International Maternal Pediatric AIDS Clinical Trials (IMPAAACT) Network

Update on IMPAAACT Research Agenda: Scientific Committee’s Priorities & Accomplishments

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Overview

- Scientific Committee Updates
  - Drivers of each scientific agenda
    - What are the gaps in our current SC portfolios
    - Data to support studies in these cohorts
    - What studies are we planning to develop

- Lab Updates

- Early Career Investigator Program
What is driving the Cure agenda?
Cure Roadmap

Very Early ART (<48 hours)

Early ART (<12 weeks)

Late Treated (>12 weeks)

Behaviorally Infected Adolescents

Perinatally Infected Youth

P1115 Plus

IMPAACT 2008 VRCO1 to promote viral clearance

+ T cell based vaccines and immunotherapeutics

P1112 (VRCO1 in exposed infants co-endorsed w/Prevention)

Long-term suppression + LRAs + bNAb

Long-term suppression + LRAs + bNAb

+ T cell based vaccines and immunotherapeutics

IMPAACT 2015 (CNS and Tissue Reservoirs)

2016                    2017                    2018                   2019                   2020

P1112 (VRCO1 in exposed infants co-endorsed w/Prevention)

Long-term suppression + LRAs + bNAb

ART+LRAs+bNAb+/T-cell based vaccines & immunotherapeutics
Plans for the Cure Agenda

- Optimizing HIV-1 remission and cure strategies for:
  - Older **infants** with immunotherapeutic agents (for example, IMPAACT 2008 or potential therapeutic vaccine study)
  - Older **children and youth** to reduce residual viremia (for example, characterize anatomic reservoirs and adaptive and innate immune responses)
Study Highlight: IMPAACT 2015
Evaluating the HIV Reservoir in the CNS in Perinatally-Infected Individuals on ART

- Study in development within the Cure Research Agenda
- Cross-sectional study of perinatally-infected youth and young adults on ART with neurocognitive impairment (n=30)
- Primary objective: assess prevalence of detectable HIV RNA and DNA in cerebrospinal fluid (CSF)
What is driving the Tuberculosis agenda?
<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>13.6% case fatality rate</td>
<td></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>

TB Roadmap

MDR-TB

P1108 (Bedaquiline)
IMPAACT 2005 (Delamanid)
IMPAACT 2003 / ACTG 5300 (PHOENIx Feasibility and PHOENIx)
BDQ/DLM Co-Treatment (phase 1)
Clofazimine PK (phase 1)

Pregnancy

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

Infants

P1113 (TB Vaccine)

Perinatally Infected Youth

Co-endorse TB Meningitis RO1

Ultrashort Treatment Regimen

2016 2017 2018 2019 2020
Plans for the TB Agenda

- **MDR-TB**
  - Injectable sparing short-course MDR-TB treatment for children
  - PK of clofazimine

- **DS TB**
  - Treatment shortening with rifampin dose optimization
  - Use of novel drugs

- Nest multiomic and imaging biomarker studies for treatment response

- Understand and expand site capacity for TB and MDR TB studies
What is driving the Treatment agenda?
Rates of viral suppression among 649 perinatally-infected youth, US

Time since diagnosed with HIV

Proportion of adolescents

- On ART
- Viral Suppression
- On ART >6 mo
- Adherence >90%

Kahana, JAIDS, 2015
Rates of viral suppression among 1,547 youth with behaviorally acquired HIV, US

![Graph showing rates of viral suppression by time since diagnosed with HIV](image-url)

Kahana, JAIDS, 2015
Table 4 (C). Drug dosing of liquid formulations for twice-daily dosing in infants less than 4 weeks of age*

**NOTE: LPV/r not recommended for use in infants less than 2 weeks of age**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength of liquid (mg/mL)</th>
<th>2-3 kg</th>
<th>3-4 kg</th>
<th>4-5 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT</td>
<td>10 mg/mL</td>
<td>1 mL</td>
<td>1.5 mL</td>
<td>2 mL</td>
</tr>
<tr>
<td>NVP</td>
<td>10 mg/mL</td>
<td>1.5 mL</td>
<td>2 mL</td>
<td>3 mL</td>
</tr>
<tr>
<td>3TC</td>
<td>10 mg/mL</td>
<td>0.5 mL</td>
<td>0.8 mL</td>
<td>1 mL</td>
</tr>
<tr>
<td>LPV/r****</td>
<td>80/20 mg/mL</td>
<td>0.6 mL</td>
<td>0.8 mL</td>
<td>1 mL</td>
</tr>
</tbody>
</table>

**** Do not use LPV/r solution in infants <2 weeks of age
~1.5 million Pregnant HIV-Infected Women Globally

Considerations for evaluating new drugs during pregnancy

**Pregnant Women**
- **PK** – ensure proper dosing
- **Safety** – identify safety concerns of drug or drug combinations
- **Efficacy** – viral suppression

**Children**
- **Safety** – teratogenicity, birth outcomes, life course impact (short and long term effects)
- **Efficacy** – perinatal transmission, maternal viral suppression
Treatment Roadmap

New ARVs and Pediatric Formulations
- P1093 (DTG dosing)
- P1090 (ETR dosing)

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)
Plans for the Treatment Agenda

- Safety and pharmacokinetics of ARVs in infants, children, and adolescents
  - Doravirine in HIV-Infected Adolescents (IMPAACT 2014)
  - Triumeq® in HIV-Infected Children (Capsule 525)
  - Oral & Injectable Cabotegravir in HIV-Infected Children & Adolescents (Capsule 524)
  - Dolutegravir in HIV-Exposed Neonates (Capsule 521)
Study Highlight: IMPAACT 2010
Efficacy & Safety of DTG-Containing Vs. EFV-containing ART Regimens in HIV-Infected Pregnant Women & Their Infants

- Study in development within the Treatment Research Agenda
- Phase III study among HIV-infected pregnant women and their infants
- Purpose: compare virologic efficacy and safety of three ARV regimens
Arm 1: Maternal DTG+FTC/TAF During Pregnancy and Postpartum

- Maternal follow-up for approximately 12-26 weeks prior to delivery
- Maternal and infant follow-up for 50 weeks after delivery (infant receives local standard prophylaxis)

Arm 2: Maternal DTG+FTC/TDF During Pregnancy and Postpartum

- Maternal follow-up for approximately 12-26 weeks prior to delivery
- Maternal and infant follow-up for 50 weeks after delivery (infant receives local standard prophylaxis)

Arm 3: Maternal EFV/(FTC or 3TC)/TDF During Pregnancy and Postpartum

- Maternal follow-up for approximately 12-26 weeks prior to delivery
- Maternal and infant follow-up for 50 weeks after delivery (infant receives local standard prophylaxis)

n≈183

Weeks on Study Antepartum

- Delivery
- 12-26 weeks
- 6
- 14
- 26
- 38
- 50

Weeks on Study Postpartum
It’s not just about the ARVs

- Where does adherence fit in?
- What about the different populations?
  - Pregnant women
  - Infants
  - Adolescents
Adherence Working Group

- Established in June 2015 with 14 members from IMPAACT, NIH, and external experts
- Purpose to review and provide guidance on IMPAACT studies
  - IMPAACT 2009
  - IMPAACT 2010
  - PHOENIx
Adherence Working Group

- **Collaborative projects**
  - IMPAACT 2010: capsule proposed to explore adherence post-delivery
  - PROMISE: data sharing to evaluate adherence data over time to model adherence over the course of pregnancy and post-delivery

- **Independent projects**
  - Intervention to promote adherence post-delivery
  - Intervention to promote adherence in youth
What is driving the Complications & Comorbidities agenda?
Complications & Comorbidities Roadmap

Vaccines
- IMPAACT 2002
- IMPAACT 2011
- IMPAACT 2012
- IMPAACT 2013

Neuro-Complications
- P1080
- IMPAACT 2006 Inflammation Substudy

Inflammation
- NWCS 602
- IMPAACT 2006 Inflammation Substudy
- IMPAACT 2002
- CAP 519 (international mental health intervention)

Metabolic complications: TDF-TAF
Study Highlight: IMPAACT 2011

RSV Candidate Vaccine Study

- Study OPEN TO ACCRUAL within the Complications Research Agenda
- Phase I placebo-controlled study among healthy RSV-seronegative children 6-24 months of age
- Purpose: determine whether the LID ΔM2-2 1030s vaccine candidate is attenuated and immunogenic
Next Priorities for Vaccines

- Expanded safety and immunogenicity study of promising RSV vaccine candidate
- Expansion of RSV vaccine studies to HIV+ children
- Explore differences in responses between HIV-exposed/uninfected and HIV-unexposed; characterize underlying mechanisms
- Initiate RSV vaccine efficacy trial with NIH
Next Priorities for Neurodevelopmental Research

- Determine best treatment strategies for [depression, ADHD, anxiety, etc.] in HIV-infected youth
- International interventional study addressing mental health
- Define role of inflammatory and immune activation in neurobehavioral and neuropsychologic outcomes
  - Identify anti-inflammatory or other neuroprotective factors that warrant further study
  - Reservoirs; including the CNS
Next Priorities for Inflammation and Immune Activation

- Assess correlations of inflammation/immune activation and HIV complications (CNS, CV, renal, metabolic)
  - Neurobehavioral/neuropsych outcomes and inflammation/immune activation (New Works Concept Sheet 602)
  - International settings
- Incorporate markers of inflammation into studies of mental health interventions (e.g., 2002)
- Anti-inflammatory intervention trial?
  - End-organ assessments
  - Neurobehavioral/neuropsych assessments
What is driving the Prevention agenda?
Prevention

Young Women at High Risk for HIV

- Pregnancy doubles your risk of acquiring HIV infection
- Seroconversion during pregnancy increases:
  - risk to male partners
  - risk to infant

UNAIDS 2016: Global AIDS Update
More Pronounced in Sub-Saharan Africa

- Harmful gender norms and inequalities, insufficient access to education and sexual and reproductive health services, poverty, food insecurity and violence, are at the root of the increased HIV risk of young women and adolescent girls.

- Female centered HIV prevention strategies are needed to protect this vulnerable population, and IMPAACT’s agenda is aligned with other networks to address this need (such as HPTN and MTN).
Prevention Roadmap

**Young Women at Risk**
- PROMISE

**HIV+ Pregnant Women**
- IMPAACT 2009 (oral PrEP in pregnancy)
- VRC07 (LA-bnAb acceptability)

**HIV Exposed Infants**
- IMPAACT 2004 (ALVAC vaccine study)
- P1112 (VRC01)
- CH505 (protein vaccine study)

- PEPFAR PROMOTE
Study Highlight: IMPAACT 2009

PrEP in Pregnant Women

- Study in development within the Prevention Research Agenda
- Purpose: determine feasibility, acceptability, and safety of oral PrEP among HIV-uninfected young women during pregnancy

Diagram:
- 350 pregnant women
- Behavioral HIV risk reduction package
- Accept PrEP
- Decline PrEP
Study Highlight: IMPAACT 2004
HIV Vaccines for Infants

- Study in development within the Prevention Research Agenda
- Purpose: Safety and immunogenicity of Clade C ALVAC-HIV (vCP2438) and bivalent Subtype C gp120/MF59®
- Same vaccine product as in HVTN 100 and HVTN 702
108 Infants Born to HIV-Infected Mothers

Group 1: gp120 only

Group 1A
n=27
Study Product Regimen
Wk 0: gp120
Wk 2: gp120
Wk 8: gp120
Wk 20: gp120
Follow-up for 104 weeks
Extended follow-up for 96 additional weeks

Group 1B
n=9
Study Product Regimen
Wk 0: placebo
Wk 2: placebo
Wk 8: placebo
Wk 20: placebo
Follow-up for 104 weeks

Group 2: conventional prime-boost

Group 2A
n=27
Study Product Regimen
Wk 0: vCP2438
Wk 2: vCP2438
Wk 8: vCP2438+gp120
Wk 20: vCP2438+gp120
Follow-up for 104 weeks
Extended follow-up for 96 additional weeks

Group 2B
n=9
Study Product Regimen
Wk 0: placebo
Wk 2: placebo
Wk 8: placebo+placebo
Wk 20: placebo+placebo
Follow-up for 104 weeks

Group 3: accelerated prime-boost

Group 3A
n=27
Study Product Regimen
Wk 0: vCP2438 +gp120
Wk 2: vCP2438 +gp120
Wk 8: vCP2438 +gp120
Wk 20: vCP2438 +gp120
Follow-up for 104 weeks
Extended follow-up for 96 additional weeks

Group 3B
n=9
Study Product Regimen
Wk 0: placebo+placebo
Wk 2: placebo+placebo
Wk 8: placebo+placebo
Wk 20: placebo+placebo
Follow-up for 104 weeks

IMPAACT 2014
Plans for the Prevention Agenda

- Phase I/II, Placebo-Controlled study of safety & immunogenicity of Clade C ALVAC-HIV (vCP2438) & Bivalent Subtype C gp120/MF59® in South African Infants (IMPAACT 2004)
- Phase I study to evaluate safety & immunogenicity of HIV-1 envelope sequential vaccine (EnvSeq-1) immunization in HIV-exposed infants (Capsule 523)
- Long acting ARV formulations in pregnancy
Samples Shipped This Year

- Site laboratories to repositories:
  - 21 laboratories shipped to BRI
  - 23 laboratories shipped to Fischer
- Shipped almost 230,000 samples of about 1 million stored at sites
- From five studies
  - PROMISE (1077HS, 1077BF, 1077FF)
  - P1078
  - P1060
Early Career Investigator Program

- 2015 Cycle: Fourteen submissions, with three funded
  1. Florence Momplaisir: Effects of Perinatal Depressive Symptoms on Maternal ARV Adherence, HIV Viral Suppression and Infant Outcomes
  2. David Bearden: Biomarkers of Immune Activation and Cognitive Impairment in Children with HIV

- 2016 Cycle: Three submissions, with decisions pending and funding expected by September 2016
Upcoming Meetings

- IMPAACT leadership retreat in January 2017
  - Interface between the lab and the SC agenda
- Annual Meeting in May 2017

More details to come!