State of the Network

Sharon Nachman, MD
IMPAAACT Network Chair
IMPAAACT Community Advisory Board Session
24 June 2021
IMPAAACT’s Goals

To improve health outcomes for infants, children, adolescents and pregnant/postpartum women who are impacted by or living with HIV by evaluating novel treatments and interventions for HIV and its complications and for tuberculosis and other HIV-related conditions.
IMPAAACT in the context of HIV and COVID-19
Response to COVID-19

- Accrual into all IMPAACT studies was paused in March 2020 and resumed in most studies beginning in July 2020, with careful consideration of study conduct in the context of the pandemic and detailed guidance issued for participating sites.
- Ongoing studies continued with high rates of visit completion and protocol compliance and minimal disruption thanks to the awesome diligence and dedication of site staff!!
- The safety and well-being of participants, study staff and their communities remains of utmost importance.

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In addition to implementing ongoing studies in the context of COVID-19, accrual has been initiated or resumed in five studies.
IMPAACT Activities and Achievements in the Past Two Years
Successful Re-Competitions!

- The IMPAACT Network was awarded the grant for another seven years of support by the National Institutes of Health.
- Clinical Research Sites continuing, with the same overall number in the same locations (26 international sites; 19 in the US)

**NIH Announces Restructured HIV Clinical Trials Networks**

Grant Awards Set Stage for Next Seven Years of Science-Driven HIV Clinical Research
Contributions to Expanded Treatment Options

- Three studies have had recent regulatory submissions (P1090/ETV, P1093/DTG, IMPAAACT 2007/MVC)
- Two additional studies (IMPAAACT 2014/DOR, 2017/CAB+RPV) are anticipated to be submitted within the next year
- Over the course of the last grant cycle and moving forward: 12 licensure studies, some with multiple regulatory submissions (RAL, DTG, ETV, MVC, DOR, CAB/RPV, DTG/ABC/3TC, DTG/RPV, remdesivir)
Current Portfolio

includes evaluation of the following interventions/agents

**Treatment**
- DTG/RPV in Children
- DTG in Neonates, Infants, Children and Adolescents
- Selected ARV and TB drugs in Pregnant/ Postpartum Women
- ABC/DTG/3TC in Children
- LA CAB/RPV in Children
- DOR/3TC/TDF in Children
- Oral PrEP (TDF/FTC) in Pregnant & Postpartum Women
- bNAbs in Infants

**Tuberculosis**
- VPM1002/BCG in Pre- Adolescents
- Pretomanid in Children
- RPT/INH in Children
- BDQ in Children
- DLM in Children
- RPT/INH in Pregnant/ Postpartum Women

**Cure**
- LPV and NVP containing early intensive treatment, RAL and NVP containing early intensive treatment, and VRC01 in Infants
- Cord Blood Transplantation with CCR5Δ32 Donor Cells

**Complications**
- RSV vaccines in children
- Group-based counseling intervention in treatment non- adherent Adolescents
### Current Portfolio

#### 30 active studies

<table>
<thead>
<tr>
<th></th>
<th>9 Protocols in Development</th>
<th>3 Pending and Open</th>
<th>9 Enrolling</th>
<th>5 in Follow-Up</th>
<th>4 Closed to Follow-Up*</th>
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<tbody>
<tr>
<td><strong>Complications</strong></td>
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<td>2021</td>
<td>2018</td>
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<td><strong>Cure</strong></td>
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<td>2028</td>
<td>P1115</td>
<td>2008</td>
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<td><strong>COVID-19</strong></td>
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<td>2032</td>
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Approximately 30 additional studies and ancillary studies (NWCS, DACS, DR) in analysis and manuscript writing phase.

*closed to follow-up in the last year
IMPAAACT Participants on Study
June 2019 to May 2020

Total On Study = 1,191 participants
Newly Enrolled = 247 participants
IMPAAACT Participants on Study
June 2020 to May 2021 (during pandemic)

Total On Study = 603 participants
Newly Enrolled = 197 participants
Study Updates and Achievements
Study Highlight: P1093
PK, Safety, & Antiviral Activity of Dolutegravir

▶ Landmark study of child-friendly dolutegravir formulations in children that continues to contribute to FDA and EMA approvals, with ODYSSEY study

▶ Completed accrual with 181 participants enrolled at 35 sites in Botswana, Brazil, Kenya, South Africa, Tanzania, Thailand, Uganda, the United States, and Zimbabwe

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Study Highlight: P1108
PK and Safety of Bedaquiline in Infants, Children, and Adolescents with MDR-TB Disease and with or without HIV

- Addressing critical need for better medications to treat children with MDR-TB
- All five sites approved to resume accrual during the COVID-19 pandemic
- 15 participants enrolled in the past year with 30 evaluable enrolled overall

Anticipate Version 2 issued by July with accrual completion by September 2022

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Study Highlight: P1112
Safety and PK Parameters of Potent Anti-HIV Neutralizing Monoclonal Antibodies

- First of its kind monoclonal antibody study of potential early intervention among infants exposed to HIV
- 83 participants enrolled at sites in South Africa, the United States, and Zimbabwe
- Results from Dose Group 4 recently published in *JID*

Anticipate completing follow-up by February 2022
Study Highlight: P1115
Very Early Intensive Treatment of Infants with HIV to Achieve HIV Remission

- Network’s flagship proof-of-concept study for HIV remission in infants
- 76 mother-infant pairs have enrolled since accrual was approved to resume

- 18 sites have met requirements to resume accrual during pandemic
  - Accrual into Steps 1 and 2 approved to resume in July 2020
  - Entry into Step 3 approved on a site-by-site basis in May 2021

Anticipate enrollment completion by December 2023
Study Highlight: IMPAACT 2008
Study of Monoclonal Antibody Combined with ART

- First to evaluate monoclonal antibodies for treatment (and potential remission) in infants living with HIV
- 61 infants enrolled in Botswana, Brazil, Malawi, and Zimbabwe

Successfully completed follow-up as of 11 February 2021
Study Highlight: IMPAAACT 2014
Doravirine as Fixed-Dose Combination for Adolescents

▶ New fixed-dose, one-pill/once-a-day combination for adolescents
▶ 10 participants enrolled at 4 sites in the US in Cohort 1
▶ 45 participants enrolled at 5 sites in South Africa, Thailand, and the US in Cohort 2

Anticipate completing follow-up by December 2021
Study Highlight: IMPAACT 2017
PK & Safety of Long-Acting Injectable Cabotegravir & Rilpivirine

▷ First study of long-acting injectable regimens in adolescents with HIV
▷ 24 adolescents and 10 parents/caregivers enrolled at 8 sites in the United States
▷ International sites working on approvals to start enrolling

Anticipate completing accrual by July 2022

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Study Highlight: IMPAACT 2019
ABC/DTG/3TC as Fixed-Dose Combination for Children

- New fixed-dose, dispersible, once-a-day combination for young children
- Fully enrolled but pending confirmation of evaluability for lowest weight band
- Participants enrolled at 15 sites in Botswana, Thailand, South Africa, and United States

IMPAACT Annual Meeting 2021
Community Engagement

- Community representation and input on all network groups and levels – clinical research sites, leadership groups, scientific and other committees, protocol teams, cross-network activities

- ICAB ensures that the principles of community participation and partnership are at the foundation of all community engagement activities and provides community input throughout the research process (concept development, study implementation, and results dissemination)
Publications

- 65 publications submitted for IMPAACT review in past 12 months

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Cross Network Study Initiatives

- Pregnancy Studies (IMPAACT 2026)
- MDR-TB Prevention (PHOENIX)
- TB Vaccine Studies (IMPAACT 2036)
- Dolutegravir (P1093/ODYSSEY)
- RSV and VRC Studies (IMPAACT 2011/2012/2013, IMPAACT 2018, IMPAACT 2021; P1112, IMPAACT 2008)

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Plans for the Upcoming Year

- Finalize and begin implementing IMPAACT 2023 and 2029
- Complete follow-up in IMPAACT 2014 and P1107
- Continue follow-up in P1093 and P1112
- Finalize IMPAACT 2034 and 2035
- Finalize P1108 and IMPAACT 2005 amendments
- Continue enrollment in P1115
- Publish IMPAACT 2008, 2010, and 2018 results
- Initiate IMPAACT 2026 and 2028
- Initiate PrEP Comparison Component of IMPAACT 2009
- Continue supporting sites during COVID-19 pandemic
- Continue activating IMPAACT 2017 sites
- Complete accrual in IMPAACT 2019 and 2032
- Publish P1026s, P1080, PROMISE, and P1106 results
Thank you to site staff, to the communities, and to all of the individuals and families engaged in clinical research!

Let’s continue to move the science forward!

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THANKS!

Any questions?
Looking Ahead: IMPAACT Scientific Agenda

IMPAACT Community Advisory Board Session
24 June 2021
Why Do We Need Research in Infants, Children, Adolescents and Pregnant Women?
In 2019, there were 150,000 new pediatric HIV infections.

New diagnoses disproportionately affect adolescents and young adults.

The number of new HIV diagnoses was highest among people aged 25 to 34.

High ART coverage (88%) of pregnant women in focus countries, 2010 – 2019

However, approximately 1.4 million women living with HIV become pregnant annually.
Ethical Obligation for Inclusion

Are Pregnant Women Being Excluded From Clinical Trials?

The “inclusion benefit” in clinical trials

Inclusion of Children in Clinical Trials of Treatments for Coronavirus Disease 2019 (COVID-19)

Inclusion of pregnant and breastfeeding women in research – efforts and initiatives

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Why Do We Need Research in Infants, Children, Adolescents and Pregnant Women?

- The immune system in fetuses and newborns is still developing. This immaturity may alter the pathogenesis and treatment of HIV and other co-occurring conditions.
- Throughout growth and in pregnant women, physiologic changes occur that may affect the use of antiretrovirals and other medications and interventions.
- Developing brains are affected by HIV, what are the effects, can they be prevented or treated?
IMPAAACT Research Agenda, 2020 – 2027
Research Agenda

▷ Advance treatment of pregnant and postpartum women with HIV, aiming to optimize maternal and child health outcomes, and accelerate the evaluation (PK, safety, antiviral efficacy), licensure and optimal use of potent and durable ARVs for pregnant women and infants, children and adolescents with HIV.

▷ Evaluate novel approaches for tuberculosis prevention, diagnosis and treatment in pregnant and postpartum women and infants, children and adolescents with and without HIV that will lead to optimal dosing and regimens, licensing and improved treatment outcomes.

IMPAACT Annual Meeting 2021
Research Agenda

- Determine optimal and feasible methods for the prevention and management of complications of HIV and co-occurring conditions and its treatment in infants, children, adolescents and pregnant and postpartum women.
- Evaluate the potential for ART-free remission through therapeutic interventions aimed at prevention, clearance and post-treatment control of HIV reservoirs in infants, children and adolescents with HIV.
The Network has a robust and growing portfolio of current studies and new concepts in the pipeline across all scientific focus areas.
Overall TB Scientific Committee Goals

“Evaluate novel approaches for TB prevention, diagnosis and treatment in HIV-infected and uninfected infants, children, adolescents, and pregnant and postpartum women that will lead to optimal dosing and regimens, licensing and improved care.”
Global burden of TB in children (< 15 years)

- 12% global burden
- Estimated mortality:
  - <15 years: 240,000
  - <5 years: 190,000
  - Excess TB mortality in HIV: 17%
  - TB: top 10 cause of deaths in children < 5 years
- >95% of the disease burden is DS-TB
- Diagnosis remains challenging
Global burden of TB in children (< 15 years)

- >95% of the disease burden is drug-susceptible TB
- Diagnosis remains challenging

<table>
<thead>
<tr>
<th>Age Group</th>
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<th>Reported</th>
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<tbody>
<tr>
<td>0-4 years</td>
<td>64.8%</td>
<td>35.2%</td>
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<tr>
<td>5-14 years</td>
<td>48.9%</td>
<td>51.1%</td>
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<tr>
<td>All &lt;15 yrs</td>
<td>56.4%</td>
<td>43.6%</td>
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<tr>
<td>All &gt;15 yrs</td>
<td>25.2%</td>
<td>74.8%</td>
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Estimates vs. reporting: estimated global TB case detection gap in children in different age groups, 2019*

*from data reported to WHO, 2020 Global Tuberculosis Report
Age related risk of disease progression to TB: “natural history”

Marais et al. Int J Tuberc Lung Dis. 2004
TB incidence and disease spectrum: a function of age

Figure 1: Conceptual framework to demonstrate the pattern of change in tuberculosis incidence with age. This represents a composite of risk of infection and risk of subsequent disease progression. The presentation of disease is demonstrated by a representative X-ray in a box colored according to the disease phenotype legend.
TB mortality in children < 15 years

Estimated mortality:
- <15 years: 240,000
- <5 years: 190,000
- Excess TB mortality in HIV: 17%
- TB: a top 10 cause of deaths in children < 5 years

Early ART reduces TB in 1st year of life by >3 fold (per 100 patient years)

## Five TB Protocols Currently in Development

<table>
<thead>
<tr>
<th>Year</th>
<th>Protocol Description</th>
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<tbody>
<tr>
<td>2035</td>
<td>Phase I/II Study of the Safety and Immunogenicity of VPM1002 Vaccination and BCG Re-Vaccination against Tuberculosis in South African Pre-Adolescents Living with and without HIV</td>
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<tr>
<td>2034</td>
<td>Phase I Study of PK, Safety, &amp; Acceptability of Pretomanid in Children with Rifampicin-Resistant TB</td>
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<tr>
<td>2025</td>
<td>Safety &amp; PK of 1-Month of Daily versus 3-Months of Weekly Isoniazid and Rifapentine in Pregnant and Postpartum Women with HIV</td>
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<tr>
<td>2024</td>
<td>Phase I/II Dose Finding &amp; Safety of Daily Rifapentine Combined with Isoniazid (1HP) for Tuberculosis Prevention in Children and Adolescents</td>
</tr>
<tr>
<td>2020</td>
<td>Phase II Study of Shortened Oral Treatment for Multidrug-Resistant Tuberculosis in Children (SMaRT Kids)</td>
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</tbody>
</table>
Study Highlight: IMPAACT 2034
PK and Safety of Pretomanid in Infants, Children, and Adolescents with RR-TB with or without HIV

▸ Addressing critical need for better medications to treat children with drug resistant tuberculosis
▸ Collaborative study with TB Alliance

Anticipate Version 1 by December 2021
Study Highlight: IMPAACT 2035
Safety and Immunogenicity of VPM1002 Vaccination and BCG Revaccination against TB in Pre-Adolescents with and without HIV

- Addressing critical need for vaccinations against tuberculosis
- Collaborative study with HVTN

Anticipate Version 1 by end of 2021

Children with TB in South Africa ©WHO/TBP/Gary Hampton

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Planned TB Studies

▸ Evaluate the efficacy, PK and safety of new and shorter drug regimens to prevent TB in infants, children, adolescents and pregnant and postpartum women with and without HIV.

▸ Evaluate novel tools diagnosis of active TB, correlates of TB treatment response and markers of disease progression in infants, children and adolescents with and without HIV.

▸ Evaluate the efficacy, PK, safety and acceptability of new drug regimens, optimize existing drug dosing and evaluate novel drugs for the treatment of TB disease in infants, children, adolescents and pregnant and postpartum women with and without HIV.
  ▪ Study new agents
  ▪ Better understanding of existing TB drugs and optimizing dosing at site-of-disease.

▸ Evaluate novel TB vaccines for prevention of TB disease in infants, children, adolescents and pregnant women.
Access to TB and HIV care during COVID era

• Delayed health care seeking behavior
  • Anxiety to get COVID at hospital
  • Lockdown/ messaging “stay home”

• Decreased focus of health services
  • Overburdened health services
  • Overlapping symptoms
  • Fear to collect respiratory samples

• Decreased laboratory services
  • Overburdened system
  • Supply chain/ Xpert platform

• Reduced access to child health services,
  clinical research, delay of much-needed data
Short-term plan: IMPAACT TBSC

- P2024: protocol completion: 1 HP for TB prevention
- P2034: protocol completion: Pretomanid in DR-RB (single dose PK)
- P2035: protocol completion: VPM vaccine in children LWHIV
- P2020: protocol completion: 6 month all oral MDR-TB treatment
- Develop RFPT bridging study (S31) to extrapolate to children (new WHO recommended 4 month regimen for DS-TB)

- Implement P1108, P2005, P2026 (TB arms)
- Implement A5300/P2003
- Strengthen socio-behavioural research in protocols
- P2201: Disseminate
- P1078 (sub studies)
- P1113: disseminate
- Collaborate on TB pregnancy registry (TBTC, WHO)
- Expand on Mentored Investigator programme including ICAB
5 year plan...

- Complete P1108
- Complete 2005
- Complete A5300/P2003
- Complete P2024
- Complete P2034
- Complete P2035
- Complete P2020

- Develop and implement treatment shortening study: SHINE Plus
drug-susceptible TB – can we shorten treatment to 2 months?
TBSC Mentored programme

- Ethel Weld: MD, Pharm D, JHU
- Yael Hirch-Moverman, PhD: CU
- Sylvia La Course, MD: UW
- Lisa Cranmer, MD: Emory
- Jeff Tornheim, MD: JHU
- Mandar Paradkar, MD: BJMC-JHU CRS
- Pauline Howell, MD: Sizwe, South Africa
- Christy Beneri MD: Stony Brook
- Jennifer Hughes MD: SU
- Nicole Salazar-Austin, MD: JHU
- Louvina van der Laan, MD, Pharmometrics: SU
- Megan Palmer, MD: South Africa
- Faeeza Patel, Shandukani
THANK YOU

Photo taken with permission, Sue Purchase
Anneke Hesseling, Desmond Tutu TB Centre,
Cape Town, South Africa
Complications and Comorbidities
Scope and Priorities

Allison Agwu, MD ScM
IMPAACT C&C Chair
IMPAACT Community and Science Session
June 24, 2021
Complications & Comorbidities Scientific Committee

Chair: Allison Agwu
Vice Chair: Jackie Hoare*
Linda Auriplub*
Sandy Burchett⊥
Steve Innes*
Suad Kapetanovic
MacPherson Mallewa*
Evans Mpabalwani*
Savita Pahwa
Kunjal Patel⊥
Adriana Weinberg

NICHD Rep: Jack Moye
NIAID Rep: Ellen Townley
NIMH Rep: Pim Brouwers
DMC Rep: Alex DiPerna
SDAC Primary Rep: Jane Lindsey
SDAC Secondary Rep: Meredith Warshaw
ICAB Rep: Gwyneth Hendricks*;
Angie Partap
LC Rep: Dale Dayton
Ops Center Coordinator: Jen Libous,
Rachael Jeffrey, Sarah Buisson
SLG Liaison: Grace John-Stewart

*International; ⊥ PHACS
How will WICY with HIV infection be impacted?

- HIV
- ART
- Social determinants
- Co-infections
- Other

What are you going to do about it?
## Summary of Priorities by Region

<table>
<thead>
<tr>
<th>Priorities</th>
<th>Asia</th>
<th>Africa</th>
<th>South America</th>
<th>U.S.</th>
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<td>Cognitive impairment</td>
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<tr>
<td>Psychiatric &amp; mental health (depression, anxiety)</td>
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What's the plan?

ICAB survey 2017
Priorities Specified in IMPAACT Proposal, Aug 2019

• How is ART affecting the brain? Investigate potential neuroprotective and neurotoxic effects of ART to preserve neurocognitive development and mental health in infants, children, and adolescents

• How do we best evaluate and treat the effects on the brain? Refining and optimizing the evaluation and treatment of neurocognitive and mental health disorders, particularly executive dysfunction, depression and PTSD

• Are there new ways to prevent/treat other things that affect children with HIV? Evaluating novel preventive and/or therapeutic approaches to high-priority diseases among pediatric populations with or affected by HIV, including respiratory syncytial virus (RSV), working with NIAID and other partners

• What other conditions are affecting WICY with HIV? How do we best address those? Evaluating other co-morbidities and complications of importance for pediatric, adolescent and pregnant populations with HIV, with other partners and NIH institutes
Priorities Specified in IMPAACT Proposal, Aug 2019

- How is ART affecting the brain (good or bad)?
  - Effect of Maraviroc on neuroinflammation and executive function.
  - MVC added to a suppressive ART regimen in children and adolescents with neurocognitive deficiencies.

- How do we best evaluate and treat the effects on the brain?
  - Interventions for depression in adolescents with HIV, pregnant women with depression
  - Adaption and testing of interventions to improve executive function in children and adolescents with HIV and neurocognitive deficits.

- Are there new ways to prevent/treat other things that affect children with HIV?
  - Phase I-III studies of investigational RSV vaccines in HEU and HIV-unexposed infants and children.

- What other conditions are affecting WICY with HIV? How do we best address those?
  - Low dose aspirin for prevention of preterm birth in women living with HIV (IMPAACT 2027)
  - Outcomes timing of preterm birth; other birth complications and inflammatory cytokines
Overall Critique of Priorities Specified in Proposal

• Lacking investigation into:
  • social and behavioral determinants of health that hinder effective delivery and retention in care
  • older adolescents transitioning to adulthood
  • nutrition
  • growth
  • cardiovascular/cerebrovascular disease

• Lacking expertise in:
  • Development of psychiatric interventions to improve cognition or psychiatric outcomes
  • “Implementation science” within the adolescent population
Overall Critique of Priorities Specified in Proposal

• Overall agenda for neurocognitive studies is not innovative and only proposed adapting research protocols that did not work well in other populations or diseases

• Many of the objectives will be hindered by ability to perform LPs, especially in LMIC

• “Aim 4 is extremely weak. It seems unlikely that many of the proposed studies would actually get off the ground successfully, and even less likely that results would significantly affect the field.”

• “Several intervention studies are planned apparently to take place in LMICs despite that fact that cognitive and neuropsychiatric impairment in children in LMICs with HIV is relatively poorly understood, with few studies evaluating what the drivers/causal pathways of cognitive impairment are.”
Complications Portfolio & Roadmap

NWCS 619 Mechanisms of Preterm Labor with Antiretroviral
CS# 5023: Sofosbuvir/velpatasvir in Pregnant Women Living with Hepatitis C with or without HIV co-infection: safety, PK, and efficacy

Prospective observational study of immune responses to SARS-CoV-2 in children and adolescents living with and without HIV

Paused due to COVID-19 as of March 2020. Full protocol amendment in development to safeguard against COVID-19 and drop a study arm.

Paused due to COVID-19. Select pre-implementation activities proceeded to completion (e.g., intervention manuals). Intervention manuals fully translated.

Permanently discontinued study development due to FDA Blackbox warning around use ASA and NSAIDs in pregnant women of 20 weeks gestation or greater.
Additional Committee Proposals and Responses

Brain:
- Brian games*
- ART intensification
- Inflammatory markers
- Depression, other mental health

Heart:
- Pulse wave velocity*

Inflammation:
- Fish oil*
- Microbicides

Kidney:
- TDF vs. TAF

Liver:
- Hepatitis B
- Hepatitis C*

Premature birth:
- Aspirin
- Factors associated with prematurity

What are you going to do about it?

Phillips Pediatrics 2016; Malee AIDS Care 2011; Scharko AIDS Care 2006; Earnshaw AIDS & Behavior 2018; Griffith OFID 2017; Li JPIIDS 2020; Venkataramani AIDS Pt Care 2010; Tieh et al. J Virus Eradication; Angrand AIDS Care 2018; Agwu JAMA 2012; Jao CID 2017; Lundberg Br J Inf Dis 2017
C&C Scientific Committee Survey Results, April 2021 (N=7)

The committee has put forward proposals that address the priorities.

99% AGREE
Challenges and Opportunities

Challenges:
• Wide-ranging scientific agenda
• Each area requires specified expertise
• Many studies require complicated designs
• Difficult to know what to prioritize/what the SLG and NIH will support

Opportunities:
• Clarify the ask
• Develop strategies to engage or expand expertise
• Consider an RFA-like process
• Revamp the committee
Chair Considerations and Observations

• Consider if/how/when to rotate off the committee/revise committee infrastructure and composition, including leadership
• Evaluate expertise/mechanism to obtain ad hoc expertise
• Evaluate committee member participation and productivity
• Invest in junior investigators ($$, mechanism to quickly/reliably provide them support for time and projects)
• Clarity about network priorities as it relates to C&C
What is the plan?

- Meeting with SLG about next steps
- Seek more clarity from the leadership regarding the most high priority areas for the network
- Committee infrastructure and format
- Capsule/idea process revisited
# Priorities

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A Tribute

William Borkowsky, MD
(1947-2021)
Acknowledgements

Committee Members
Vice Chair : Betsy McFarland
(William Borkowsky)
Yvonne Bryson
Ellen Chadwick
Ann Chahroudi
Mark Cotton
Katherine Luzuriaga
Betsy McFarland
Steve Spector
Thor Wagner

Committee Specialists: Anne Coletti and Charlotte Perlowski

Community Advisory Board Representative
Steven Mphonda
NIAID: Patrick-Jean Phillipe, Judi Miller, Dwight Yin
NICHD: Eric Lorenzo, Sai Majji
NIMH: Pim Brouwers
Biostatisticians: Camlin Tierney, Bryan Nelson, Jane Lindsey, Meredith Warshaw
IMPAACT SLG Liason: John Sleasman
IMPAACT Leadership: Sharon Nachman, James McIntyre, Pat Flynn and Philippa Musoke

New Protocol Team Investigators
Julie Rosebush, DO (2028)
Shaun Barnabas, MD, PhD (2028)
Samantha Fry, MD (2028)
Alka Khaitan, MD (2008)

Clinical Site Investigators
Parents, Guardians and the Children
Community Representatives
Overarching Goal of the HIV Cure/ART-free Remission Scientific Committee

- Find new ways to treat HIV infection in infants, children and adolescents that will allow HIV to remain controlled to undetectable levels in plasma without antiretroviral drugs (sustained ART-free HIV remission and cure)
Goal: Limit the Cells that allow HIV to survive for a lifetime despite ART: Barriers to a Cure

Cases of HIV Cure (N=2)

2021

Berlin Patient (2009)

Hematopoetic stem cell transplant with CCR5 Δ32/Δ32 homozygous cells as part of cancer treatment

London Patient (2019)
What do we mean by HIV Cure

**Cure:** The therapies got rid of all of the HIV reservoirs to allow ART to be stopped with no return of plasma virus

**Berlin patient:** no virus return for 12 years up to his passing from cancer relapse

**London patient:** no virus return for 30 months off ART 16 months after his transplant; considered cured

Reviewed in: Chun TW, Eisinger RW, and Fauci AS. JAMA 2019
Cure and Remission

**Cure**: Complete eradication of HIV reservoirs to allow ART discontinuation

**Sustained virologic remission**: Control of viral rebound off ART even though HIV reservoirs are present

Reviewed in: Chun TW, Eisinger RW, and Fauci AS. JAMA 2019
Cases of Sustained HIV Remission in Children
Optimism and Hope for Remission in Perinatal Infection: Very Early and Early ART

**Mississippi Baby (2013)**
- No plasma virus for 27 months off ART

**French Adolescent (2016)**
- No plasma virus rebound for >12 years

**South African Boy (2019)**
- No plasma virus rebound for 8.5 years

IMPAAACT HIV Cure Clinical Trials (2013—

Very early and early ART Plus Immunotherapeutics (broadly neutralizing antibodies-IMPAACT P1115 and P2008
IMPAACT P1115
Prospective Phase I/II
Proof-of-Concept Study of Very Early ART to Achieve ART-free HIV Remission in Infants

Protocol Chairs: Ellen Chadwick, Jennifer Jao
Vice Chairs: Mark Cotton and Yvonne Bryson (Chair for V1.0)
Step 1: Initiation of ART within 48 hours of life for high-risk infants

Step 2: Continued ART with confirmed HIV-1 infection with monitoring to determine eligibility for ART cessation between 2 - 4 yrs of age

Step 3: ART cessation with close monitoring for viral rebound if antibody negative and no HIV infected cells detected

Step 4: ART re-initiation for infants who experience viral rebound

Primary Objective:
To assess HIV remission among *in utero* -infected neonates who initiate very early therapy within 48 hours of birth

HIV remission: Case Definition
No confirmed plasma HIV RNA ≥ limit of detection of the viral load assay through 48 weeks of stopping ART

clinicaltrials.gov NCT02140255
IMPAACT P1115: Progress to Date

- 440 high-risk HIV-exposed infants enrolled at 30 sites in 11 countries (Version 1.0)
- Countries: Brazil, Haiti, Kenya, Malawi, South Africa, Tanzania, Thailand, USA, Uganda, Zambia and Zimbabwe
- 34 infected infants in Cohort 1 and 20 infants in Cohort 2
- Version 2.0 is open and enrolling (raltegravir-based ART +/- VRCO1; 100 mother-infant pairs enrolled so far
- Study participants on study beginning to undergo evaluation for Step 3
What have we learned from IMPAAACT P1115 (V 1.0)

- Early infant testing is feasible in resource-constrained settings
- Very early ART can be successfully implemented at IMPAAACT clinical trial sites
- Pre-emptive ART with nevirapine-based regimen is safe and well-tolerated
- PK established for treatment dosages of nevirapine for neonates (Ruel T et al. Lancet HIV 2020)
- Virologic effects of very early ART on reservoir size (manuscript in preparation)
- Strategy successful enough to have 8 of 54 infants on study to assess the primary outcome of HIV remission
IMPAACT 2008
Phase I/II Multisite, Randomized, Controlled Study of Monoclonal Antibody VRC01 with Combination Antiviral Therapy to Promote Clearance of HIV-1-Infected Cells in Infants

IMPAAACT 2008

Study treatment: Four VRC01 doses (0, 2, 6, 10 weeks +ART)

Kwong PD et al. Nature Reviews/Immunology 2013

Protocol Chairs: Betsy McFarland, Alka Khaitan and William Borkowsky (NYU); Collaboration with the Vaccine Research Center at the NIH (Rick Koup; Lucio Gama, Julie Ledgerwood and John Mascola and Barney Graham)
Accrual ended March 2020
61 of 64 infants planned for enrollment due to COVID pandemic
Countries: Botswana, Brazil, Malawi and Zimbabwe
Analysis of primary endpoint anticipated Late Summer 2021
What have we learned from IMPAACT 2008

- Accrual was feasible
- Subcutaneous infusion of multiple doses of broadly neutralizing antibodies are feasible and well tolerated
IMPAACT 2015
Evaluation of the HIV-1 Reservoir in the Central Nervous System of Perinatally-Infected Youth and Young Adults with Cognitive Impairment

Protocol Chairs: Ann Chahroudi & Thor Wagner
Study Objectives (P2015)

Primary Objective:
To assess the CNS as HIV-1 reservoirs

Secondary Objective:
To assess for associations of CNS HIV-1 reservoirs and biomarkers of inflammation and neuronal injury in blood and CSF
Study Schema

**Study Population:** Youth and young adults (13-24 years of age) living with perinatal infection; on suppressive antiretroviral therapy; history of neurocognitive impairment

**Study sites:** U.S based sites only

**Sample size:** Up to 45 to achieve 30
plasma HIV-1 RNA <20 copies/mL
minimum required volume (10 mL) of CSF for study goals.

**Design:** Cross-sectional, multisite, exploratory observational study.
Participating Sites and Study Update

- 58 individuals screened at 10 of 12 sites starting in Oct 2018
- 24 participants enrolled at 9 sites
  - aged 13-18 years (N=8)
  - 16 aged 19-24 years (N=16)
  - 22 participants underwent LP; successful in 20
- Data analysis expected to be completed in next 2-3 months
- **Lessons learned:** Spinal tap as part of HIV cure studies was acceptable to our site staff and study participants.
IMPAACT P1107
Cord Blood Transplantation Using CCR5 delta 32 Donor Cells in HIV-1-Infected Persons who Require BMT and its Observed Effects on HIV-1 Persistence

Protocol Chair: Yvonne Bryson in collaboration with ACTG (Marshall Glesby and Koen van Biesen at Weill-Cornell Medical College)

Two participants enrolled: One alive and in follow-up African American woman s/p haplocord transplant with CCR5 delta 32 homozygous cells in 8/2017
Summary of IMPAACT HIV Cure/Remission Trials

- Substantial progress in protocol development, study participation and study completion in IMPAACT cure/remission-related clinical trials in pediatrics and across the age-spectrum
- Specific emphasis in resource-constrained settings
- Studies have contributed to the pipeline of novel therapies and approaches for perinatal infection in neonates and infants
- Information from current studies will inform our future trials aimed at boosting HIV-specific immune responses through use of therapeutic vaccines and combinations of broadly neutralizing antibodies
Acknowledgements

Committee Members
Vice Chair : Betsy McFarland
(William Borkowsky)
Yvonne Bryson
Ellen Chadwick
Ann Chahroudi
Mark Cotton
Katherine Luzuriaga
Betsy McFarland
Steve Spector
Thor Wagner

Committee Specialists: Anne Coletti and Charlotte Perlowski

Community Advisory Board Representative
Steven Mphonda

NIAID: Patrick-Jean Phillipe, Judi Miller, Dwight Yin
NICHD: Eric Lorenzo, Sai Majji
NIMH: Pim Brouwers

Biostatisticians: Camlin Tierney, Bryan Nelson, Jane Lindsey, Meredith Warshaw

IMPAACT SLG Liaison: John Sleasman
IMPAACT Leadership: Sharon Nachman, James McIntyre, Pat Flynn and Philippa Musoke

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Thank you and Questions
Acknowledgments

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Treatment Scientific Committee Activities

Pat Flynn, MD
CAB Session
24 June 2021
IMPAAACT Research Agenda, 2020 – 2027
IMPAACT Annual Meeting 2021
Advance treatment of pregnant and postpartum women with HIV, aiming to optimize maternal and child health outcomes, and accelerate the evaluation (PK, safety, antiviral efficacy), licensure and optimal use of potent and durable ARVs for pregnant women and infants, children and adolescents with HIV.
HIV Treatment

Scientific Committee Chairs: Theodore Ruel and Moherndran Archary
### HIV Treatment

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<tr>
<th>Priority</th>
<th>Description</th>
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<td><strong>Priority 1</strong>:</td>
<td>Characterize the PK properties and dosing of ARVs and relevant drug-drug interactions (DDIs) among women during pregnancy and lactation, and their infants</td>
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<td><strong>Priority 2</strong>:</td>
<td>Evaluate novel prophylaxis regimens for infants born to women with HIV</td>
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<td><strong>Priority 3</strong>:</td>
<td>Identify and rapidly evaluate the PK, safety, antiviral efficacy of the most promising ARVs for first line treatment, accelerating licensure for pediatric populations living with HIV. Preventative and/or therapeutic approaches for high-priority diseases</td>
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<td><strong>Priority 4</strong>:</td>
<td>Conduct PK and clinical studies necessary to optimize use of current ARVs in achieving virologic suppression among pediatric populations with ARV experience</td>
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Priority 1: Characterize the PK properties and dosing of ARVs and relevant drug-drug interactions (DDIs) among women during pregnancy and lactation, and their infants

- P1026S – investigation of PK in pregnant and postpartum women receiving commercially available agent
  - 32 publications and 42 abstracts

- IMPAACT 2026 – Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum
  - Pregnant WLHIV receiving oral ARVs and no TB drugs, and their infants
  - Pregnant WLHIV and HIV-uninfected women who received long-acting/extended release ARVs during pregnancy, and their infants
  - Pregnant WLHIV receiving ARVs and first-line TB treatment, and their infants
  - Pregnant WLHIV and HIV-uninfected women receiving second-line TB treatment, and their infants
  - Postpartum WLHIV breastfeeding while receiving oral ARVs, and their infants
IMPAACT 2010 / VESTED - 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

- When started in pregnancy, DTG-containing regimens had superior virological efficacy at delivery compared with the EFV/FTC/TDF
- DTG/FTC/TAF had the lowest frequency of composite adverse pregnancy outcomes and of neonatal deaths

Lockman S et al. Lancet: 397, 1276, 2021
Priority 2: Evaluate novel prophylaxis regimens for infants born to women with HIV

- Building on IMPAACT 1097 and 1110 studies of raltegravir
- IMPAACT 2023 - A Phase I Study of the Safety, Tolerability, and Pharmacokinetics of Dolutegravir in Neonates Exposed to HIV-1
  - Awaiting final version, June 2021
- Trial sites in US, South Africa, Thailand, Brazil
Priority 2: Evaluate novel prophylaxis regimens for infants born to women with HIV

- IMPAACT – WHO Collaboration
  - Goal - generate a consensus on the optimal design to investigate innovative strategies to prevent vertical transmission in the perinatal and postnatal period
    - Reworking currently available ARVs
    - Exploration of new ARVs, including long-acting injectables
    - Broadly neutralizing antibodies
    - Delivery mechanisms
    - Delivery frequency
    - Study design
Priority 3: Identify and rapidly evaluate the PK, safety, antiviral efficacy of the most promising ARVs for first line treatment, accelerating licensure for pediatric populations living with HIV. Preventative and/or therapeutic approaches for high-priority diseases

- P1093 – pediatric dosing of DTG – Film-coated and dispersible tablets
Priority 4: Conduct PK and clinical studies necessary to optimize use of current ARVs in achieving virologic suppression among pediatric populations with ARV experience

- 2014 – defining appropriate population for adult tablet, complete
- 2017 – first trial of long-acting injectable agents in adolescents, enrolling
- 2019 – dose confirmation of ABC/DTG/3TC dispersible, near completion
- 2022 – long-acting injectables in non-adherent youth, pending
- 2029 - DTG/RPV – *Juluca* switch, anticipating late 2021
- 2036 – long-acting injectables in children 2-<12 years of age, in development, expected late 2021

IMPAACT Annual Meeting 2021
We will be busy! 2020-2027

IMPAACT Annual Meeting 2021
Thank you!

It takes a village!
We couldn’t do it without you!