Cure Research in Maternal/Pediatric Setting

Deborah Persaud, MD
Chair, HIV Cure Scientific Committee
Forum for Collaborative HIV Research
June 17th, 2014
Global Impact of HIV/AIDS Epidemic in Children (<15 years)

2012 global HIV and AIDS estimates
Children (<15 years)

<table>
<thead>
<tr>
<th>Children living with HIV</th>
<th>3.3 million [3.0 million – 3.7 million]</th>
</tr>
</thead>
<tbody>
<tr>
<td>New HIV infections in 2012</td>
<td>260 000 [230 000 – 320 000]</td>
</tr>
<tr>
<td>Deaths due to AIDS in 2012</td>
<td>210 000 [190 000 – 250 000]</td>
</tr>
</tbody>
</table>

52% reduction from 2001
Latent Reservoir Size and Timing of ART in Perinatal Infection

Model: Persaud D
Perinatal HIV Infection: Opportunity to Assess Immediate ART and Cure

- Timing of HIV exposure is known
- Early reservoir formation may be restricted under routine antiretroviral prophylaxis to prevent mother-to-child transmission
- Reduced viral reservoirs may also occur from the underdeveloped and tolerogenic nature of the infant immune system
Sustained HIV Remission in a Perinatally-Infected Child

- Born in rural Mississippi (US)
- 35 weeks gestation; spontaneous vaginal delivery
- Mother positive for HIV during labor (rapid test)
- No antiretroviral prophylaxis during labor
- Post-exposure prophylaxis with a three drug regimen - AZT/3TC/NVP
- Nevirapine-twice daily dosing; started at 31 hours of age
- Managed at a tertiary care center (University of Mississippi Medical Center)

Sustained HIV Remission (23 months off cART)


Remains under the care of Dr. Hannah Gay of the University of Mississippi Medical Center
Implementing Immediate ART for HIV Cure Research

- Scalable
- Build on PMTCT programs

Added value:
- Focus on early infant diagnosis
- Potential to enhance identification and treatment of HIV-infected infants
- Promote retention in care
- Prolong lives
Cure Scientific Agenda

- Evaluate very early ART to reduce viral reservoirs in neonates to achieve viral remission/cure
- Evaluate specific interventions in chronically infected- youth to reduce HIV reservoirs
  - HIV Vaccines
  - Immunomodulatory agents
  - Inflammatory blockade
- Elucidate relationships between viral reservoirs and the developing immune system
Approaches to HIV Cure

- Latency Reversal Agents (HDAC inhibitors)
- Immune Based Therapies
- Bone Marrow Transplant [Berlin Patient]
- Therapeutic Vaccines
- Gene Therapy
- Very Early Antiretroviral Therapy [Mississippi Child]
- Treatment Intensification
Summary

- HIV-infected children face a life-time of antiretroviral treatment (30 or more years)
- Medication fatigue, antiretroviral toxicities, stigma and social factors promote nonadherence and self-directed treatment interruption
- The developing immune system, opportunity for very early and early treatment, along with thymic reserve set pediatric HIV infection apart
- Provide the scientific rationale for simultaneous conduct of studies towards HIV cure or sustained remission in children
- Approaches guided by scientific reasoning with special attention to risks, benefits and false expectations
International Maternal Pediatric Adolescent AIDS Clinical Trials Group-HIV CURE Scientific Committee

Deborah Persaud (Chair); Ellen C Chadwick (Vice Chair)

**Members**
Jintanat Ananworanich
William Borkowsky
Yvonne Bryson
Mark Cotton
Katherine Luzuriaga
Betsy McFarland
Steve Spector
Thor Wagner
NICHD: Rohan Hazra
NIAID: Patrick-Jean Phillipe, Sarah Read
Biostatisticians: Camlin Tierney, Min Quin
Community Advisory Board Representatives: Sandra Boyd
Committee Specialist: Anne Coletti and Charlotte Perlowski

**Ex-Officio Members**
Dan Barouch
John Mellors
Mike McCune
Steve Nesheim
Bret Rudy
Jeff Safrit

**Former Members**
Ted Ruel
John Sleasman
Rich Daquila

**Mission**
Identify interventions to block establishment and/or maintenance of HIV reservoirs in infected infants, children and adolescents, leading to cure
Acknowledgements

University of Mississippi
Hannah Gay

Parents and their Children

Persaud Laboratory
Carrie Ziemniak
Ya Hui Chen
Kaitlin Rainwater-Lovett
Priyanka Uprety

Katherine Luzuriaga

Yvonne Bryson

National Institute of Allergy and Infectious Diseases
IMPAAACT P1115

Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof of Concept Study
Rationale

• HIV remission reported in a U.S. born child treated with a 3 drug ARV regimen by 31 hours of life for high-risk HIV-exposure from untreated maternal infection

• Emerging data that very early therapy during acute HIV infection in adults and children quantitatively modifies HIV persistence

• Hypothesis: very early ART in neonates with in utero HIV infection permits long-term control of HIV-1 replication off ART and leads to HIV remission, defined as HIV RNA below the limit of detection (LOD) for 48 weeks following ART cessation
Rationale

- HIV remission reported in a U.S. born child treated with a 3 drug ARV regimen by 31 hours of life for high-risk HIV-exposure from untreated maternal infection
- Emerging data that very early therapy during acute HIV infection in adults and children quantitatively modifies HIV persistence
- Hypothesis: very early ART in neonates with \textit{in utero} HIV infection permits long-term control of HIV-1 replication off ART and leads to \textit{HIV remission}, defined as HIV RNA below the limit of detection (LOD) for 48 weeks following ART cessation
P1115 Objectives

Primary Objective

• To assess HIV remission among HIV-infected neonates who initiate ART within 48 hours of birth

Secondary Objectives

• Safety of very early ART in neonates
• Pharmacokinetics in neonates/young infants
  – nevirapine (NVP) at treatment (i.e. higher than prophylaxis) doses
  – lopinavir exposures when dosed with NVP in neonates/young infants
• Relationship between time to reach plasma HIV RNA < LOD and achievement of virologic and immunologic criteria for ART cessation
• Extent of HIV persistence in infants who achieve HIV remission
• Immune activation and host and viral determinants, including maternal factors and HIV-specific immune responses, associated with HIV remission
P1115 Study Design

• **Four operational steps**

• **Two cohorts** of infants enrolled in pairs with their mothers (some breastfeeding, some formula feeding)

  – Cohort 1: *(High Risk)* Infants born to HIV+ mothers receiving no ART during gestation (except in labor/delivery)

  – Cohort 2: *(Early Treated)* Infants initiated ART <48 hrs as clinical care (outside study), and enrolled <10 days of age when birth PCR is positive
# P1115 Study Steps

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td>Initiation of intensive ART for high-risk infants while awaiting HIV test results (if infected, enter Step 2; if uninfected, exit study after four weeks)</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>Continued intensive ART for confirmed HIV-infected infants with monitoring to determine eligibility for cessation of ART between 2 and 4 years of age</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td>ART cessation with monitoring for viral rebound, followed through 5 years of age</td>
</tr>
<tr>
<td><strong>Step 4</strong></td>
<td>ART re-initiation for children who experience viral rebound, followed through 5 years of age</td>
</tr>
</tbody>
</table>
### Accrual into Step 1

**Cohort 1**

**High-Risk Infants**

of unknown HIV status whose mothers received no ARVs during pregnancy, identified within 48 hours of birth:

- up to 320 formula feeding
- up to 120 breastfeeding

- Infants with negative birth PCR exit study at 4 weeks and resume standard HIV perinatal prophylaxis

### Accrual into Step 2

**Cohort 1**

Infants with HIV infection confirmed in Step 1:

- 16 formula feeding
- 6 breastfeeding

**Cohort 2**

**Early Treated Infants**

with at least one positive HIV test who initiated ART within 48 hours of birth outside the study:

- up to 16 formula feeding
- up to 16 breastfeeding
# P1115 Study Drug Regimens

<table>
<thead>
<tr>
<th>Step 1</th>
<th>2 NRTIs + NVP (6 mg/kg twice daily)</th>
</tr>
</thead>
</table>
| **Step 2**   | **START WITH** 2 NRTIs + NVP (6 mg/kg twice daily)  
ADD LPV/r at ≥14 days of age and ≥42 weeks postmenstrual age  
**STOP NVP** when HIV RNA < LOD for ≥12 weeks |
| **Step 3**   | **No ARVS** |
| **Step 4**   | Resume ART if viral rebound in Step 3 |
# Eligibility for Cohort 1

<table>
<thead>
<tr>
<th>Mother</th>
<th>Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Presumed or confirmed HIV infection</td>
<td>• <strong>Step 1: Cohort 1</strong></td>
</tr>
<tr>
<td>• No receipt of ARVs during current pregnancy</td>
<td>• ≤48 hours of age</td>
</tr>
<tr>
<td></td>
<td>• ≥34 weeks gestational age at birth</td>
</tr>
<tr>
<td></td>
<td>• No clinically significant diseases (other than HIV infection) that, in the investigator’s opinion, would interfere with study participation or interpretation</td>
</tr>
<tr>
<td></td>
<td>• <strong>Step 2: Cohort 1</strong></td>
</tr>
<tr>
<td></td>
<td>• Confirmed evidence of <em>in utero</em> HIV infection</td>
</tr>
</tbody>
</table>
# Eligibility for Cohort 2

<table>
<thead>
<tr>
<th>Mother</th>
<th>Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Presumed or confirmed HIV infection</td>
<td>• ≥34 weeks gestational age at birth</td>
</tr>
<tr>
<td>• May have received ARVs during current pregnancy</td>
<td>• ≤10 days of age</td>
</tr>
<tr>
<td></td>
<td>• ≥1 positive nucleic acid test for HIV infection on a sample collected within 48 hours of birth</td>
</tr>
<tr>
<td></td>
<td>• Started ART within 48 hours of birth (clinical decision) and continued daily</td>
</tr>
</tbody>
</table>
Virologic Monitoring
Virologic Monitoring in Step 2

• HIV RNA PCR intensely followed and infants whose viral load is not suppressed <LOD by Week 24 exit the study

• After Week 24, infants with confirmed HIV RNA rebound will exit the study

Infants whose viral load remains suppressed <LOD through Step 2 Week 84 are evaluated for possible entry into Step 3
Criteria to Enter Step 3 and Cease ART

- Has reached Week 96 on study
- Has not breastfed for >6 weeks
- Achieved plasma HIV RNA <LOD by Week 24
- Has had no confirmed HIV RNA ≥LOD after Week 24
Lab Criteria to Enter Step 3 and Cease ART

- All of the following between Weeks 84 and 192
  - Two consecutive negative HIV antibody tests by ≥ third generation ELISA tests ≥8 weeks apart
  - Two consecutive negative HIV DNA tests ≥8 weeks apart
  - No detectable HIV RNA
  - CD4 ≥ 25% and normal for age
Monitoring in Steps 3-4

- **Step 3:** After ART cessation, HIV RNA PCR is intensely monitored
  - If HIV RNA $\geq$ LOD is confirmed on two consecutive tests, the infant enters Step 4

- **Step 4:** Participant re-initiates ART and is closely followed for virologic re-suppression
Safety Monitoring

• **Maximize safety for parts of the protocol outside of standard practice**
  – Investigational “treatment dosing” of NVP for first 2 weeks of life
  – 4 drug ART (LPV/r + NVP + 2NRTIs) until ~6 months
  – ART cessation

• **P1115 Clinical Management Committee** (subset of protocol team) will regularly review clinical and laboratory toxicity data reports

• **IMPAACT Study Monitoring Committee** (independent of protocol team) will review study data approximately every 6 months
  – Primary safety outcome data
  – Permanent discontinuations of ARVs for safety reasons
Guideline for Ad hoc SMC Review of ART Cessation

• Each cohort will be monitored separately

• If 10 out of the first 10 children in a cohort who cease ART have viral rebound, ART cessation will be suspended in that cohort

• If 5 children in a cohort do not re-suppress HIV by 6 weeks after ART re-initiation, ART cessation will be suspended in that cohort

• After any ART suspension, SMC will evaluate future direction of protocol
Panel Discussants

- Sandra Nusinoff Lehrman (Merck, Forum industry co-chair), moderator
- Yvonne Bryson (UCLA, P115)
- Ellen Chadwick (Northwestern, P115)
- Mark Cotton (UStellenbosch, P1115)
- Linda Lewis (CDER/FDA)
- Boris Renjifo (Abbvie)
- Seema Shah (DAIDS/NIH)