International Maternal Pediatric AIDS Clinical Trials (IMPAAACT) Network

State of the Network
2016 Annual Meeting

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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
- 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)
- Lurie Children’s Hospital of Chicago
- Pediatric Perinatal HIV, Miami
- St. Jude Children’s Research
- Texas Children’s Hospital
- University of California, UC San Diego
- University of Puerto Rico Pediatric

University of Colorado Denver
- South Florida CDC Ft Lauderdale
- Rush University Cook County Hospital Chicago
- Johns Hopkins University Baltimore
- David Geffen School of Medicine at UCLA
- The Children’s Hospital of Philadelphia (CHOP)
- Bronx-Lebanon Hospital Center
30 International NIAID and NICHD Sites

**NICHD (red)**
- Inst of Pediatrics Fed Univ Rio de Janeiro
- Hospital Federal dos Servidores Rio de Janeiro
- SOM Federal University Minas Gerais Brazil
- Univ of Sao Paulo Brazil
- Hospital General de Agudos Buenos Aires Argentina
- Hospital Geral De Nova Iguacu Brazil
- Siriraj Hospital, Department of Pediatrics-Mahidol University

**NIAID (blue)**
- Baylor-Uganda
- Blantyre
- Byramjee Jeejeebhoy
- Chiang Mai University
- Desmon Tutu TB Centre
- FAM-CRU, Cape Town
- Gaborone
- George
- Harare Family Care

**Les Centers GHESKIO**
- Malawi
- Molepolele
- MU-JHU Research Collaboration
- Seke North
- Shandukani
- Soweto IMPAACT
- St. Mary’s
- Umlazi

**PHPT Chiangrai Prachanukroh Hospital**
- Hospital Nossa Senhora da Conceicao
- KCMC Kilimanjaro Christian Medical Centre
- Fundacion Huesped, Hospital Juan A Fernandez
- The Henry M. Jackson Foundation for the Advancement Military Medicine, Inc.
Cure Scientific Agenda

- Functional Cure: Evaluate early aggressive ART to reduce viral reservoir in neonates
- Reservoirs: Evaluate specific interventions in chronically infected-youth
  - Antiretroviral treatment
  - HIV vaccines
  - Immunomodulatory agents
- Future plans: Elucidate relationship between these reservoirs, treatments, and possibility of sterilizing cure
Cure Roadmap

Very Early ART (<48 hours)

- P1115 Plus
  - IMPAACT 2008 VRCO1 to promote viral clearance
  - + T cell based vaccines and immunotherapeutics

Early ART (<12 weeks)

- P1112 (VRCO1 in exposed infants co-endorsed with Prevention)
  - Long-term suppression + LRAs + bNAbS
  - + T cell based vaccines and immunotherapeutics

Late Treated (>12 weeks)

- Long-term suppression + bNAbS

Behaviorally Infected Adolescents

- IMPAACT 2015 (CNS and Tissue Reservoirs)

Perinatally Infected Youth

- ART+LRAs+bNAbS/±-T-cell based vaccines & immunotherapeutics

Timeline:
- 2016
- 2017
- 2018
- 2019
- 2020
## Tuberculosis

<table>
<thead>
<tr>
<th>Estimated total cases in children</th>
<th>1,000,000 (10% global burden)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood cases notified</td>
<td>360,000</td>
</tr>
<tr>
<td>TB deaths</td>
<td>136,000 (81,000 HIV-)</td>
</tr>
<tr>
<td></td>
<td>13.6% case fatality rate</td>
</tr>
<tr>
<td>Pediatric MDR-TB cases</td>
<td>32,000 (underestimate)</td>
</tr>
<tr>
<td>TB infections</td>
<td>6.6 million</td>
</tr>
</tbody>
</table>

WHO 2015 Global TB report www.who.int
Tuberculosis Scientific Agenda

- In HIV-infected infants, children, and pregnant women, evaluate novel:
  - Drugs and regimens for TB treatment
    - DS and MDR TB
  - Approaches for prevention of TB
  - Tools for diagnosis of TB
TB Roadmap

MDR-TB

- IMPAACT 2005 (Delamanid)
- IMPAACT 2003 / ACTG 5300 (PHOENIx Feasibility and PHOENIx)
- BDQ/DLM Co-Treatment (phase 1)
- Clofazimine PK (phase 1)

Pregnancy

- P1108 (Bedaquiline)
- IMPAACT 2003 / ACTG 5300 (PHOENIx Feasibility and PHOENIx)
- BDQ/DLM Co-Treatment (phase 1)
- Clofazimine PK (phase 1)

Infants

- P1078 (INH vs. placebo)
- IMPAACT 2001 (INH + RIF)
- P1026s (TB and MDR-TB)

Perinatally Infected Youth

- P1113 (TB Vaccine)

Co-endorse TB Meningitis RO1

Ultrashort Treatment Regimen

2016  2017  2018  2019  2020
The Global Treatment Environment

Test earlier and closer to birth
Treat earlier and better
Tailor service delivery

- PEPFAR pivot; treating more with less; going faster further, including new initiatives: ACT, DREAM
- Introduction of routine viral load monitoring and ‘point of care’ technologies for early infant diagnosis and viral load monitoring

90% of all living with HIV will know their HIV status
90% of all living with HIV will receive sustained antiretroviral therapy
90% of all receiving antiretroviral therapy will have durable viral suppression
### WHO 2016 Guidelines: When to Start ART

#### 4.3 When to start ART

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4.3.1 When to start ART in adults (&gt;19 years old)</strong></td>
<td>ART should be initiated in all adults living with HIV regardless of WHO clinical stage and at any CD4 cell count (<strong>strong recommendation, moderate quality evidence</strong>). As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count ≤250 cells/mm³ (<strong>strong recommendation, moderate quality evidence</strong>).</td>
</tr>
<tr>
<td><strong>4.3.2 When to start ART in pregnant and breastfeeding women</strong></td>
<td>ART should be initiated in all pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count (<strong>strong recommendation, moderate quality evidence</strong>).</td>
</tr>
<tr>
<td><strong>4.3.3 When to start ART in adolescents (10–19 years of age)</strong></td>
<td>ART should be initiated in all adolescents (10–19 years of age) living with HIV regardless of WHO clinical stage and at any CD4 cell count (<strong>strong recommendation, moderate quality evidence</strong>). As a priority, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adolescents with CD4 count ≤350 cells/mm³ (<strong>strong recommendation, moderate quality evidence</strong>).</td>
</tr>
<tr>
<td><strong>4.3.4 When to start ART in children younger than 10 years of age</strong></td>
<td>ART should be initiated in all children living with HIV, regardless of WHO clinical stage or at any CD4 cell count. Infants diagnosed in the first year of life (<strong>strong recommendation, moderate quality evidence</strong>). Children living with HIV one year old to less than 10 years old (<strong>conditional recommendation, low quality evidence</strong>). As a priority, ART should be initiated in all children ≤2 years old or children younger than 5 years with WHO HIV clinical stage 3 or 4 or CD4 count ≤750 cells/mm³ or CD percentage &lt;25% and children 5 years and older with WHO HIV clinical stage 3 or 4 or with CD4 count ≤350 cells/mm³.</td>
</tr>
</tbody>
</table>
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, PK, and Efficacy of ARVs
- Drug-drug interactions (e.g., ARVs, TB drugs and contraceptives)
## Treatment Roadmap

### New ARVs and Pediatric Formulations
- **P1093 (DTG dosing)**
- **P1090 (ETR dosing)**
- **Triumeq in Young Children**
- **Doravirine**
- **Cabotegravir**

### Pregnancy
- **P1026s (opportunistic look at ARVs in pregnant women)**
- **IMPAACT 2010 (DTG-regimen vs EFV-regimen)**

### Neonates
- **P1106 (ARVs and TB meds in LBW infants)**
- **IMPAACT 2007 (MVC in HIV-exposed)**
- **Dolutegravir in Neonates**
- **IMPAACT 2006 (DTG vs LPV/r in children)**

### ARVs
- **P1092 (ARVs in malnourished children)**
- **P1101 (RAL in HIV+/TB+ children)**

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<table>
<thead>
<tr>
<th>Year</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>IMPAACT 2006 (DTG vs LPV/r in children)</td>
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<tr>
<td>2017</td>
<td>IMPAACT 2007 (MVC in HIV-exposed)</td>
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<tr>
<td>2018</td>
<td>Dolutegravir in Neonates</td>
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<td>2019</td>
<td>IMPAACT 2010 (DTG-regimen vs EFV-regimen)</td>
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<tr>
<td>2020</td>
<td>P1026s (opportunistic look at ARVs in pregnant women)</td>
</tr>
</tbody>
</table>
HIV/ARV Complications & Comorbidities Scientific Agenda

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

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

- Role of inflammation
  - Disease progression, diagnostics, and treatments
Complications & Comorbidities Roadmap

Vaccines
- IMPAACT 2011
- IMPAACT 2012
- IMPAACT 2013

Neuro-Complications
- P1080
- IMPAACT 2002 (depression intervention)

Inflammation
- NWCS 602 (biomarkers)
- IMPAACT 2006 Inflammation Substudy
- Metabolic complications: TDF-TAF
- CAP 519 (international mental health intervention)
HIV Prevention Scientific Agenda

- Prevent perinatal 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
Activities in the Past Year
IMPAAACT Participants on Study
June 2015 to May 2016

Total On Study = 9,946 participants
Newly Enrolled = 2,130 participants
Study Highlight: P1115
Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission

As of 31 May 2016, 99 mother-infant pairs were enrolled across 17 sites in 8 countries (9 pairs in Cohort 2; 90 pairs in Cohort 1).

18 HIV-infected infants as of 31 May 2016
Study Highlight: P1078
Antepartum vs. Postpartum INH Initiation in HIV-Infected Pregnant Women

As of 4 April 2016, accrual was completed with 956 mother-infant pairs enrolling across 13 sites in 8 countries.

Accrual was completed about 4 months ahead of schedule!

Tuberculosis Research Agenda
Study Highlight: IMPAACT 2003
PHOENIx Feasibility, ACTG 5300

- **Tuberculosis** Research Agenda in collaboration with ACTG
- First participant enrolled October 2015
- Last participant enrolled April 2016
- 308 index cases and 1,018 household contacts enrolled
Study Highlight: P1092
PK of ZDV, 3TC, and LPV/r in Severely Malnourished HIV-Infected Children

- **Treatment**
  - Research Agenda
- **Completed enrollment into Cohort 2 in March 2016**
- **Sites in Malawi, Tanzania, Uganda, and Zimbabwe**
Study Highlight: P1106
PK Characteristics of ARVs & TB Medications in LBW Infants

- **Treatment** Research Agenda
- Completed enrollment into Arm 1 (HIV-exposed infants on NVP) in May 2016
- Two sites in South Africa
Study Highlight: IMPAACT 1077
PROMISE Studies

More than 9,000 participants enrolled

- South Africa, 25%
- Malawi, 26%
- Zimbabwe, 15%
- Zambia, USA, Tanzania, China, Haiti, Argentina, Peru, 7%
- Botswana, 5%
- Brazil, 6%
- Thailand, 3%
- India, 2%
- Uganda, 11%

Total: More than 9,000 participants
### Study Highlight: IMPAACT 1077

#### by the Numbers

<table>
<thead>
<tr>
<th>Metric</th>
<th>Count</th>
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</thead>
<tbody>
<tr>
<td>Studies</td>
<td>4</td>
</tr>
<tr>
<td>(1077BF, 1077FF, P1084s, 1077HS)</td>
<td></td>
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<tr>
<td>Countries</td>
<td>15</td>
</tr>
<tr>
<td>Sites</td>
<td>65</td>
</tr>
<tr>
<td>Participants enrolled</td>
<td>&gt;9,000</td>
</tr>
<tr>
<td>Visits completed*</td>
<td>155,946</td>
</tr>
<tr>
<td>CRFs completed*</td>
<td>2,434,824</td>
</tr>
<tr>
<td>Samples stored*</td>
<td>1,223,910</td>
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<tr>
<td>Sites continuing with PROMOTE</td>
<td>8</td>
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<tr>
<td>Lab queries*</td>
<td>&gt;2,500</td>
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<tr>
<td>Data queries*</td>
<td>39,472</td>
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<tr>
<td>DSMB reviews</td>
<td>11</td>
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<tr>
<td>Abstracts presented or accepted</td>
<td>8</td>
</tr>
<tr>
<td>to CROI, AIDS, or Peds Workshop*</td>
<td></td>
</tr>
<tr>
<td>Manuscript accepted to NEJM</td>
<td>1</td>
</tr>
</tbody>
</table>

*and counting!
# 30 Active Studies

## May 2015 to June 2016

<table>
<thead>
<tr>
<th></th>
<th>3 Pending and Open</th>
<th>13 Enrolling</th>
<th>10 In Follow-up</th>
<th>3 Closed to Follow-up*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td>2007</td>
<td>P1026s, P1090, P1092, P1093, P1097, P1101, P1106, P1110</td>
<td>P1060, P1066, P1102</td>
<td>P1070</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td></td>
<td>P1112</td>
<td>1077HS, 1077BF, 1077FF</td>
<td></td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td>P1080</td>
<td>P1076, P1104s</td>
<td>P1084s, P1114</td>
</tr>
<tr>
<td><strong>Tuberculosis</strong></td>
<td>P1108, 2001</td>
<td>P1113</td>
<td>P1078, 2003/5300</td>
<td></td>
</tr>
<tr>
<td><strong>Cure</strong></td>
<td></td>
<td>P1107, P1115</td>
<td></td>
<td></td>
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</tbody>
</table>

*closed to follow-up in the last year
IMPAAACT Science Generation
June 2015 to May 2016

10 New Capsules
- 4 Treatment
- 1 Prevention
- 3 Complications
- 1 Tuberculosis
- 1 Cure

3 New Concepts
- 1 Treatment
- 2 Cure

8 New Protocols
- 2 Treatment
- 1 Prevention
- 3 Complications
- 2 Cure
## Seven New Protocols Currently in Development

<table>
<thead>
<tr>
<th>Year</th>
<th>Protocol Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>Evaluating the HIV Reservoir in the CNS in Perinatally-Infected Individuals on ART</td>
</tr>
<tr>
<td>2014</td>
<td>Phase I/II Trial of the Pharmacokinetics, Safety, and Efficacy of MK-1439 (Doravirine or DOR) and MK-1439A (FDC of DOR + lamivudine + TDF) in HIV-infected Adolescents</td>
</tr>
</tbody>
</table>
### New Protocols
Currently in Development (cont’d)

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>Phase I Placebo-Controlled Study of the Infectivity, Safety &amp; Immunogenicity of a Single Dose of a Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine, RSV/NS2/N/ΔM2-2-HindIII, Lot RSV#011A, Delivered as Nose Drops to RSV-Seronegative Infants 6 to 24 Months of Age</td>
</tr>
<tr>
<td>2012</td>
<td>Phase I Placebo-Controlled Study of the Infectivity, Safety &amp; Immunogenicity of a Single Dose of a Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine, LID cp ΔM2-2, Lot RSV#009A, Delivered as Nose Drops to RSV-Seronegative Infants 6 to 24 Months of Age</td>
</tr>
<tr>
<td>Year</td>
<td>Study Description</td>
</tr>
<tr>
<td>------</td>
<td>-------------------</td>
</tr>
<tr>
<td>2010</td>
<td>Phase III Study of the Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy Regimens in HIV-1-Infected Pregnant Women and their Infants</td>
</tr>
<tr>
<td>2008</td>
<td>Phase I/II Multisite Randomized Controlled Study of Monoclonal Antibody VCR01 Combined with ART to Promote Clearance of HIV-1 Infected Cells in Infants</td>
</tr>
</tbody>
</table>
Publications

- 27 publications submitted in past 12 months
Abstracts

15 abstracts at CROI 2016
- DTG PK in HIV-infected Pregnant and Postpartum Women
- NVP Dosing for Treatment in First Months of Life
- Impact of Maternal TDF Use on HIV-Exposed Newborn BMC
- Breast Milk and In Utero HIV-1 Transmission Select for Unique Envelope Signatures

8 IMPAACT abstracts at AIDS 2016
- 3 abstracts from PROMISE (with 6 abstracts for the HIV Pediatrics Workshop)

Additional abstracts accepted to ICAAC, ICAAP, ICASA, and ID week
Cross Network Study Initiatives

- MDR-TB Prevention (PHOENIX)
- TB and HIV Vaccine Studies (Aeras/P1113 and IMPAACT 2004)
- RSV and VRC01 Studies (IMPAACT 2011/2012/2013 and P1112)
Pharma Collaborations: New Formulations/Products
Site Information

- Updated site profiles including site capacity August 2015
- Aids in network-wide planning, rapidly identifying sites with specific capabilities for specific studies
- Avoids duplication of data collected 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.
Plans for the Upcoming Year... What is on the horizon?

• Continue to work with other networks, partners, community, and scientific experts to develop robust collaborations
• Prioritize new capsules/concept sheets
• Continue Early Career Investigator Program
Plans for the Upcoming Year...

- Complete PROMISE
- Complete enrollment in P1092
- Begin (and complete) the RSV studies
- Finalize IMPAAACT 2006 & 2009
- Complete P1078
- Begin IMPAAACT 2001
- Continue P1026s & P1093
- Develop IMPAAACT 2014 & 2015
- Begin IMPAAACT 2002
- Begin IMPAAACT 2005 and P1108
- Begin IMPAAACT 2007 & 2008
- Begin IMPAAACT 2010
Thank you to the sites, to the community, and to all the individuals and families engaged in clinical research.

Let’s continue to move the science forward!