Early Antiretroviral Therapy in Newborns: Opportunities and Challenges

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Conflict of Interest Disclosures for
Ellen Chadwick MD

<table>
<thead>
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<th>Details</th>
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Global increase in number of pregnant women with HIV receiving ARVs for PMTCT, 2005-2013

- HIV+ pregnant women receiving ARVs for PMTCT:
  - 2005: 1,640,000
  - 2013: ~1,450,000

- HIV+ pregnant women needing ARVs for PMTCT:
  - 2005: 1,640,000
  - 2013: ~1,450,000

Transmission Risk:
- ≤5%
  - 2005: 13%
  - 2013: ~67%
- ~25%
  - 2005: 67%
  - 2013: ~67%

Slide courtesy E. Abrams
Objectives

• Early Antiretroviral Therapy in Newborns
  – Opportunities:
    • Attenuation of establishment of viral reservoirs
    • Prevention early morbidity/mortality
  – Challenges:
    • Early infant diagnosis
    • What ARV regimen to start
      – Pharmacokinetics, formulation and toxicity concerns
    • Barriers to implementation
    • Ethical considerations
Absence of Detectable HIV-1 Viremia after Treatment Cessation in an Infant

Deborah Persaud, M.D., Hannah Gay, M.D., Carrie Ziemniak, M.S., Ya Hui Chen, B.A., Michael Piatak, Jr., Ph.D., Tae-Wook Chun, Ph.D., Matthew Strain, M.D., Ph.D., Douglas Richman, M.D., and Katherine Luzuriaga, M.D.
Cellular HIV-1 DNA Reservoir is Established Early and Decays During Suppressive cART

Decay rate of total HIV-1 DNA: 0-24 wk (-0.04 log10 cpm/wk; p < 0.0001); 24-48 wk (-0.02 log10 cpm/wk; p < 0.0001); 48-96 wk (-0.001 log10 cpm/wk; p = 0.295).

Median half-life of HIV-1 in first two years of life is 26.8 weeks. Individual colored line indicates patient-specific slopes and thick black line indicates lowess curve for all patients.

Upety et al. CROI 2015; Abs. #374
Smaller Latently-infected Reservoir in Infants Initiating cART <6 weeks vs. 6 weeks-6 months of age P1030

HIV-1 DNA level exceeded replication competent DNA by 148-fold at 96 weeks
Time to Virologic Suppression Correlates with Size of Reservoir at 96 Weeks \( P_{1030} \)
Proviral Reservoir Size Is Smaller in Perinatally HIV-Infected Youth Who Achieved Viral Suppression Before 1 Year of Age

<table>
<thead>
<tr>
<th>Age of virologic control:</th>
<th>&lt;1 year old</th>
<th>1-5 years old</th>
<th>&gt;5 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=</td>
<td>14</td>
<td>53</td>
<td>77</td>
</tr>
<tr>
<td>Proviral Load (copies/million PBMCs) IQR</td>
<td>4.2 [2.6, 8.6]</td>
<td>19.4 [5.5, 99.8]</td>
<td>70.7 [23.2, 70.7]</td>
</tr>
</tbody>
</table>

Open circles indicate <LOD, which varies by number of cells for analysis.

Persaud et al. Abst # 72 CROI 2014
Decay in HIV-1 proviral DNA level over time in youth with long-term suppression of HIV-1 replication who initiated cART <3 months of age.
HIV-1 antibody levels over time in youth with long-term suppression of HIV-1 replication who initiated combination antiretroviral therapy early or late
Absent IFN-γ enzyme-linked immunospot (ELISpot) responses to Gag and Nef in 4 children treated within 24 hrs of birth

Candidate Biomarkers to Evaluate for Possible Remission

- Plasma HIV RNA < 2 copies/mL
- HIV DNA < 2 copies/million
- Undetected replication-competent HIV
- Absent HIV-specific immune responses (antibody and cell-mediated immunity)
ART Cessation in 4 Children Treated Within 4 days of birth

Viral rebound within 14 days in 3/4 children

Dublin Child (8 days; VL=11,230 c/ml))

Canadian Child (14 days; VL=7797 c/ml)

Milan Child (14 days; VL 36,840 c/ml)

Mississippi Child (828 days; VL=16 copies/ml)

- No plasma HIV RNA (standard or ultrasensitive assays)
- HIV DNA < 10 copies/million PBMCs
- HIV antibody negative

Adapted from Rainwater-Lovett in CUREiculum

Comparison between Mississippi Child and Other Children with Faster Viral Rebounds

<table>
<thead>
<tr>
<th>Case</th>
<th>Initial VL (c/mL)</th>
<th>ART Initiation</th>
<th>ART Duration</th>
<th>Remission Duration</th>
<th>Rebound VL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mississippi Child</td>
<td>19,812</td>
<td>30 hours</td>
<td>18 months</td>
<td>27 months</td>
<td>16</td>
</tr>
<tr>
<td>Dublin Child</td>
<td>653</td>
<td>&lt;24 hours</td>
<td>4 years</td>
<td>8 days</td>
<td>11,230</td>
</tr>
<tr>
<td>Canadian Child</td>
<td>808</td>
<td>&lt;24 hours</td>
<td>3 years</td>
<td>14 days</td>
<td>7,797</td>
</tr>
<tr>
<td>Milan Child</td>
<td>152,560</td>
<td>4 days</td>
<td>3 years</td>
<td>14 days</td>
<td>36,840</td>
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</tbody>
</table>

Possible Factors Contributing to Differences

- Stage of *in-utero* infection
- Viral load of mother
- Infant’s time to HIV suppression
- Genetic differences in immune response
- ART adherence
- Co-infections
- Latent reservoir size
- Viral strain
- ART regimen and dose

Adapted from Rainwater-Lovett and CUREiculum

What Has Been Learned from Early-treated infants?

• Reservoirs established very early after infection
• Early cART may restrict but not eradicate HIV reservoirs
  – Potency of regimen and time to viral suppression?
• Periods of remission off ART possible
• Does absence of HIV-specific immunologic response contribute to viral rebound when ART is stopped?
  – Can immunotherapeutic approaches lengthen remission?
• Sensitive biomarkers are needed to predict potential for prolonged remission
  – Target other non-blood reservoirs (gut, CNS)
IMPAACT P1115

“Very Early Intensive Treatment of HIV-infected Infants To Achieve HIV Remission: A Phase I/II Proof of Concept Study”

• Primary Objective: Assess remission (HIV RNA <50 copies/mL for ≥ 48 weeks off ART) in infants treated with cART from birth

• Newborns at high risk of vertical HIV transmission
  – 3 drug cART within 48 hours of birth
  – Infected infants add 4\textsuperscript{th} ARV until HIV RNA <50 copies/ml for >12 weeks; then drop to 3 ARVs

• Sustained viral suppression for ≥ 2 years
  – Evaluate for cART cessation based on state-of-the-art biomarkers
  – Intensive monitoring for viral rebound X 5 years

Miami enrolled the first study subject!
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  – Challenges:
    • Early infant diagnosis
    • What to start
      – Pharmacokinetics, formulation and toxicity concerns
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cART in Infants <3 Months Associated with Improved Clinical Outcomes

European Infant Collaboration Group

Lack of clinical outcome data for treatment of HIV-infected neonates

- Extrapolation from older infants
- Risk vs. clinical benefit needs further study

AIDS 2009; 23(5):597-604

CHER trial, South Africa

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Newborn Treatment Requires Targeted Diagnostic Testing at Birth

- PCR at 4-6 weeks of age
- Challenges:
  - Misses window for early treatment
  - PCR results can take weeks, especially in rural settings
Alere q HIV-1/2 Detect Test

Hsiao N-Y et al. CROI 2015. Seattle, WA. Abs. 34

• Qualitative POC nucleic acid test for HIV-1/2
• Real time PCR system targeting unspliced DNA
• Simple user interface designed for clinic
• Cartridge-based
  • Sample input 25 ul whole blood
  • Duration of test ~55 minutes
  • Throughput: 1 sample per instrument and cartridge

Courtesy L Mofenson
Alere q HIV-1/2 Detect POC
Performance in 90 Newborns <7 days of age

<table>
<thead>
<tr>
<th>Alere q (first test)</th>
<th>Roche CAP/CTM HIV-1 PCR</th>
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<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Positive</td>
<td>14</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
</tr>
<tr>
<td>Inconclusive*</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
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</table>

*Results inconclusive, required repeat testing

- Sensitivity: 93%
- Specificity: 100%
- Inconclusive Rate: 10%

Hsiao N-Y et al. CROI 2015. Abs. 34
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Few ARVs Suitable for Neonates

- Limited drugs with infant formulations
  - NRTI’s
    - Liquids available in high-/middle-income countries
    - Fixed dose dispersible tablets in low-income countries
      - ZDV/3TC tablets (60/30 mg)
        » 5X dose for full-term infants, 7.5X dose for preemies
  - NNRTI’s: NVP syrup
  - PI’s: LPV/r solution
Neonatal Pharmacokinetics

• Changing PK: development and maturation of metabolic pathways in liver and kidney
  – Especially challenging in preterm infants

• NRTIs
  – Term and preterm infants: ZDV
  – Term infants: 3TC/FTC; d4T

• NNRTI’s
  – NVP neonatal *prophylaxis* dose established
    • Investigational dose to achieve *treatment-level exposures* in neonates – 3-4X prophylaxis dose
    • Preterm infants?
Lopinavir Exposure Lower in Infants <6 Weeks of Age (Cohort 1) vs. 6 Weeks-6 months (Cohort 2) \( \text{PACTG P1030} \)

Comparison of lopinavir (LPV) concentration AUCs by Cohort at week 2 of treatment (Tx) and 12 months of age

\[ \text{LPV AUC (mcg*h/ml)} \]

\[ \text{Cohort 1 Week 2 of Tx} \]
\[ \text{Cohort 2 Week 2 of Tx} \]
\[ \text{1 year of Age} \]
\[ \text{1 year of Age} \]

\( P=0.027 \)
\( P=0.94 \)

Chadwick et al. AIDS 2011; 25:643
Severe Toxicity in 10 Neonates Treated with LPV/r

**FDA Pediatric Advisory Committee Report September 23, 2011**

- 8/10 were **preterm** infants (28-35 wks); 1 death
  - Cardiac (n=7)
  - Elevated lactate (2)
  - CNS impairment (3)
  - Acute renal failure (5)
  - Respiratory distress/failure (3)

- Propylene glycol and alcohol in liquid suspension contributing factors

- FDA issued warning against use in infants <42 weeks gestational age
  - unless the *benefit outweighs risk*
Other ARVs Need Further Study

– Raltegravir (RAL) Phase I/II study for term infants enrolling (IMPAACT P1110)
  • RAL competes for bilirubin binding sites → risk for bilirubin toxicity

– Maraviroc neonatal PK study in development in IMPAACT Network

– In the pipeline for study
  • RAL for premature infants
  • Dolutegravir for term and preterm infants
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    • Ethical considerations
Barriers to Early Initiation of cART

• High-income countries
  – Mothers delivering HIV-infected babies may be least amenable to neonatal cART

• Low-middle income countries
  – Different clinical sites for each step of the prenatal → postnatal continuum
    • Early diagnosis and retention in care challenging
Prospective Follow-up of HIV-exposed Infants in a Hospital-based PMTCT Program, Johannesburg, SA

29/38 had IU infection: 8 defaulted for 6 week PCR
Enhanced Support Needed to Treat Newborns

• Interventions to ensure delivery of test results
  – POC virologic testing should facilitate

• Service delivery system to support treatment
  – Long-term engagement in care
    • Distance from health provider, monitoring for toxicity
  – Consistent supply of ARVs
  – Adherence support
  – Psychosocial support
    • Disclosure, stigma, lack of autonomy to make decisions, maternal work schedule
Ethical Issues Surrounding Remission Research in Neonates

- Question: Is the potential for great benefit that carries moderate risk a reasonable alternative to lifelong ART?
- Exposure of uninfected infants to intensive cART
  - Only enroll population at highest risk for infection
  - Carefully monitor safety
  - Rapid diagnosis → remove uninfected infants from study
- Treatment cessation required to test for remission
  - Rigorous criteria for stop and restart of ARVs
- Announcement of favorable interim results → premature adoption as standard of care
Early Antiretroviral Therapy in Newborns

Summary

• Opportunities:
  – Attenuate establishment of viral reservoirs
    • Feasible but further investigation needed
      – IMPAACT P1115: “Very Early Intensive Treatment of HIV-infected Infants To Achieve HIV Remission: A Phase I/II Proof of Concept Study”
  – Prevent early morbidity/mortality
    • Clinical outcomes in neonates needed
Early Antiretroviral Therapy in Newborns

Summary

• Challenges:
  – Early infant diagnosis
    • Point of care testing
  – What regimen to start
    • ZDV, 3TC, NVP, + addition of LPV/r after 2 weeks
      – What if transmitted virus is NVP-resistant?
    • Newer ARVs: need PK and toxicity data
  – Barriers to implementation
    • Enhanced support for treatment and safety monitoring
  – Ethics of remission research
Future Directions

• Enhanced Prevention of MTCT
  – Reduces need for neonatal therapy

• Continued research on feasibility, efficacy, risk/benefit and cost-effectiveness of neonatal therapy
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