International Maternal Pediatric AIDS Clinical Trials (IMPAACT) Network

2015 Annual Meeting Plenary Session
Sharon Nachman, MD – Network Chair
James McIntyre, MD – Network Vice Chair
Grace Aldrovandi, MD – Laboratory Center PI
David Shapiro, PhD – Statistical & Data Management Ctr PI
Mission

- To decrease incident HIV and HIV-associated infections including mother-to-child transmission among infants, children, youth and pregnant/postpartum women
- To decrease HIV-associated mortality and morbidity among these populations
21 US Domestic NIAID and NICHD Sites

NICHD (red)
- Boston Medical Center Pediatric HIV Program
- Jacobi Medical Center Bronx
- University of Washington Children's Hospital Seattle
- Emory University School of Medicine
- San Juan City Hospital PR
- SUNY Stony Brook
- University of Southern California LA
- University of Florida Jacksonville

NIAID (blue)
- University of California, UC San Diego
- U Miami
- Lurie Children's Hospital of Chicago
- St Jude
- Texas Childrens
- University of Puerto Rico Pediatric HIV/AIDS Research Program
31 International NIAID and NICHD Sites

NICHD (red)
- Inst of Pediatrics Fed Univ Rio de Janeiro
- Hospital dos Servidores Rio de Janeiro
- SOM Federal University Minas Gerais Brazil
- Univ of Sao Paulo Brazil
- Hospital General de Agudos Buenos Aires Argentina
- Fundacion Huesped - Hospital Juan A Fernandez
- Hospital Geral De Nova Iguacu Brazil
- Hospital Santa Casa Porto Alegre Brazil

NIAID (blue)
- Siriraj Hospital, Department of Pediatrics-Mahidol University
- PHPT Chiangrai Prachanukroh Hospital
- Hospital Nossa Senhora da Conceicao
- KCMC Kilimanjaro Christian Medical Centre
- Fundacion Huesped, Hospital Juan A Fernandez
- MUHAS University of Health and Allied Sciences
- The Henry M. Jackson Foundation for the Advancement Military Medicine, Inc.

Other Sites
- Makerere University
- Harare Family Care Clinical Research Site
- Seke North Clinical Research Site
- St. Mary’s Clinical Research Site
- George Clinic Clinical Research Site
- Malawi Clinical Research Site
- Soweto IMPAACT Clinical Research Site
- Shandukani Clinical Research Site
HIV Treatment Scientific Agenda

In HIV-infected infants, children and adolescents:

- Safety, pharmacokinetics (PK), and drug-drug interactions
  - new ARVs and formulations
  - novel drug combinations

In HIV-infected pregnant women:

- Safety and PK of ARVs
- Drug-drug interactions
  - e.g., ARVs, TB drugs and contraceptives
HIV Prevention Scientific Agenda

- Prevent mother to child transmission and optimize infant and maternal health outcomes
- Reduce HIV infections in youth combining behavioral and biomedical interventions
  - Primary Prevention
    - Pre-exposure prophylaxis (PrEP)
  - Secondary Prevention
    - Adherence to biomedical interventions, retention and care
HIV/ARV Complications & Comorbidities Scientific Agenda

- Evaluate novel vaccines in HIV-exposed infants
  - Safety and immunogenicity of RSV/other vaccine candidates (building on successful collaboration with NIAID Intramural)

- Prevent & treat cognitive impairment
  - Evaluate long-term neurocognitive outcomes, drug-drug interactions, and relationship to specific ARV therapies
Tuberculosis Scientific Agenda

In HIV-infected infants, children, and pregnant women, evaluate novel:

- Tools for **diagnosis** of TB
- Approaches for **prevention** of TB
- Drugs and regimens for TB **treatment**
Cure Scientific Agenda

- Evaluate early aggressive ART to reduce viral reservoir in neonates and achieve “functional cure”
- Evaluate specific interventions in chronically infected youth to reduce HIV reservoirs
  - Antiretroviral treatment
  - HIV vaccines
  - Immunomodulatory agents
- Elucidate relationships between viral reservoirs and infant immunity
What have we done in the past year...
IMPAAACT Participants on Study
June 2014 to May 2015

Total On Study = 10,681 participants
Newly Enrolled = 1,736 participants
Study Highlight: P1078

Antepartum vs. Postpartum INH Initiation in HIV-Infected Pregnant Women

- Enrolling study within the **Tuberculosis** Research Area
- Primary objective: compare the overall safety and toxicity of immediate vs. deferred INH preventive therapy in HIV-infected pregnant women

950 pairs

R

Arm A (immediate INH)

Arm B (deferred INH)
Study Highlight: P1078
Antepartum vs. Postpartum INH Initiation in HIV-Infected Pregnant Women
Study Highlight: P1078
Antepartum vs. Postpartum INH Initiation in HIV-Infected Pregnant Women

As of 1 June 2015, 337 mother-infant pairs were enrolled across 11 sites in seven countries.
# 30 Active Studies

**June 2014 to May 2015**

<table>
<thead>
<tr>
<th></th>
<th>Pending and Open</th>
<th>13 Enrolling</th>
<th>9 In Follow-up</th>
<th>5 Closed to Follow-up*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td>P1106, P1092</td>
<td>P1110, P1101, P1097, P1093, P1090, P1070, P1026s</td>
<td>P1060, P1066, P1102</td>
<td>P1020a</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td>P1112</td>
<td>(P1081)</td>
<td>1077HS, 1077FF, 1077BF</td>
<td></td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td>P1080</td>
<td>P1104s, P1084s, P1076</td>
<td>P1114, 2000, P1063, P1074</td>
</tr>
<tr>
<td><strong>Tuberculosis</strong></td>
<td></td>
<td>P1078, P1113</td>
<td></td>
<td></td>
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<tr>
<td><strong>Cure</strong></td>
<td></td>
<td>P1107, P1115</td>
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</table>

*closed to follow-up in the last year
## Studies Newly Opened or Enrolling
### June 2014 to May 2015

<table>
<thead>
<tr>
<th>Category</th>
<th>Study Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>P1101: Raltegravir in ART-Naïve HIV &amp; TB Co-Infected Children</td>
</tr>
<tr>
<td>Treatment</td>
<td>P1092: PKs of ZDV, 3TC, and LPV/r in Severely Malnourished HIV-Infected Children</td>
</tr>
<tr>
<td>Prevention</td>
<td>P1112: Safety &amp; PK of VRC01 in HIV-Exposed Infants</td>
</tr>
<tr>
<td>Complications</td>
<td>2000: Recombinant Live-Attenuated RSV Vaccine in RSV-negative Infants &amp; Children</td>
</tr>
<tr>
<td>TB</td>
<td>P1078: Immediate vs. Deferred INH Preventive Therapy in HIV+ Women</td>
</tr>
<tr>
<td>Cure</td>
<td>P1107: Cord Blood Transplant Using CCR5Δ32 Donor Cells - Observed Effects on HIV-1 Persistence</td>
</tr>
<tr>
<td>Cure</td>
<td>P1115: Very Early Intensive Treatment of HIV+ Infants to Achieve HIV Remission</td>
</tr>
</tbody>
</table>
Study Highlight: P1115
Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission

- Enrolling study within the Cure Research Area
- Primary objective: assess HIV remission among HIV-infected neonates who initiate ART within 48 hours of birth
- 12 US sites currently activated, one HIV-infected infant currently on-study; additional sites expected to be activated soon
Study Highlight: P1115 Study Sites

Breastfeeding sites in:
- Haiti
- India
- Kenya
- Malawi
- South Africa
- Tanzania
- Uganda
- Zambia
- Zimbabwe

Formula feeding sites in:
- Argentina
- Brazil
- Thailand
- USA
<table>
<thead>
<tr>
<th>Step 1</th>
<th>Initiation of intensive ART for high-risk infants while awaiting HIV test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2</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>Step 3</td>
<td>ART cessation with monitoring for viral rebound through 5 years of age</td>
</tr>
<tr>
<td>Step 4</td>
<td>ART re-initiation for infants who experience viral rebound after ART cessation through 5 years of age</td>
</tr>
</tbody>
</table>
Study Highlight: IMPAACT P1092
Pharmacokinetics of ZDV, 3TC, and LPV/r in Severely Malnourished HIV-Infected Children

- **Treatment**
- **Research Area**
- Expected to open to accrual in early July
- Sites in Malawi, Tanzania, Uganda, and Zimbabwe
IMPAACT Science Generation
June 2014 to May 2015

18 New Capsules
- 7 Treatment
- 5 Prevention
- 3 Tuberculosis
- 3 Cure

11 New Concepts
- 2 Treatment
- 3 Prevention
- 1 Complications
- 4 Tuberculosis
- 1 Cure

8 New Protocols
- 2 Treatment
- 1 Prevention
- 1 Complications
- 4 Tuberculosis
Eight New Protocols Currently in Development

<table>
<thead>
<tr>
<th>Year</th>
<th>Protocol Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1108</td>
<td>Bedaquiline for Multidrug-Resistant TB (MDR-TB), Study of bioequivalence in crushed form in healthy adults</td>
</tr>
<tr>
<td>2001</td>
<td>Phase I/II Study of Rifapentine and Isoniazid in Pregnant and Postpartum Women with Latent TB</td>
</tr>
<tr>
<td>2002</td>
<td>Treatment of Depression in HIV-Infected Youth: Combined Cognitive Behavioral Therapy and Medication Management</td>
</tr>
<tr>
<td>2003</td>
<td>Protecting Households on Exposure to Newly Diagnosed Index MDR-TB Patients (PHOENIIX)</td>
</tr>
</tbody>
</table>
## New Protocols Currently in Development (cont’d)

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Phase I/II Study of Clade C ALVAC-HIV and gp120 HIV Vaccines in African Infants</td>
</tr>
<tr>
<td>2005</td>
<td>PK &amp; Safety of Delamanid in Combination with OBR for MDR-TB in Children with MDR-TB and HIV Co-Infection</td>
</tr>
<tr>
<td>2006</td>
<td>NextGen Strategy Trial comparing Lopinavir/ritonavir versus Raltegravir-based ART in Children &lt;3 Years of Age</td>
</tr>
<tr>
<td>2007</td>
<td>Safety and PK of Maraviroc in HIV-1-Exposed Neonates</td>
</tr>
</tbody>
</table>
Study Highlight: IMPAACT 2004
Safety and Immunogenicity of 3 Candidate HIV Vaccine Regimens in South African Breastfeeding Infants

- Study in development within the Prevention Research Area
- The primary objectives
  - To assess safety of 3 candidate vaccine regimens when given within five days of birth
  - To determine whether the candidate vaccine regimens induce an early response that is of greater magnitude than the maternally-acquired antibody levels observed among placebo recipients
Study Highlight: IMPAACT 2004

Safety and Immunogenicity of Clade C HIV Vaccine Regimens in South African Breastfeeding Infants

- Population and Sample Size:
  - Breastfeeding infants born to HIV-infected mothers in South Africa
  - 108 mother-infant pairs

- Vaccine Regimens:
  - Infants are randomly assigned to one of six active or placebo vaccine regimens
    (same products as HVTN 100)
Study Highlight: IMPAACT 2004

Infants Born to HIV-Infected Mothers, n=108

Group 1: gp120 only
- Group 1A: n=27
  - Study Vaccination
    - Wk 0: gp120
    - Wk 2: gp120
    - Wk 8: gp120
    - Wk 20: gp120
  - Follow-up for 104 weeks with immunogenicity assessments at Weeks 0, 2, 4, 10*, 14, 22, 36, 52, 76, and 104
  - Extended follow-up for 96 additional weeks with immunogenicity assessments every 24 weeks

- Group 1B: n=9
  - Study Vaccination
    - Wk 0: placebo
    - Wk 2: placebo
    - Wk 8: placebo
    - Wk 20: placebo
  - Follow-up for 104 weeks with immunogenicity assessments at Weeks 0, 2, 4, 10*, 14, 22, 36, 52, 76, and 104

Group 2: conventional prime-boost
- Group 2A: n=27
  - Study Vaccination
    - Wk 0: vCP2438
    - Wk 2: vCP2438
    - Wk 8: vCP2438 + gp120
    - Wk 20: vCP2438 + gp120
  - Follow-up for 104 weeks with immunogenicity assessments at Weeks 0, 2, 4, 10*, 14, 22, 36, 52, 76, and 104
  - Extended follow-up for 96 additional weeks with immunogenicity assessments every 24 weeks

- Group 2B: n=9
  - Study Vaccination
    - Wk 0: placebo
    - Wk 2: placebo
    - Wk 8: placebo + placebo
    - Wk 20: placebo + placebo
  - Follow-up for 104 weeks with immunogenicity assessments at Weeks 0, 2, 4, 10*, 14, 22, 36, 52, 76, and 104

Group 3: accelerated prime-boost
- Group 3A: n=27
  - Study Vaccination
    - Wk 0: vCP2438 + gp120
    - Wk 2: vCP2438 + gp120
    - Wk 8: vCP2438 + gp120
    - Wk 20: vCP2438 + gp120
  - Follow-up for 104 weeks with immunogenicity assessments at Weeks 0, 2, 4, 10*, 14, 22, 36, 52, 76, and 104
  - Extended follow-up for 96 additional weeks with immunogenicity assessments every 24 weeks

- Group 3B: n=9
  - Study Vaccination
    - Wk 0: placebo + placebo
    - Wk 2: placebo + placebo
    - Wk 8: placebo + placebo
    - Wk 20: placebo + placebo
  - Follow-up for 104 weeks with immunogenicity assessments at Weeks 0, 2, 4, 10*, 14, 22, 36, 52, 76, and 104

Notes:
gp120 = Bivalent Subtype C gp120/MF59®
vCP2438 = Clade C ALVAC-HIV (vCP2438)
* Primary immunogenicity outcomes are evaluated at Week 10
Study Highlight: IMPAAACT 2004
Safety and Immunogenicity of Clade C HIV Vaccine Regimens in South African Breastfeeding Infants

- Status:

  Protocol is currently being reviewed by the IMPAAACT Multidisciplinary Protocol Review Group and is projected to be finalized in August 2015.
Publications

- **26** publications submitted in past 12 months
  - **12** manuscripts published in JAIDS, Vaccine, Clinical Pharmacology and Therapeutics, PIDJ, CID
  - **14** approved, pending publication

- Contributed to guidelines
  - OI guidelines in HIV+ children
  - Early inclusion of children in TB drug studies
15 Abstracts Accepted

Treatment
- Long Term Outcomes of Children Initiating NVP vs LPV/r Based Treatment
- PK of Rilpivirine During Pregnancy and Postpartum

Prevention
- Efficacy and Safety of Strategies to Prevent Perinatal HIV Transmission

Complications
- Mortality of HIV-Infected Youth in the cART Era

Cure
- Decay Rate and HIV-1 DNA Reservoir Size Following Early Infant ART
- Selectively Eliminating HIV Latently Infected Cells Without Viral Reactivation
Study Highlight: IMPAACT P1026s
PK of ARV and Related Drugs During Pregnancy and Postpartum

- Study in development within the Treatment Research Area
- Enrolling since March 2003, with over 1,000 participants enrolled across six countries
- Current version – 5 new study arms, AP & PP
- 19 published manuscripts
- 22 presented abstracts
Cross Network Study Initiatives

- MDR-TB Prevention (PHOENIX)
- TB and HIV Vaccine Studies (Aeras/P1113 and IMPAACT 2004)
- RSV and VRC01 Studies (IMPAACT P1114, 2000 and P1112)
- PrEP in pregnant women (Mirror study with HPTN HERS)
Pharma Collaborations: New Formulations/Products

- Dolutegravir PKs in children and pregnant women (P1093, P1026s)
- Maraviroc in infants (IMPAACT 2007)
- Raltegravir in neonates (P1097, 1110)
- Etravirine in infants and children (P1090)
- TB vaccine in infants (P1113)
External Review of Network Science

- IMPAACT External Scientific Advisory Group
- Convened in December 2014
- Charge to panel:
  - Provide critical feedback on the current and planned overall scientific portfolio
  - Identify gaps in the research agenda
  - Provide recommendations for prioritization, future directions, and areas for expansion or contraction
External Review of Network Science

- Overall comments:
  - Science of network is appropriate and addresses the needs of the network
  - Priorities and focus aligned with the epidemic
  - Opportunities for collaboration/synergies with other research groups of continued importance
Site Information

- Completed site portfolios/ site capacity (August 2014)
- Aids in network-wide planning, rapidly identifying sites with specific capabilities for specific studies
  - Avoids duplication of data collection for site selection
- Includes drug regulatory and ethical review requirements
Collaboration between IMPAACT and ACTG to make the large body of specimens collected for HIV research available to investigators

The specimen repositories are a collaboration between the ACTG and IMPAACT clinical trial networks to make the large body of specimens collected for HIV research available to investigators.

ACTG (The AIDS Clinical Trials Group) and IMPAACT (The International Maternal Pediatric Adolescent AIDS Clinical Trials) are two large global efforts studying HIV and related infections.

The specimens stored at the repositories were initially collected for specific studies that have concluded, and are now available to investigators conducting new research.

Using this website

You can use the interactive search tool on this website to learn about the types of specimens available at the repositories. After completing a search, you can see the number of specimens and unique participants available, information about the studies for which they were collected, and what research was published for those studies. The search tool will also provide you with a report that lists your specimens of interest. You can then use this report to help write your research proposal to the network.

<table>
<thead>
<tr>
<th>What's in the repositories?</th>
<th>ACTG</th>
<th>IMPAACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimens</td>
<td>133,046</td>
<td>304,700</td>
</tr>
<tr>
<td>Protocols</td>
<td>195</td>
<td>17</td>
</tr>
<tr>
<td>Types of specimens</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Cryopreserved PBMCs</td>
<td>260,716</td>
<td>579,32</td>
</tr>
<tr>
<td>Plasma</td>
<td>881,257</td>
<td>195,289</td>
</tr>
<tr>
<td>Serum</td>
<td>146,910</td>
<td>107,34</td>
</tr>
</tbody>
</table>

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Early Career Investigator Mentored Research Award

- RFA issued in March 2015; responses due May 27 2015
- 14 applications received with review underway
- Scientific areas, often with overlap, included:
  - Tuberculosis: 3
  - Prevention: 5
  - Treatment: 5
  - Complications: 5
Results Changing Standards of Care

**PROMISE 1077BF/1077FF**

Significantly reduced perinatal transmission among women who took a **triple ARV regimen during pregnancy** compared to zidovudine during pregnancy with nevirapine at delivery and tenofovir/emtricitabine tail.

**IMPAACT P1060**

Long-term virologic suppression was superior in children on **LPV/r-based ART**. Early modest gains in CD4% and growth associated with NVP were no longer statistically significant after 1 year of ART.
Plans for Coming Year:
Continue to push the science forward!