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 Immuno-deficiency Virus (HIV) is identified as the cause of AIDS.

Acquired Immuno-deficiency Syndrome (AIDS) is defined for the first time.

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

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

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.

An HIV outbreak in Eastern Europe is detected (among injecting drug users).

Scientists develop the first treatment regimen to reduce mother-to-child transmission.

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

The first efficacy trial of a potential HIV vaccine in a developing country starts in Thailand.

UNAIDS is created.

The International Council of AIDS Service Organizations (ICASO) and the Global Network of People Living with HIV/AIDS are founded.

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

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

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)

Heterosexual contact
IDU
Pediatric cases

Quarter-Year

Number of Cases
Perinatal HIV-1: What Do We Know Now?

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

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

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

**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

- **HIV-1 RNA copies / ml plasma**

- **In utero**
- **Intrapartum**
- **Uninfected**

○ Rapid
○ Intermediate
● Slow
Potential Factors Influencing Perinatal Transmission of HIV

**Viral**
- Virus load (cell ass./cell free)
- Phenotype (SI, tropism)
- Genotype

**Immune**
- Decreased CD4 count
- Humoral (NAb, ADCC/ gp120 V3 loop Ab, other)
- Cell mediated (CTL, CD8 supression)
- Mucosal immunity

**Maternal**
- Clinical advanced disease
- Primary HIV infection
- Co-infection
- Twins-first born
- Obstetrical Events
- Timing of Infection

**Fetal/Placental**
- Prematurity
- Chorioamnionitis
- Infant host-immune response
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.)
**HIV-1 PLASMA RNA & PERINATAL TRANSMISSION**

(Mofenson et al., ACTG 185 NEJM 8/5/99)

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>P Value (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT BASELINE</td>
<td>2.4 (1.2-4.7)</td>
<td>.02</td>
</tr>
<tr>
<td>AT DELIVERY</td>
<td>3.4 (1.7-6.8)</td>
<td>.001</td>
</tr>
</tbody>
</table>

• **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 and Antiretroviral use during Pregnancy: Impact on Perinatal Transmission

- None
- ZDV Mono (<4/94)
- ZDV Mono (>4/94)
- Multi-ART
- HAART
Interrupting 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 months
- **Labour and Delivery**
  - 6 months
- **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

Gestation

Labour

Oral

Zidovudine or placebo

Infant

6 weeks

Post delivery

Infection outcome
## RESULTS PACTG 076

<table>
<thead>
<tr>
<th></th>
<th>PLACEBO</th>
<th>ZDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERINATAL HIV</td>
<td>25%</td>
<td>8%</td>
</tr>
<tr>
<td>TRANSMISSION</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P < .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>
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</tbody>
</table>

P<0.001
## C-SECTION WITH/WITHOUT ZDV VERTICAL HIV-1

<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>
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<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
## HIVNET 012 STUDY

### %PERINATAL TRANSMISSION

<table>
<thead>
<tr>
<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>.35</td>
</tr>
<tr>
<td>6-8 WEEKS</td>
<td>21.3</td>
<td>11.9</td>
<td>.0027</td>
</tr>
<tr>
<td>14-16 WEEKS</td>
<td>25.1</td>
<td>13.1</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:

Arm 1 - NVP NVP

Arm 2 - NVP PL

Arm 3 - PL PL

Does SD NVP provide added efficacy?

Interim analysis April 2002 after ~50% enrollment: PL/PL arm discontinued; continued enrollment into NVP arms

Interim analysis April 2002 after ~50% enrollment: PL/PL arm discontinued; continued enrollment into NVP arms

Is infant NVP dose needed?

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

AZT Backbone

28 wk oral 1 wk

Plus:

Arm 1 - NVP NVP

Arm 2 - NVP PL

Arm 3 - PL PL

Does SD NVP provide added efficacy to SD AZT?

N=686

N=349
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
  - Birth <48h
  - <48h
  - 2-4d
  - 5-7d
  - 2wk
  - 6 wk
  - n=5
  - ZDV x 6 wk
  - Target: 3TC + ZDV x 6 wk

- **Arm 2**: NVP
  - Birth <48h
  - <48h
  - 2-4d
  - 5-7d
  - 2wk
  - 6 wk
  - n=5
  - ZDV x 6 wk
  - NVP
  - Target: 3TC + ZDV x 6 wk

- **Arm 3**: NVP
  - Birth <48h
  - <48h
  - 2-4d
  - 5-7d
  - 2wk
  - 6 wk
  - n=5
  - ZDV x 6 wk
  - NVP
  - Target: 3TC + ZDV x 6 wk

**Target:** 1731

**Follow-up:** 6 mo f/up

**NICHID HPTN 040**
Statistical comparisons between single and multiple ARV arms:

Hochberg’s modified Bonferroni approach
Timing of HIV Infection for Infants Testing Positive After Birth by Study Treatment Arm (Intrapartum Only)
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 w/ NVP may be preferable.

- Resistance testing is ongoing and will provide further insight as to choice of combination regimen.
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
Antenatal Antiretroviral Treatment and Perinatal Transmission in WITS, 1990-1999

Blattner W. XIII AIDS Conf, July 2000, Durban S Africa (LBO or 4)

<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:

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

Rates per 100 (95% confidence interval)

Cooper E et al., JAIDS 2002;29(5):484-494
Placental transfer of ARV

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

- **Poor transfer**
  - Protease inhibitors
  - NFV
  - Ritonavir
  - Lopinavir
  - Atazanavir
  - Amprenavir,
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 FAMILES 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
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.
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+ TFV/FTC</td>
<td>13%</td>
<td>(AZT) SD NVP+ TFV/FTC</td>
<td>19%</td>
</tr>
<tr>
<td>(N=15)</td>
<td></td>
<td>(N=43)</td>
<td></td>
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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
Duration and Pattern of Breastfeeding and Postnatal Transmission
Becquet R et al. 15th CROI, Boston, MA, 2008

• 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 or Stage 1-2 and CD4 ≥200

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% MTCT at 6 Wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short AZT</td>
<td>10.9%</td>
</tr>
<tr>
<td>AZT+</td>
<td>3.6%</td>
</tr>
<tr>
<td>AZT/3TC+</td>
<td>3.5%</td>
</tr>
<tr>
<td>HAART</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

SD NVP
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?
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

- 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>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>
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

AP 28 to Labor Onset
IP
PP for Duration BF
Weaning

HAART
HAART

HAART
Mother

Stop All ARVs

Continue HAART

Infant AZT x1 wk*

Infant (if <18 mos old and HIV - at time of weaning)

Infant NVP

Infant NVP

AZT + SD NVP+ SD TRV

AZT

AZT + SD NVP+ SD TRV

Late presenters

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

CTX to 18 months
No CTX
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

Phone: 310-206-6369

Fax: 310-825-9175