection.

- Lower toxicity profile (< neutropenia) and ease of use suggests a 2 drug regimen with NVP may be preferable.

- Resistance testing is ongoing and will provide further insight as to choice of combination regimen.
Design of Ongoing/Planned Infant BF Prophylaxis Trials

<table>
<thead>
<tr>
<th></th>
<th>AP</th>
<th>IP</th>
<th>PP -- Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>36 wks</td>
<td>1 wk</td>
<td>14 wks 6 mo</td>
</tr>
<tr>
<td>Botswana</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIMBA/MITRA</td>
<td>28 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPTN 046</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethiopia/India/Uganda</td>
<td>34 wks</td>
<td>6 wks</td>
<td></td>
</tr>
<tr>
<td>Malawi (CDC/NICHD)</td>
<td></td>
<td></td>
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<tr>
<td>S. Africa/Brazil</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>DITRAME+1</td>
<td>1 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malawi (</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zambia (Harvard)/SA/</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HPTN 057</td>
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</tbody>
</table>

AP: Optimal duration? Is it needed?
Prevention of breast feeding MTC T

• Prevention of breast feeding transmission
• Improvement of HIV free survival
• Balance between avoiding breast milk transmission by early weaning and surviving other childhood illness (diarrhea)
• Options (vaccine and Immune globulin, not for a while)
• ARV treatment of the mother during breast feeding
• ARV prophylaxis of infant (NVP or other ARV) during breast feeding
• Use of antibiotic prophylaxis (bactrim) enhanced hygiene post weaning
## PEPI-Malawi Study Design

*(Taha TE et al. 15th CROI, Boston, MA 2008 Abs 42LB)*

<table>
<thead>
<tr>
<th></th>
<th>Intra-partum*</th>
<th>Birth</th>
<th>Post-partum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>NVP x1*</td>
<td>Infant NVP x1</td>
<td>Infant NVP x1*</td>
</tr>
<tr>
<td><strong>Suspended</strong></td>
<td></td>
<td>NVP x1</td>
<td>ZDV x1 wk</td>
</tr>
<tr>
<td><strong>Aug 2007</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Extended NVP</strong></td>
<td>NVP x1*</td>
<td>Infant NVP x1</td>
<td>Infant NVP x1*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NVP x1</td>
<td>ZDV x1 wk</td>
</tr>
<tr>
<td><strong>Extended NVP + AZT</strong></td>
<td>NVP x1*</td>
<td>Infant NVP x1</td>
<td>Infant NVP x1*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NVP x1</td>
<td>ZDV x1 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Infant: NVP + ZDV x1 14 wks</td>
</tr>
</tbody>
</table>

*If mothers diagnosed in time for intra-partum prophylaxis*

**Mothers counseled to exclusively breastfeed and wean by 6 months**
PEPI-Malawi: Visit-Specific Breastfeeding Frequencies Among HIV Uninfected Infants at Prior Visit

Decreases from 89-91% at 6 mos to 22-25% at 9 mos
Probability of HIV-1 Infection in Infants Uninfected at Birth by Treatment Arm: PEPI-Malawi

<table>
<thead>
<tr>
<th>Age</th>
<th>1 wk</th>
<th>6 wks</th>
<th>9 wks</th>
<th>14 wks</th>
<th>6 mos</th>
<th>9 mos</th>
<th>12 mos</th>
<th>15 mos</th>
<th>18 mos</th>
<th>24 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.3</td>
<td>5.1</td>
<td>7.4</td>
<td>8.4</td>
<td>10.1</td>
<td>10.6</td>
<td>11.5</td>
<td>12.4</td>
<td>13.9</td>
<td>14.5</td>
</tr>
<tr>
<td>Extended NVP</td>
<td>0.1</td>
<td>1.7</td>
<td>2.6</td>
<td>2.8</td>
<td>4.0</td>
<td>5.2</td>
<td>7.0</td>
<td>7.8</td>
<td>10.1</td>
<td>11.2</td>
</tr>
<tr>
<td>Extended NVP+ZDV</td>
<td>0.2</td>
<td>1.6</td>
<td>2.4</td>
<td>2.8</td>
<td>5.2</td>
<td>6.4</td>
<td>8.1</td>
<td>8.7</td>
<td>10.2</td>
<td>12.3</td>
</tr>
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**PEPI-Malawi Study Design**

(Taha TE et al. 15th CROI, Boston, MA 2008 Abs 42LB)

<table>
<thead>
<tr>
<th></th>
<th>Intra-partum*</th>
<th>Birth</th>
<th>Post-partum</th>
<th>1 - 7 d</th>
<th>8 - 98 d</th>
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</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>NVP x1*</td>
<td>Infant NVP x1</td>
<td>Infant ZDV x1 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspended</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Aug 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Extended</strong></td>
<td>NVP x1*</td>
<td>Infant NVP x1</td>
<td>Infant ZDV x1 wk</td>
<td></td>
<td>Infant: NVP x 14 wks</td>
</tr>
<tr>
<td>NVP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Extended</strong></td>
<td>NVP x1*</td>
<td>Infant NVP x1</td>
<td>Infant ZDV x1 wk</td>
<td></td>
<td>Infant: NVP + ZDV x 14 wks</td>
</tr>
<tr>
<td>NVP + AZT</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*If mothers diagnosed in time for intra-partum prophylaxis

**Mothers counseled to exclusively breastfeed and wean by 6 months**
Six Week Extended NVP (SWEN) Study
Sastry J et al. 15th CROI, Boston, MA 2008

• Risk of HIV infection and death assessed at 6 weeks and 6 months of age in infants who were uninfected at birth.

• Modified intent to treat analysis included 986 infants in the SD NVP arm and 901 infants in the extended NVP arm after excluding infants lacking specimens (N=36), indeterminate HIV status (N=8), or HIV infection at birth (N=93, 4.7% SD NVP, 4.1% extended NVP).

• Maternal baseline CD4 384-397; baseline HIV RNA 16,457-17,400.
SWEN: Visit-Specific Breastfeeding Frequencies:
Decreases from 73% at 14 wks to 31-32% at 6 mos
SWEN: 6-Week NVP Decreases Postnatal HIV MTCT at Age 6 Wks but No Longer Significant at 6 Mos

- 6-Week NVP: 2.5% at 6 Weeks, RR 0.54, p=0.009
- SD NVP: 12% at 6 Weeks
- 6 Months:
  - 6-Week NVP: 6.9%
  - SD NVP: 9.0%
  - RR 0.80, p=0.16

Infant Age at HIV Test
ARV Prophylaxis: Postnatal Birth - 6 Month HIV Transmission Rates (uninfected at birth) Various Studies

<table>
<thead>
<tr>
<th>Study/Regimen</th>
<th>% MTCT 6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>DREAM (CROI 2008)</td>
<td>1.3%</td>
</tr>
<tr>
<td>Mitra Plus</td>
<td>1.1%</td>
</tr>
<tr>
<td>Amata</td>
<td>0.6%</td>
</tr>
<tr>
<td>KIBS</td>
<td>2.6%</td>
</tr>
<tr>
<td>Mitra (infant 3TC) Mom AZT/3TC</td>
<td>0.9%</td>
</tr>
<tr>
<td>SIMBA (infant NVP) Mom AZT/ddI</td>
<td>2.4%</td>
</tr>
<tr>
<td>Mashi (infant AZT) Mom AZT</td>
<td>5.7%</td>
</tr>
<tr>
<td>SWEN (infant NVP)</td>
<td>5.7%</td>
</tr>
<tr>
<td>PEPI-Malawi (infant NVP)</td>
<td>6.9%</td>
</tr>
<tr>
<td>Maternal PP HAART</td>
<td></td>
</tr>
<tr>
<td>Infant PP ARV</td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
- **Maternal PP HAART**
- **Infant PP ARV**
- **All also AP maternal ARVs (HAART, Dual or AZT)**
- **NO AP maternal ARV**
Antenatal Antiretroviral Treatment and Perinatal Transmission in WITS, 1990-1999
Blattner W. XIII AIDS Conf, July 2000, Durban S Africa (LBOr4)

<table>
<thead>
<tr>
<th>Type ARV vs None</th>
<th>% Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (N=391)</td>
<td>21%</td>
</tr>
<tr>
<td>ZDV Mono (&lt;4/94) (N=206)</td>
<td>19%</td>
</tr>
<tr>
<td>ZDV Mono (&gt;4/94) (N=529)</td>
<td>8%</td>
</tr>
<tr>
<td>Multi- ART (N=179)</td>
<td>4%</td>
</tr>
<tr>
<td>HAART (N=187)</td>
<td>1%</td>
</tr>
</tbody>
</table>

Type ARV vs None p value:
- ZDV Mono (<4/94) vs None: 0.76
- ZDV Mono (>4/94) vs None: <0.01
- Multi- ART vs None: <0.01
- HAART vs None: <0.01
Preventing Mother-to-Child Transmission through use of HAART - USA

Trends in mother-to-infant transmission rate and maternal antiretroviral therapy: 1990–1999+ (Women and Infants Transmission Study Group). Rates per 100 (95% confidence interval)

Cooper E et al., JAIDS 2002;29(5):484-494
# Antiretrovirals pregnancy cat B/C

## Nucleosides/ NNTR
- ZDV - most data
- 3TC - crosses placenta
- ddl - requires increase of dose in pregnancy - crosses placenta
- d4T -
- Nevirapine - given during labor and to infant with prolonged half life
- other Tenofovir
- Integrase inhibitors

## Protease inhibitors
- Ritonavir -
- Indinavir - must be stopped in labor - bilirubin increases in baby
- Nelfinavir -
- Saquinavir –
- Lopinavir
- Kaletra (boosted LP)
- aprenavir
- protease Inhibitors do not cross placenta (minimal to none)
<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside(tide) RTI</td>
<td>• Retrovir (zidovudine, AZT)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>• Videx (didanosine, DDI)</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>• Hivid (zalcitabine, DDC)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>• Zerit (stavudine, D4T)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>• Epivir (lamivudine, 3TC)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>• Ziagen (abacavir, ABC)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>• Viread (tenofovir, TDF)</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>• Emtriva (emtricitabine, FTC)</td>
<td>B</td>
</tr>
<tr>
<td>Non Nucleoside RTI</td>
<td>• Viramune (nevirapine, NVP)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>• Rescriptor (delavirdine, DLV)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>• Sustiva (efavirenz, EFV)</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>• Fortovase (saquinavir, SQVHGC)</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>• Invirase (saquinavir, SQVSGC)</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>• Crixivan (indinavir, IDV)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>• Norvir (ritonavir, RTV)</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>• Viracept (nelfinavir, NFV)</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>• Agenerase (amprenavir, APV)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>• Kaletra (lopinavir/ritonavir, LPV/r)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>• Reyataz (atazanavir, ATV)</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>• Lexiva (fos-amprenavir, f-APV)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>• Aptivus (tipranavir, TPV)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>• Prezista (darunavir, DRV)</td>
<td>B</td>
</tr>
<tr>
<td>Fusion Inhibitor</td>
<td>• Fuzeon (enfuvirtide, T-20)</td>
<td>B</td>
</tr>
</tbody>
</table>

Placental transfer of ARV

- **Transfer well**
  - Nucleosides
  - ZDV
  - 3TC
  - DDI
  - D4T
  - NNRTs
  - NVP
  - Efavirenz
  - Others Tenofovir
  - raltegravir

- **Poor transfer**
  - Protease inhibitors
  - NFV
  - Ritonavir
  - Lopinavir
  - Atazanavir
  - Amprenavir,
Antiviral Pregnancy Registry Overview

• International registry designed to:
  – Monitor prenatal drug exposure
  – Assess risk of major birth defects

• Relies on health care provider voluntary reporting of antiretroviral exposures during pregnancy, including

• APR has IRB approval and requires informed consent
• Data reported from January 1989 to July 2006
  – 206 first trimester exposures to LPV/r as of July 2006

Current perinatal guidelines USA

- Routine opt out HIV testing for all pregnant women for each pregnancy
- Recommend repeat testing near delivery if done early and negative

- Recommend HIV drug genotypic drug resistance assay if HIV positive and with detectable HIV RNA viral load > 1000 RNA/ml
- HAART for all HIV positive pregnant women multiple choices (most common combivir/lopinavir)
Current Perinatal guidelines  USA

Follow HIV viral load goal to reduce HIV RNA to undetectable ASAP
If failure to respond- resistance testing and counselling for adherence
Discuss  C section if HIV RNA >1000 HIV RNA late gestation /prior to delivery or if unknown viral load

- Consider stopping HAART >6 weeks post partum if CD4T cells >500 ( new study PROMISE to assess efficacy and long term outcome)

- Do Not Recommend Breast Feeding in developed countries
- Infant has DNA HIV testing and follow up at specialized center
  - Centers in LA  CARE 4 FAMILIES UCLA
  - Harbor UCLA , USC, Long Beach/UC Irvine, CHLA
Perinatal guidelines vary by Resource/country

- Effective, Affordable---- Moving Target
  - Short course NVP mother / infant (problems NVP resistance in mother and infant - Doesn’t reduce in utero HIV
  - Use of other drugs Truvada/ ARV tail mother
  - ZDV plus mother/ infant NVP used in Thailand
  - Prevention of breast feeding transmission vs infant survival early weaning--- bottle feeding-- NVP as prophylaxis infant
  - HAART in breast feeding mother

INFANT prophylaxis-- ZDV 6 weeks developed countries / NVP 6 weeks in infants breast feeding countries.

Results of 040 – use of 2 /3 drugs in infant if mother not RX
-- Response to NNRTI Therapy After Single-Dose NVP for Prevention of MTCT

-- Prevention of NVP Resistance

Response to NVP-HAART
Response to NNRTI-HAART After SD NVP: Multicountry Study
Weidle P et al. 15th CROI, Boston, MA, 2008

• Multi-country cohort study: Zambia (N=201), Kenya (N=67) and Thailand (N=87)
  – Compared response to NVP-based HAART in women
    High proportion of women (>70%) responded to NVP-HAART at 24 weeks regardless of SD NVP exposure with (N=355) and without (N=523) prior SD NVP exposure.

• Increased risk of failure in women with SD NVP exposure within 6 mos (possibly 12 mos) of starting HAART.
Approaches to reduce NVP/ARV resistance

- Add another drug (Truvada at delivery) -- reduces NVP resistance
- or substitute Truvada mother and infant
- Add an ARV multi drug tail to maternal regimen
  Several studies show reduction of maternal ARV resistance
- Concern over NVP resistance in infant who become infected when using long term prophylaxis for prevention of breast feeding transmission. -- Need to minimize use in HIV infected infants and use different treatment regimen.
**TEmAA Study – ANRS 12109: Truvada to Reduce NVP Resistance**  
Arrive E et al. 15th CROI, Boston, MA, 2008 Abs

- **AP**  
  - AZT starting 28-38 wks

- **IP**  
  - NVP x1
    - + TFV 600 mg/FTC 400 mg

- **PP**  
  - Daily TFV 300 mg/FTC 200 mg x 1 Wk

- N=38 (19 Cote d’Ivoire, 12 Vietnam, 7 S Africa)
- Median CD4 450 (IQR 314-596)
- Median RNA 4.08

- MTCT at 4 wks: 2/39 (5.1%) (at day 3, likely in utero)
- NO AZT, NVP, TFV or FTC Resistance mom/infant at wk 4 (standard assay)

Infant SD NVP + AZT x1 wk
TEmAA Study – ANRS 12109: Population PK of Intrapartum Tenofovir

*Hirt E et al. 15th CROI, Boston, MA, 2008 Abs*

<table>
<thead>
<tr>
<th>AP</th>
<th>IP</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT starting 28-38 wks</td>
<td>NVP x1</td>
<td>+ TFV 600 mg/FTC 400 mg</td>
</tr>
</tbody>
</table>

Population PK Data:

- After 600 mg IP TFV/FTC, maternal median AUC 2.73 mg/L\(^{-1}\), peak 0.31 mg/L and trough 0.056 mg/L; similar concentrations to what seen with standard 300 mg dose non-pregnant persons.
- Absorption faster and greater for women with CS then vaginal delivery.
- Delivery infant level 0.10 mg/mL and maternal level 0.13/L – cord infant levels 76% of maternal levels, suggesting good placental transfer.
- Neonatal half-life 8.3 hr.
- Recommend re-administration if >12 hours since IP dose and delivery.
TD-2 Study: Truvada to Reduce NVP Resistance
Ultrasensitive Assay (OLA) Analysis
Chi B et al. 15th CROI, Boston, MA, 2008 Abs 631

112 random maternal specimens tested using OLA assay, with sensitivity for minority subpopulations as low as 5%

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>2 Weeks</th>
<th>Study Arm</th>
<th>6 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>(AZT) SD NVP</td>
<td>44%</td>
<td>(AZT) SD NVP</td>
<td>44%</td>
</tr>
<tr>
<td>(N=23)</td>
<td></td>
<td>(N=41)</td>
<td></td>
</tr>
<tr>
<td>(AZT) SD NVP+</td>
<td>13%</td>
<td>(AZT) SD NVP+</td>
<td>19%</td>
</tr>
<tr>
<td>TFV/FTC</td>
<td></td>
<td>TFV/FTC</td>
<td></td>
</tr>
<tr>
<td>(N=15)</td>
<td></td>
<td>(N=43)</td>
<td></td>
</tr>
</tbody>
</table>

69% reduction in NVP resistance at 2 weeks
RR 0.31 (95% CI 0.08-1.21)

58% reduction in NVP resistance at 6 weeks
RR 0.42 (95% CI 0.21-0.87)
-- Pattern of Infant Feeding and Postnatal MTCT

-- Risk Factors for Postnatal MTCT
Overall 18 month postnatal transmission was higher in S. Africa study (longer BF):
- 5% (CI 3-8%) W. Africa vs 9% (CI 7-11%) S. Africa, p=0.03.

BF duration was major determinant of MTCT - 18 month postnatal transmission by duration:
- BF <6 months: 3.9% (CI 2.3-6.5%)
- BF >6 months: 8.7% (CI 6.8-11%)
- Longer duration associated with 2.1-fold (CI 1.2-3.7) increased hazard postnatal MTCT.
MTCT Risk in Women **Not** Meeting WHO Criteria* for ART Who Receive Short-Course ARV Prophylaxis

Cote d’Ivoire Trials Data, F. Dabis 6/05

* Does **not** Meet WHO criteria if:  
  
- WHO Stage 3 and CD4 ≥350
- Stage 1-2 and CD4 ≥200

<table>
<thead>
<tr>
<th>Therapy</th>
<th>% MTCT at 6 Wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short AZT</td>
<td>10.9%</td>
</tr>
<tr>
<td>AZT+/SD NVP</td>
<td>3.6%</td>
</tr>
<tr>
<td>AZT/3TC+/SD NVP</td>
<td>3.5%</td>
</tr>
<tr>
<td>HAART</td>
<td>2.4%</td>
</tr>
</tbody>
</table>
MTCT Risk in Women Meeting WHO Criteria* for ART Who Receive HAART

Cote d’Ivoire Trials Data, F. Dabis 6/05

* WHO Criteria for ART: WHO Stage 4 or Stage 3 and CD4<350 or Stage 1-2 and CD4<200
Potential Problems with Universal HAART Solely for PMTCT in Developing Countries

• Complexity – issues of difficulty in implementation and problems with adherence (and potential resistance)
• Limited resources and cost – can’t provide ART to patients who need for own health
• Limited formulary, with choice of regimens limited by toxicity (NVP toxicity with CD4 >250, lactic acidosis); need to use PI regimen (or triple NRTI?)
• Mixed data on pregnancy outcome and HAART: preterm [Europe], LBW [Ivory Coast]
• Maternal health (issues of start-stop HAART)
Both Maternal and Infant ARV Prophylaxis Strategies Presume Early Weaning of the Infant to Avoid Continued HIV Exposure Post Prophylaxis:

How Safe is Early Weaning?
ARV Prophylaxis: Postnatal Birth - 6 Month Transmission Rates

% MTCT 6 Months

- Mitra Plus: 1.1%
- Amata: 0.6%
- Mitra infant: 0.9%
- SWEN: 7.2%
- PEPI-Malawi (NVP): 5.1%

- Maternal PP HAART
- Infant PP ARV

- NO AP maternal ARV

- All also AP maternal ARVs
MTCT Risk in Women *Not Meeting WHO Criteria* for ART Who Receive Short-Course ARV Prophylaxis

Cote d’Ivoire Trials Data, F. Dabis 6/05

* Does **not** Meet WHO criteria if:  
  WHO Stage 3 and CD4 ≥350 or  
  Stage 1-2 and CD4 ≥200
Mashi: Cumulative Rate of HIV Infection by Infant Feeding

Thior I et al. JAMA 2006;296:794-805

Significantly More HIV Infections With Breastfeeding + AZT

Breastfeeding + AZT

Formula

No. at Risk

<table>
<thead>
<tr>
<th>Formula Feeding</th>
<th>Breastfeeding + ZDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>591</td>
<td>588</td>
</tr>
<tr>
<td>523</td>
<td>536</td>
</tr>
<tr>
<td>506</td>
<td>499</td>
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<tr>
<td>490</td>
<td>474</td>
</tr>
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<td>455</td>
<td>439</td>
</tr>
<tr>
<td>426</td>
<td>416</td>
</tr>
<tr>
<td>224</td>
<td>227</td>
</tr>
</tbody>
</table>

P = .02

Cumulative Rate of HIV+

Months From Birth

0 3 6 9 12 15 18
Mashi: Cumulative Rate of Death by Infant Feeding

Thior I et al. JAMA 2006;296:794-805

Significantly More Early Deaths With Formula Feeding

7 month difference

\[ p=0.003 \]

<table>
<thead>
<tr>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula Feeding</td>
</tr>
<tr>
<td>Breastfeeding + ZDV</td>
</tr>
<tr>
<td>591</td>
</tr>
<tr>
<td>588</td>
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<tr>
<td>548</td>
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<td>487</td>
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<td>460</td>
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<tr>
<td>468</td>
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</table>

P = .21
Cumulative Rate of HIV Infection or Death by Infant Feeding

Thior I et al. JAMA 2006;296:794-805

Resulting in No Difference in HIV-Free Survival

Breastfeeding + AZT

Formula

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Formula Feeding</th>
<th>Breastfeeding + ZDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months From Birth</td>
<td>591  524  508  490  457  427  224</td>
<td>588  536  502  478  439  416  227</td>
</tr>
</tbody>
</table>

P = .48
Cumulative Rate of HIV Infection or Death by Infant Feeding

Thior I et al.  JAMA 2006;296:794-805

Resulting in No Difference in HIV-Free Survival

Breastfeeding + AZT

Formula
No Overall Benefit in HIV-Free Survival to Early Cessation vs. Continued Breastfeeding
Thea D et al. 14th CROI, 2007, Los Angeles, CA Abs. LB

Overall HIV-free Survival Among Children without HIV & Still Breastfeeding at Age 4 Months of Age by Group Assignment (Abrupt vs Standard Weaning)

\[ p = 0.21 \]
How to Optimize Infant Survival Post Weaning?
Breastfeeding Protects Against both Diarrhea Respiratory-Associated Mortality in 1st Year of Life

WHO Collaborative Study Team, Lancet 2000

Pooled Odds Ratio for Mortality if Not Breastfeeding

Odds ratio

- **6 mos - DD**: 6.1 (4.1-9.0)
- **6 mos - RD**: 2.4 (1.6-3.5)
- **6-11 mos - DD**: 1.9 (1.2-3.1)
- **6-11 mos - RD**: 2.5 (1.4-4.6)

DD = diarrheal mortality
RD = respiratory mortality
Formula-Feeding is Associated with Higher Rates of Severe Diarrhea, Wasting / Infant Mortality in HIV-Uninfected Children
Mashi Study, Botswana Lockman S et al.

<table>
<thead>
<tr>
<th>HIV-Uninfected Children</th>
<th>Breast-fed (N=534)</th>
<th>Formula-fed (N=558)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome at Age 6 Mos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11.0%</td>
<td>14.3%</td>
<td>0.10</td>
</tr>
<tr>
<td>Grade 3-4 pneumonia</td>
<td>4.2%</td>
<td>6.3%</td>
<td>0.13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32%</td>
<td>34%</td>
<td>0.39</td>
</tr>
<tr>
<td>Grade 3-4 diarrhea</td>
<td>0.8%</td>
<td>3.4%</td>
<td>0.003</td>
</tr>
<tr>
<td>Wasting</td>
<td>6.0%</td>
<td>3.2%</td>
<td>0.03</td>
</tr>
<tr>
<td>Death</td>
<td>3.6%</td>
<td>6.9%</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Proposed IMPAACT Master Perinatal Strategy Clinical Trial

- Large trial designed to address multiple questions with overall goal to maximize maternal and infant survival.

  - What is optimal and most effective (including cost-effective and implementable) PMTCT regimen in breastfeeding infants? And in formula-fed infants in low resource countries?

  - How to improve HIV-free survival in infants after weaning (does CTX help)?

  - Maternal survival and morbidity – can HAART be stopped after prophylaxis (does duration of prophylaxis make a difference)?
Kitchen SINK APPROACH

• Instead of trying to get small incremental improvements in PMTCT with very targeted studies, protocol attempts to put into place all interventions for which there are some data suggesting possible efficacy to achieve overall goal of infant and maternal survival.

• Similarities to approach in PACTG 076, where targeted all potential time points of transmission.

• Factorial design should allow some idea of differential importance of different components of the study.
PROMISE STUDY

Promoting Maternal and Infant Survival Everywhere
Overarching study proposed by IMPAACT network to answer important questions in PMTC and infant and maternal health

Maternal HAART vs ZDV plus NVP?

MATERNAL HAART VS INFANT NVP
FOR PREVENTION OF BREAST FEEDING TRANSMISSION

Regimen for late presenters?

Co trimoxazole in weaning babies vs enhanced hygiene
Prevention of morbidity/mortality in infants

Should mother stop HAART postpartum or post breast feeding if CD4Tcells >350
Evaluation of Optimal PMTCT Strategy

- Entry restricted to women with CD4 >350
  - Women with CD4 <350 should get HAART (new US guidelines, WHO pregnancy guidelines) for own health.
  - These women at greatest risk of MTCT even with short-course ART and of NVP resistance following SD NVP and giving HAART may decrease MTCT and prevent NPV resistance

- Equipoise on optimal strategy for women with CD4 >350 – HAART vs SD NVP ZDV short-course.

- “Tail” and NVP resistance – data suggests SD TFV/FTC or 7 day AZT/3TC tail may be effective in lowering resistance.
Question- to stop or continue HAART post pregnancy in women CD4>500cp/ml

- Study to assess effect of intermittent HAART use for PMTC
- On long term health of HIV infected women Drug resistance/response to treatment etc
- Part of PROMISE
**PROMISE**
Promoting Mother and Infant Survival Everywhere

**BREAST FEEDING (international) Š Sequential 2x2 Factorial Trial**

- **CD4 >350**

<table>
<thead>
<tr>
<th>AP 28 to Labor Onset</th>
<th>IP</th>
<th>PP for Duration BF</th>
<th>Weaning</th>
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<tbody>
<tr>
<td>HAART</td>
<td>HAART</td>
<td>HAART</td>
<td>Continue HAART</td>
</tr>
<tr>
<td>AZT + SD NVP + SD TRV</td>
<td>Infant AZT x1 wk*</td>
<td>Stop All ARVs</td>
<td></td>
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<tr>
<td>Infant NVP</td>
<td>Infant (if &lt;18 mos old and HIV - at time of weaning)</td>
<td>CTX to 18 months</td>
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<td>No CTX</td>
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**Late presenters**
AZT + SD NVP + SD TRV

*if mother gets <4 wks of AP ARV, infant gets AZT x 4 wks*
PROMISE STUDY

- APPROVED as PART OF IMPAACT NIH network of 67 clinical trial sites Globally
  Each country will participate in different parts depending if breast feeding or standard of HAART in mother now started 2010

- USA
- AFRICA: 7 countries
  - India
  - Thailand
- South America: Brazil, Argentina
Challenge PMTC HIV developed/ resource poor countries

- US and others: continued vigilance
- HIV drug resistance
- Identification monitoring of HIV + pregnant women
- Support of Rx /prophylaxis in women and infants- follow up infants
- Translation of science into practice
- Politics
- Need of a preventive vaccine/ Path to a CURE
For more information and referrals

Care-4-Families
HIV/AIDS treatment and research program at Mattel Children’s Hospital UCLA for pediatric and OB patients

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