State of the Network

Sharon Nachman, MD
IMPAACT Network Chair
IMPAACT Community Advisory Board Session
24 June 2021

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

IMPAACT'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

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IMPAACT in the context of HIV and COVID-19

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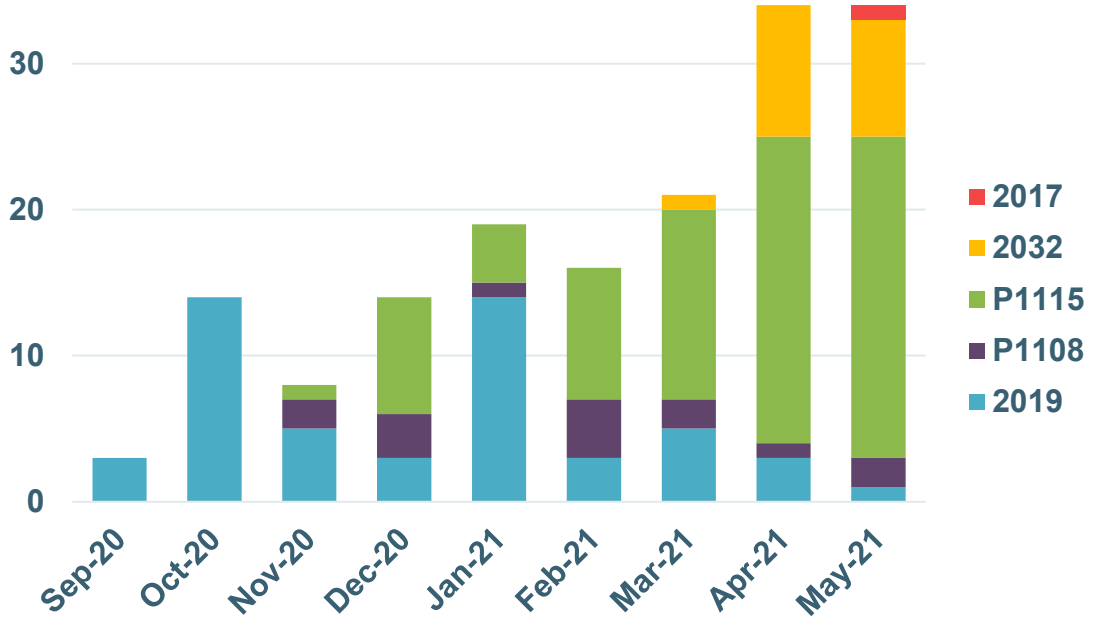
Response to COVID-19

- 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

Response to COVID-19

In addition to implementing ongoing studies in the context of COVID-19, accrual has been initiated or resumed in five studies



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IMPAACT Activities and Achievements in the Past Two Years

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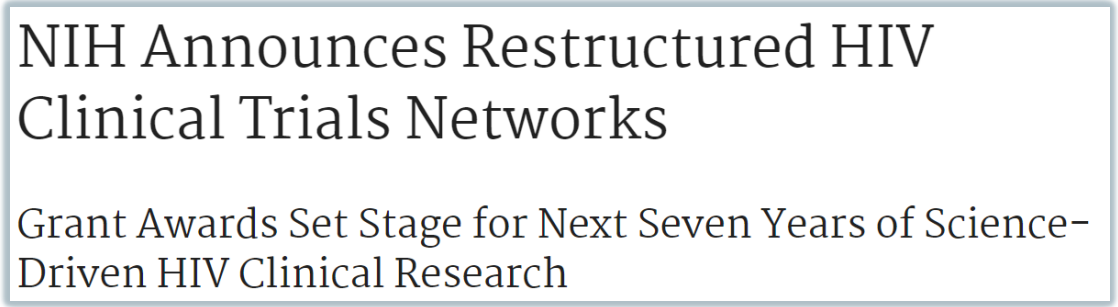
Successful Re-Competitions!

- 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)



Contributions to Expanded Treatment Options

- Three studies have had recent regulatory submissions (P1090/ETV, P1093/DTG, IMPAACT 2007/MVC)
- Two additional studies (IMPAACT 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

Complications
- RSV vaccines in children
- Group-based counseling intervention in treatment non-adherent Adolescents

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

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Current Portfolio

30 active studies

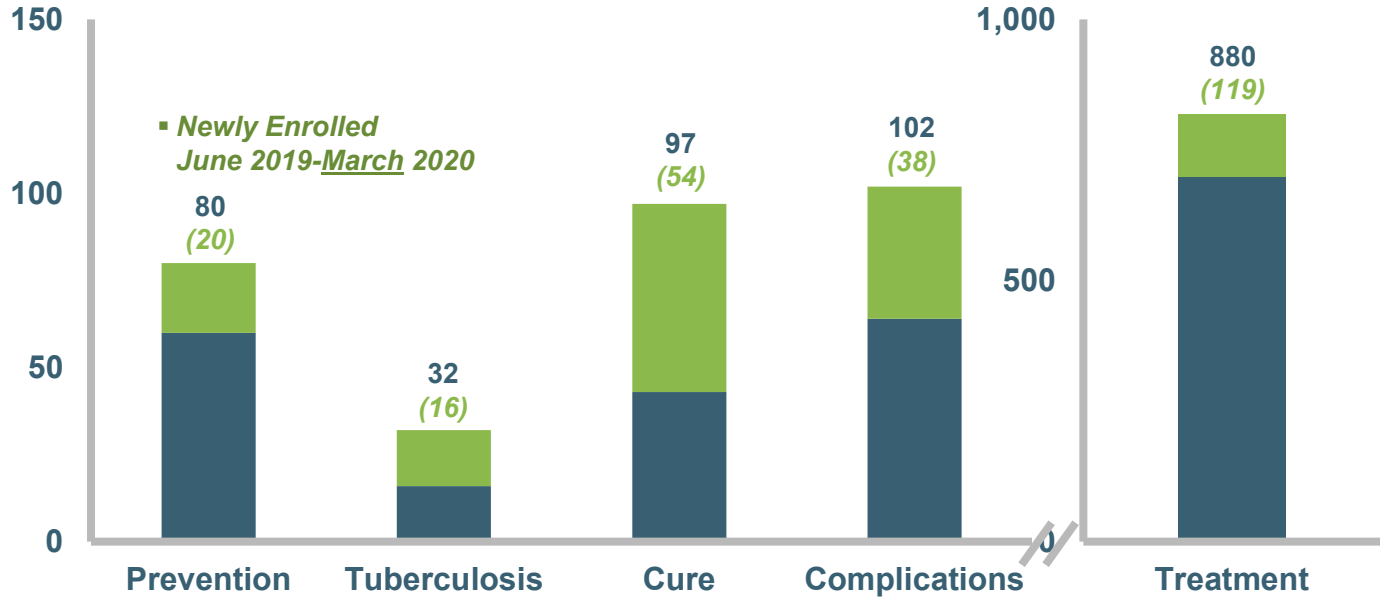
	9 Protocols in Development	3 Pending and Open	9 Enrolling	5 in Follow-Up	4 Closed to Follow-Up*
Treatment	2036, 2029, 2023, 2022	2026	2019, 2017, 2009	2014, P1112, P1102, P1093	2010, P1026s
Tuberculosis	2035, 2034, 2025, 2024, 2020		2003B/A5300B, 2005, P1108		
Complications		2016	2021		2018
Cure		2028	P1115	P1107	2008
COVID-19			2032		

Approximately 30 additional studies and ancillary studies (NWCS, DACS, DR) in analysis and manuscript writing phase

*closed to follow-up in the last year

IMPAACT Participants on Study

June 2019 to May 2020

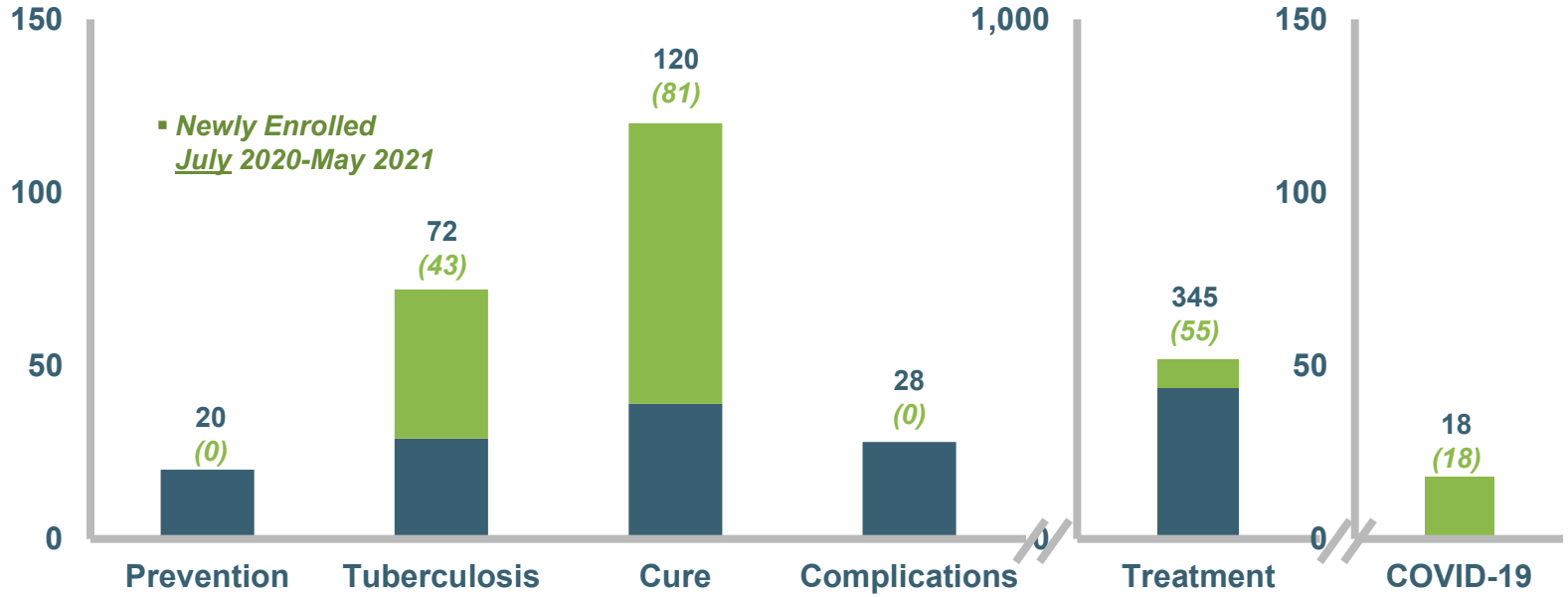


Total On Study = 1,191 participants

Newly Enrolled = 247 participants

IMPAACT Participants on Study

June 2020 to May 2021 *(during pandemic)*



Total On Study = 603 participants

Newly Enrolled = 197 participants

Study Updates and Achievements

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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

Drug Topics

FDA Approves Dolutegravir Tablets for Oral Suspension for ...

Officials with the FDA have approved dolutegravir (Tivicay PD, ViiV ... The new approval is based on data from the ongoing P1093 and ...

Jun 12, 2020

PharmaTimes

EU approval for ViiV's Tivicay for children living with HIV

... formulation of its HIV-1 treatment Tivicay (dolutegravir) in paediatric patients ... The approval is based on data from the ongoing P1093 and ...

Jan 14, 2021

Aidsmap

Dolutegravir superior to standard-of-care treatment in children ...

Dr Anna Turkova of the United Kingdom Medical Research Council presented the 96-week results of the ODYSSEY study at the 2021 virtual ...

Mar 12, 2021

MPR

Tivicay Labeling Updated to Include More Pediatric HIV Patients

... open-label, non-comparative, P1093 IMPAACT study that evaluated dolutegravir in combination regimens in HIV-1 infected infants, children, ...

Jun 10, 2016

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

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

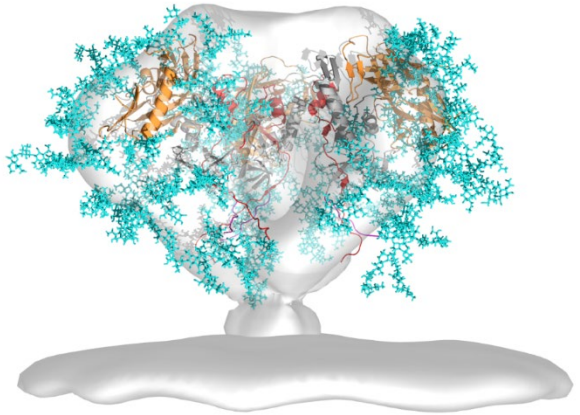
- Network's flagship proof-of-concept study for HIV remission in infants
- 76 mother-infant pairs have enrolled since accrual was approved to resume
- 18 sites have met requirements to resume accrual during pandemic
  - Accrual into Steps 1 and 2 approved to resume in July 2020
  - Entry into Step 3 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: IMPAACT 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

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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)

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Publications

- **65** publications submitted for IMPAACT review in past 12 months
- **35** manuscripts published in JAIDS, AIDS, JAMA, PLoS One, Lancet, Lancet HIV, Journal of Clinical Pharmacology, PIDJ, CID, among others

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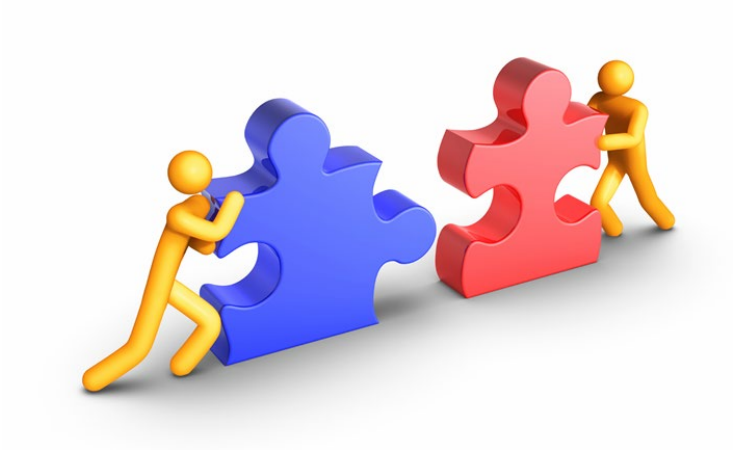
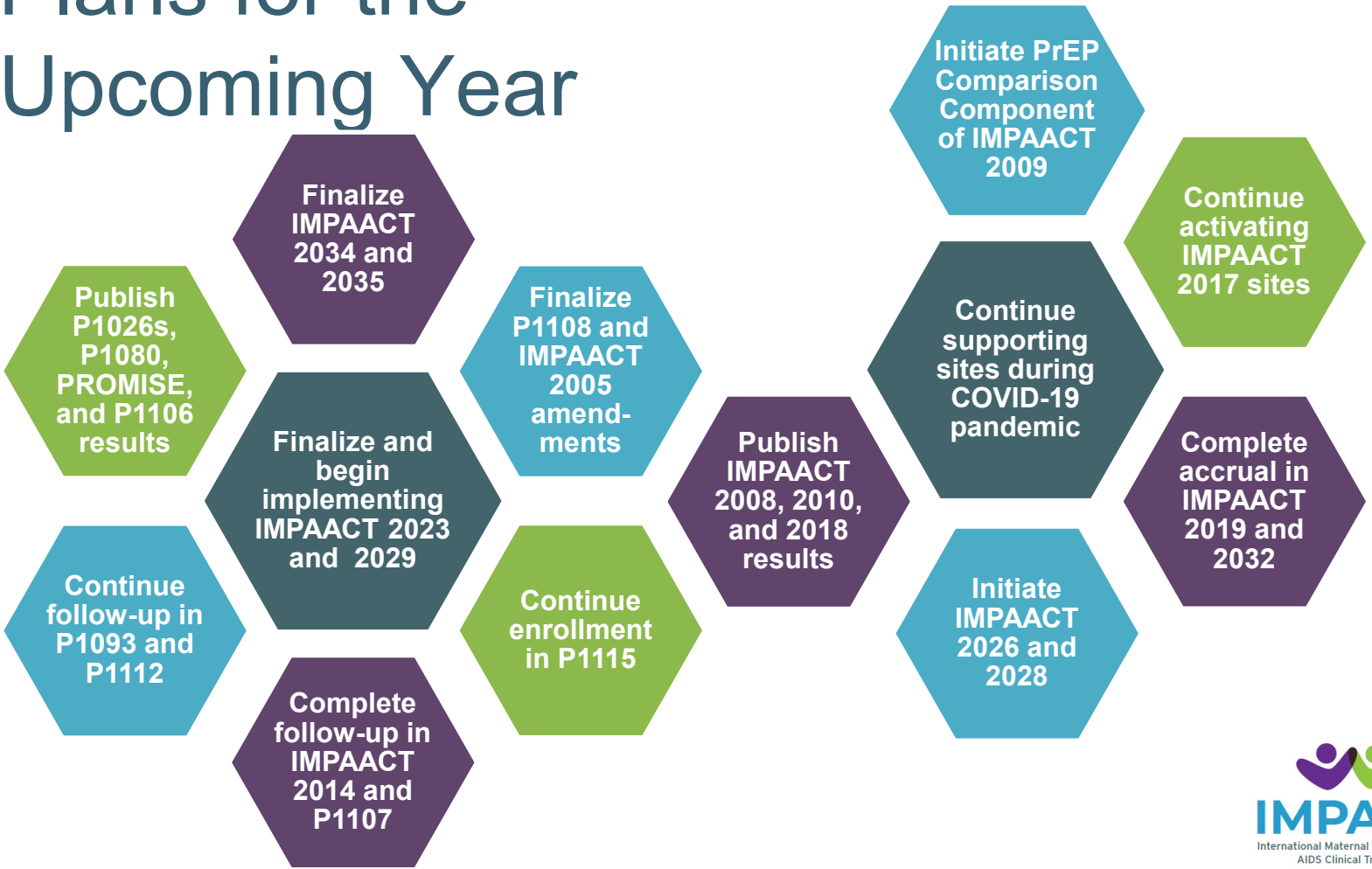
Cross Network Study Initiatives

- 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)



Plans for the Upcoming Year



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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!

THANKS!

Any questions?

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Looking Ahead: IMPAACT Scientific Agenda

IMPAACT Community Advisory Board Session
24 June 2021

IMPAACT Annual **Meeting** 2021

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

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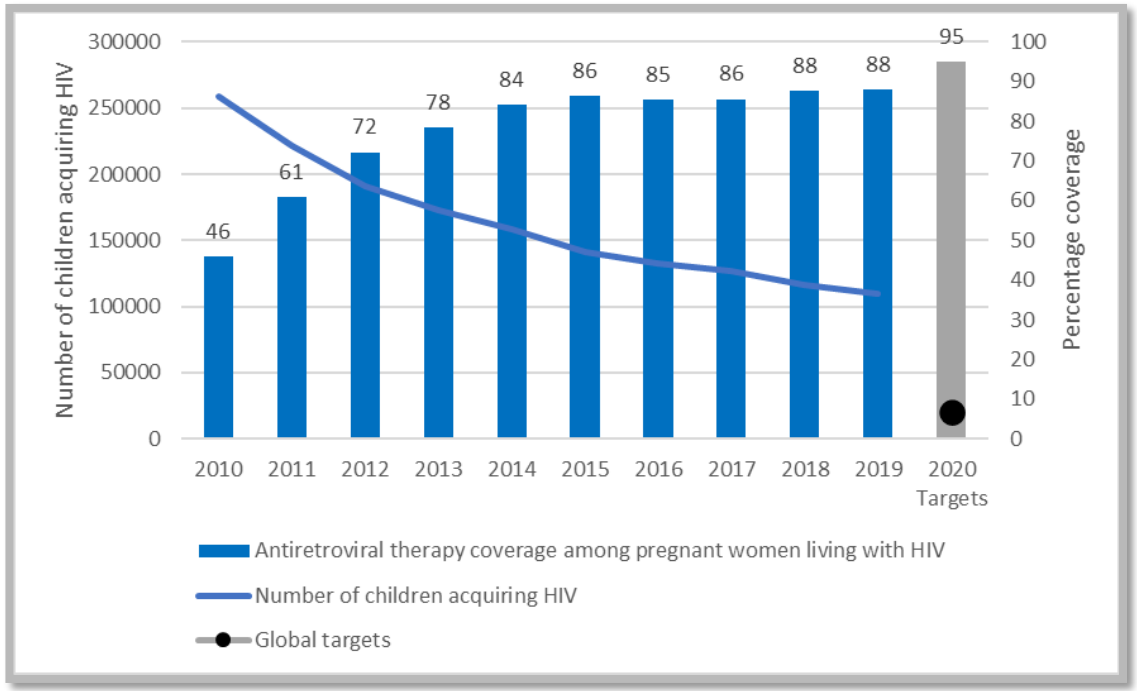
In 2019, there were 150,000 new pediatric HIV infections

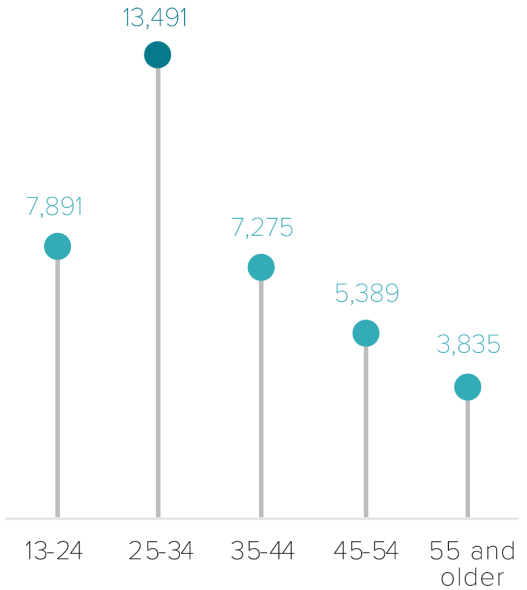


Source: UNAIDS; https://www.unaids.org/sites/default/files/media_asset/2020_aids-data-book_en.pdf

New diagnoses disproportionately affect adolescents and young adults

New HIV Diagnoses in the US and Dependent Areas by Age, 2018

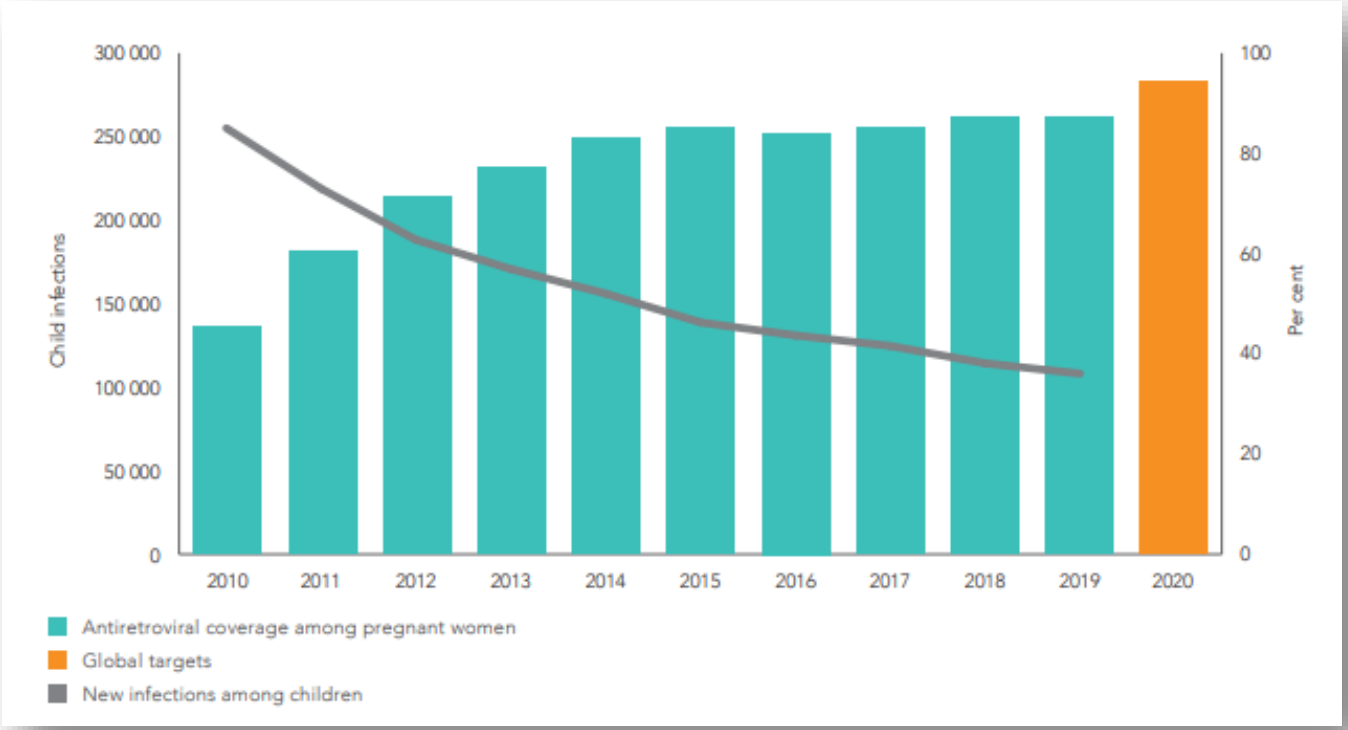
The number of new HIV diagnoses was highest among people aged 25 to 34.



Source: CDC. Diagnoses of HIV infection in the United States and dependent areas, 2018 (updated). *HIV Surveillance Report* 2020;31.

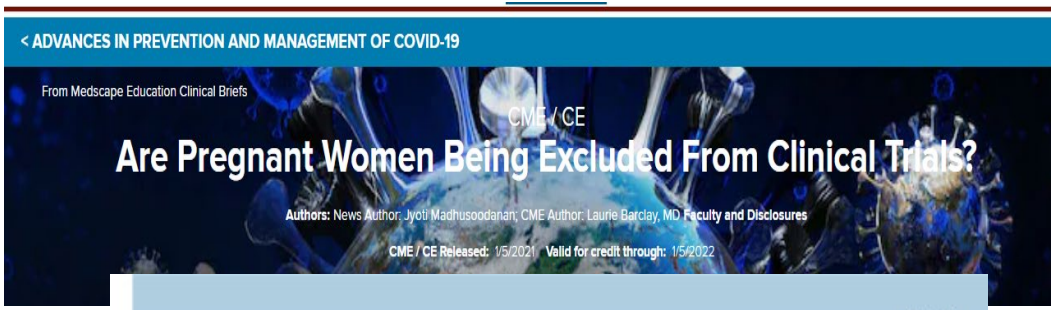
High ART coverage (88%) of pregnant women in focus countries, 2010 – 2019

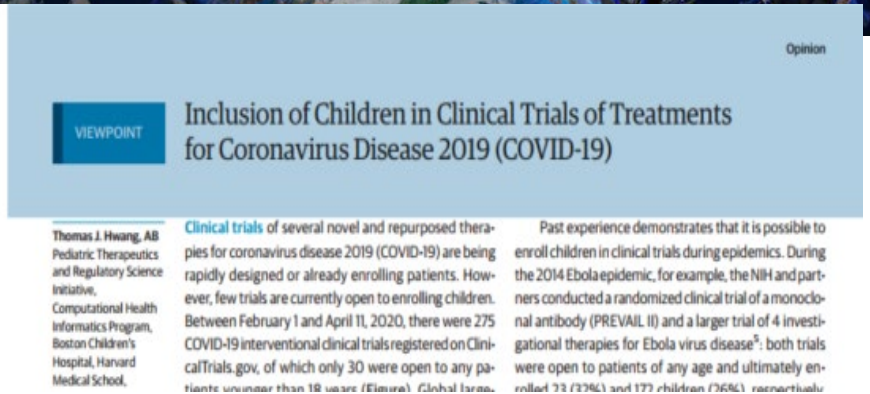
However, approximately 1.4 million women living with HIV become pregnant annually



UN Start Free, Stay Free, UNAIDS 2020

Ethical Obligation for Inclusion




Opinion

VIEWPOINT

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

Thomas J. Hwang, AB
Pediatric Therapeutics and Regulatory Science Initiative, Computational Health Informatics Program, Boston Children's Hospital, Harvard Medical School,

Clinical trials of several novel and repurposed therapies for coronavirus disease 2019 (COVID-19) are being rapidly designed or already enrolling patients. However, few trials are currently open to enrolling children. Between February 1 and April 11, 2020, there were 275 COVID-19 interventional clinical trials registered on ClinicalTrials.gov, of which only 30 were open to any patients younger than 18 years (Figure). Global large-

Past experience demonstrates that it is possible to enroll children in clinical trials during epidemics. During the 2014 Ebola epidemic, for example, the NIH and partners conducted a randomized clinical trial of a monoclonal antibody (PREVAIL II) and a larger trial of 4 investigational therapies for Ebola virus disease[5]: both trials were open to patients of any age and ultimately enrolled 23 (33%) and 172 children (26%), respectively


The JOURNAL of PEDIATRICS

EDITORIAL | VOLUME 134, ISSUE 2, P130-131, FEBRUARY 01, 1999

The "inclusion benefit" in clinical trials

John D. Lantos, MD

DOI: https://doi.org/10.1016/S0022-3476(99)70400-2


BJCP British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2018) 84 215–222 215

COMMENTARY

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

Correspondence Dr Catherine M.T. Sherwin, PhD, Division of Clinical Pharmacology, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT 84108, USA. Tel.: +1 801 587 7404; Fax: +1 801 585 9410; E-mail: catherine.sherwin@hsc.utah.edu

Received 5 June 2017; Revised 1 September 2017; Accepted 9 September 2017

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?

IMPAACT Research Agenda, 2020 – 2027

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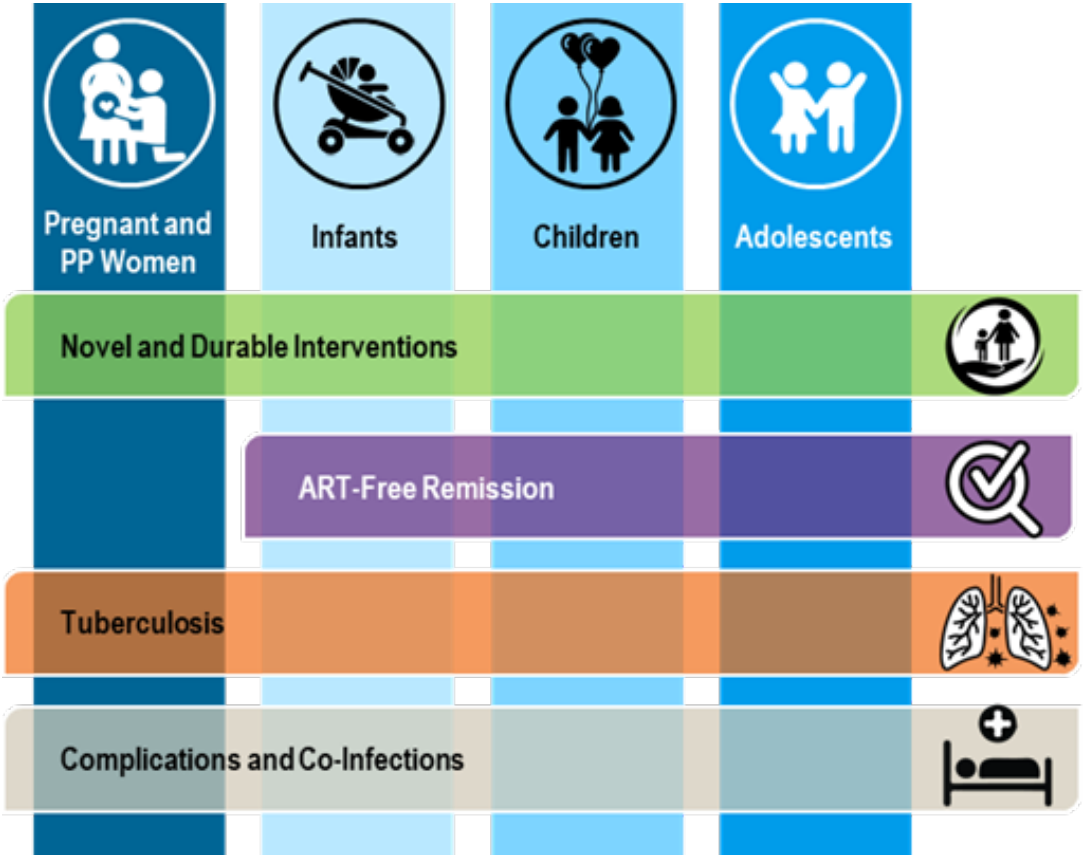

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Research Agenda

- 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.

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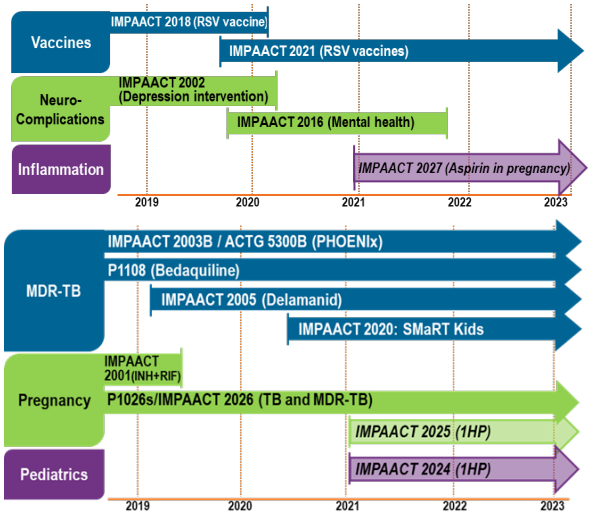
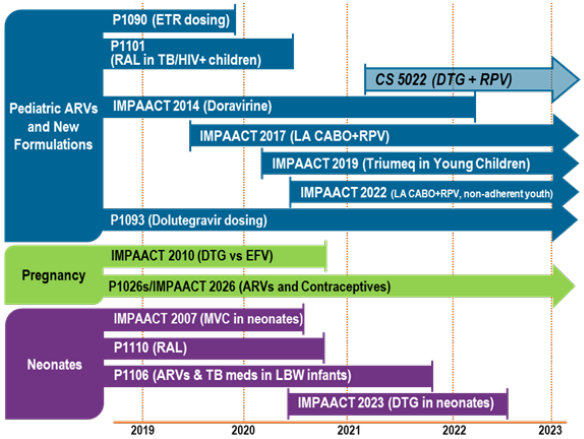
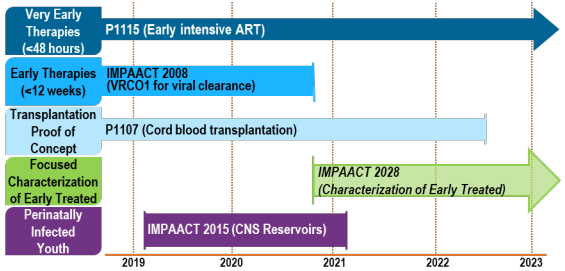
Research Agenda

- 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







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Tuberculosis

Scientific Committee Chairs: Anneke Hesseling and Amita Gupta

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Tuberculosis Scientific Committee

ICAB Session

Anneke C. Hesseling, Amita Gupta

Sharon Nachman

24 June 2021

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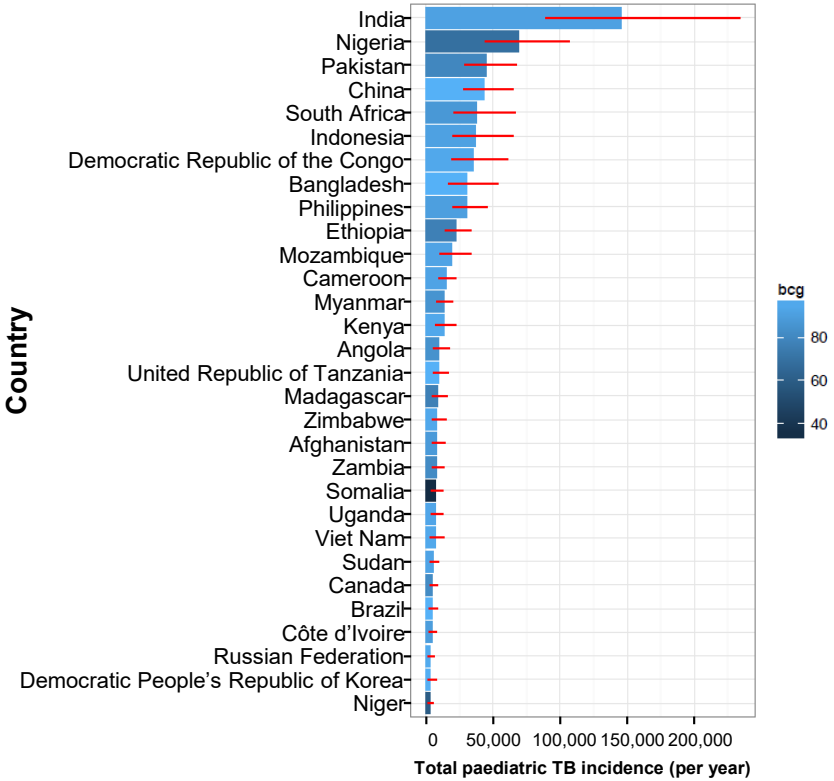
Overall TB Scientific Committee Goals

"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

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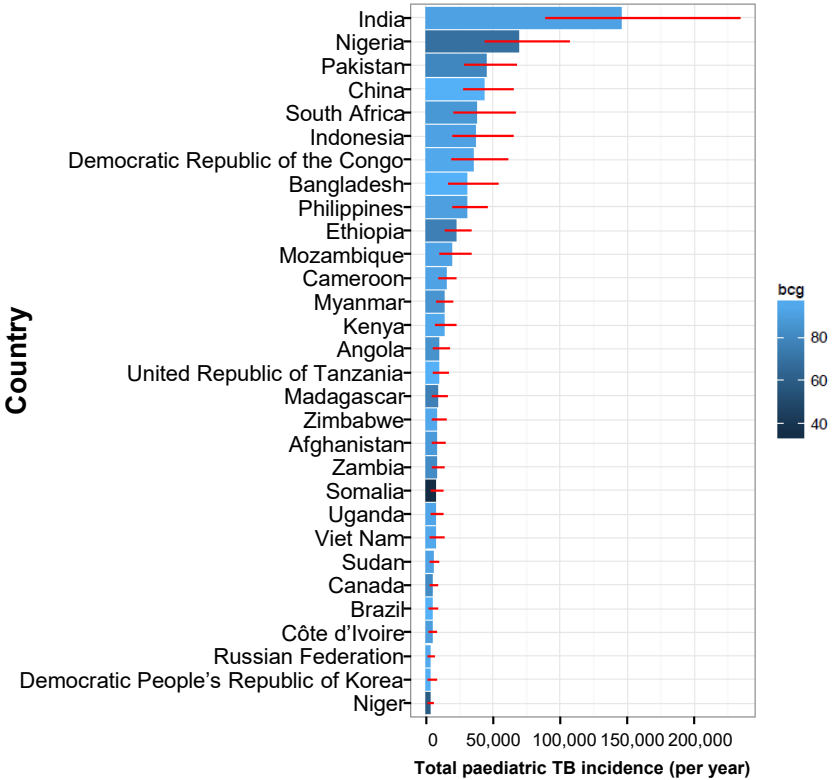
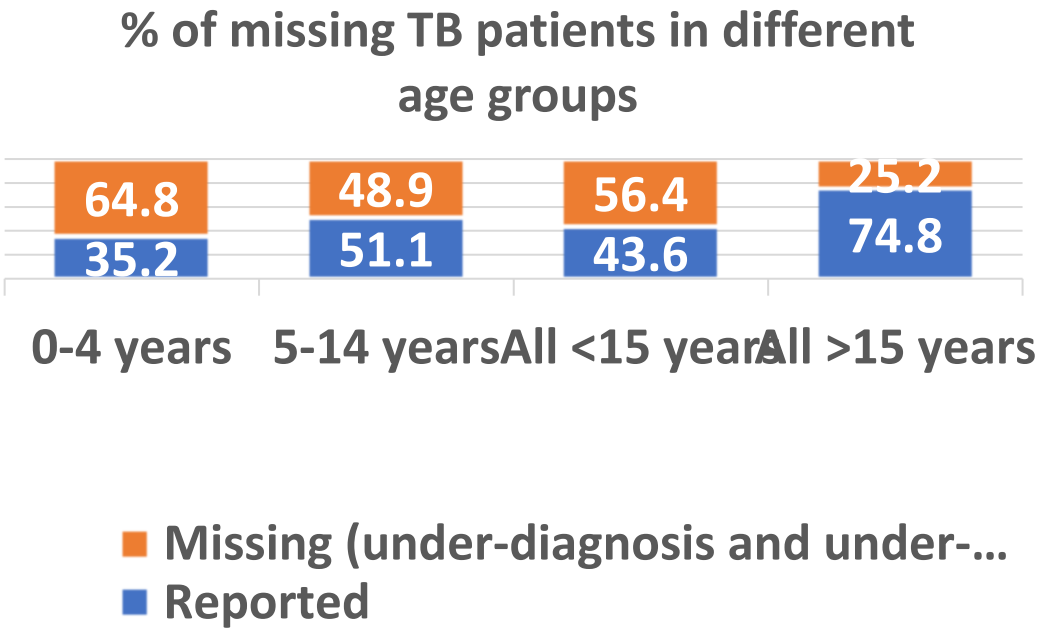
Global burden of TB in children (< 15 years)



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

1. Jenkins HE et al. Lancet 2014; 383: 1572-1579; 2. Dodd PJ et al. Lancet Glob Health 2014; 2: e453-459; 3. WHO Global Tuberculosis Report 2019

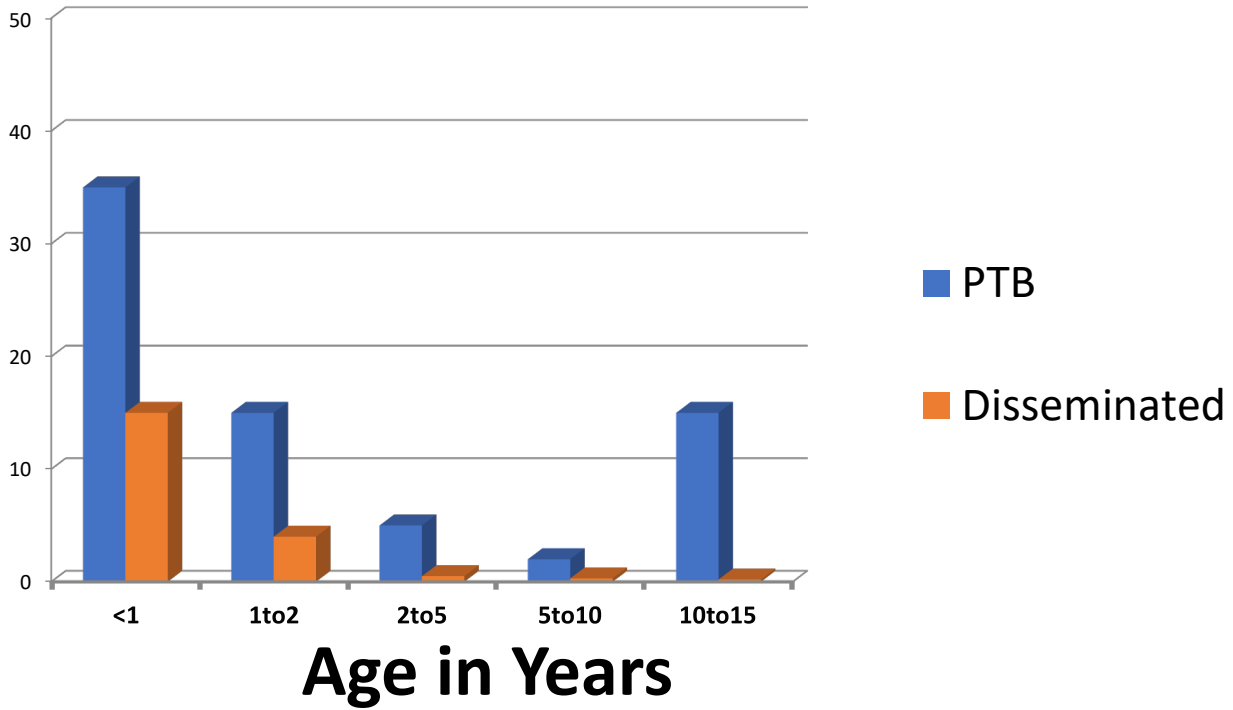
Estimates vs. reporting: estimated global TB case detection gap in children in different age groups, 2019*



*from data reported to WHO, 2020 Global Tuberculosis Report

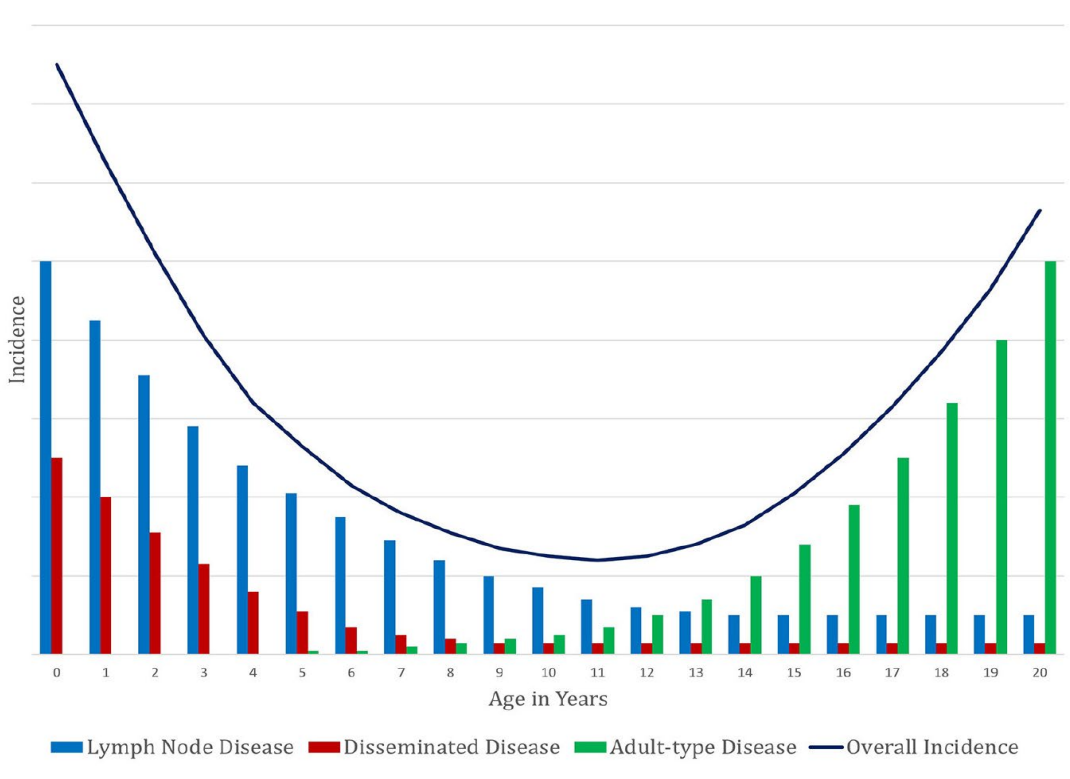
Age related risk of disease progression to TB: “natural history”

Disease Progression (Percent)



Marais et al. Int J Tuberc Lung Dis. 2004

TB incidence and disease spectrum: a function of age



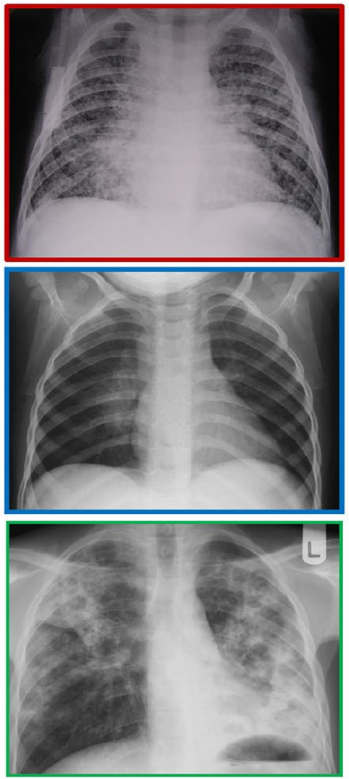
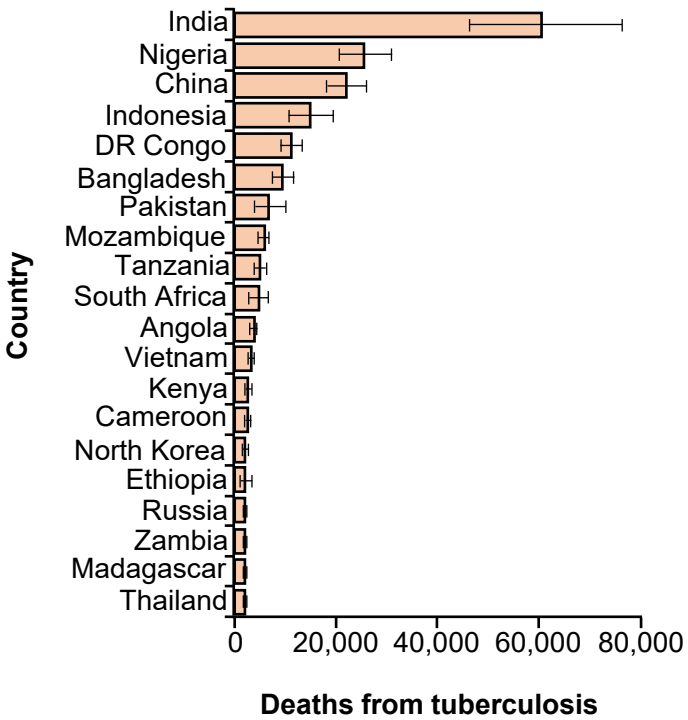


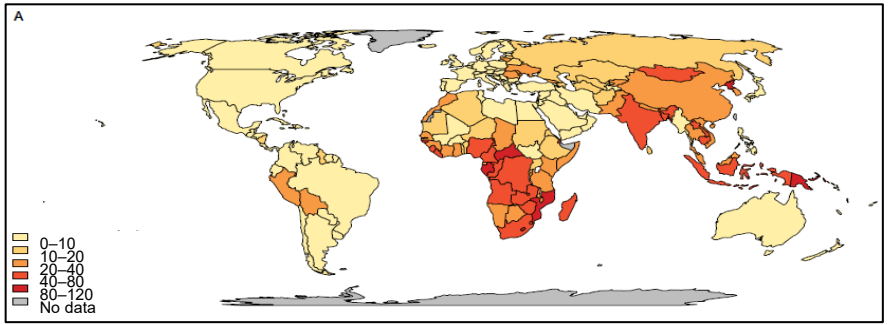
FIGURE 1 | Conceptual framework to demonstrate the pattern of change in tuberculosis incidence with age. This represents a composite of risk of infection and risk of subsequent disease progression. The presentation of disease is demonstrated by a representative X-ray in a box colored according to the disease phenotype legend.

Front Immunol. 2018; 9: 2946

TB mortality in children < 15 years



Dodd PJ et al. Lancet Glob Health 2017; 5: e898–906

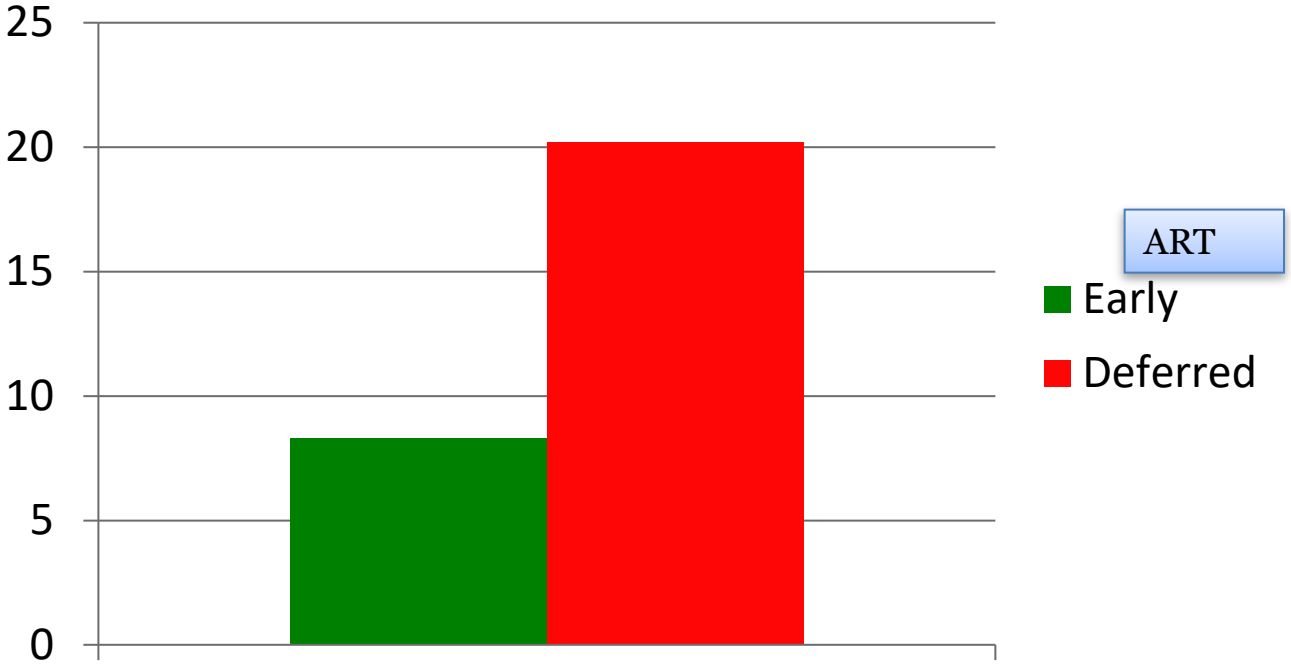


Estimated mortality:

- <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**

WHO. Global tuberculosis report. 2019. https://www.who.int/tb/publications/global_report/en/

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



The CHER Trial: Violari et al. N Engl J Med 2008

Five TB Protocols Currently in Development

2035	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
2034	Phase I Study of PK, Safety, & Acceptability of **Pretomanid** in Children with Rifampicin-Resistant TB
2025	Safety & PK of 1-Month of Daily versus 3-Months of Weekly **Isoniazid and Rifapentine** in Pregnant and Postpartum Women with HIV
2024	Phase I/II Dose Finding & Safety of **Daily Rifapentine Combined with Isoniazid (1HP)** for Tuberculosis Prevention in Children and Adolescents
2020	Phase II Study of **Shortened Oral Treatment** for Multidrug-Resistant Tuberculosis in Children (SMaRT Kids)

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

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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

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

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, P 2026 (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

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THANK YOU

Photo taken with permission, Sue Purchase Anneke Hesseling, Desmond Tutu TB Centre, Cape Town, South Africa

Complications

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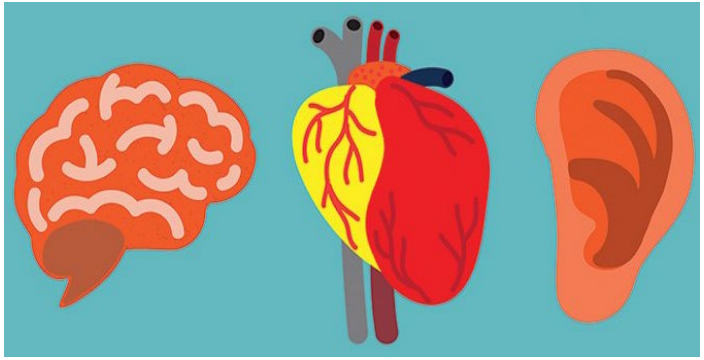
Complications and Comorbidities Scope and Priorities



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 Aurpibul*
Sandy Burchett⊥
Steve Innes*
Suad Kapetanovic
MacPherson Mallewa*
Evans Mpabalwani*
Savita Pahwa
Kunjal Patel⊥
Adriana Weinberg

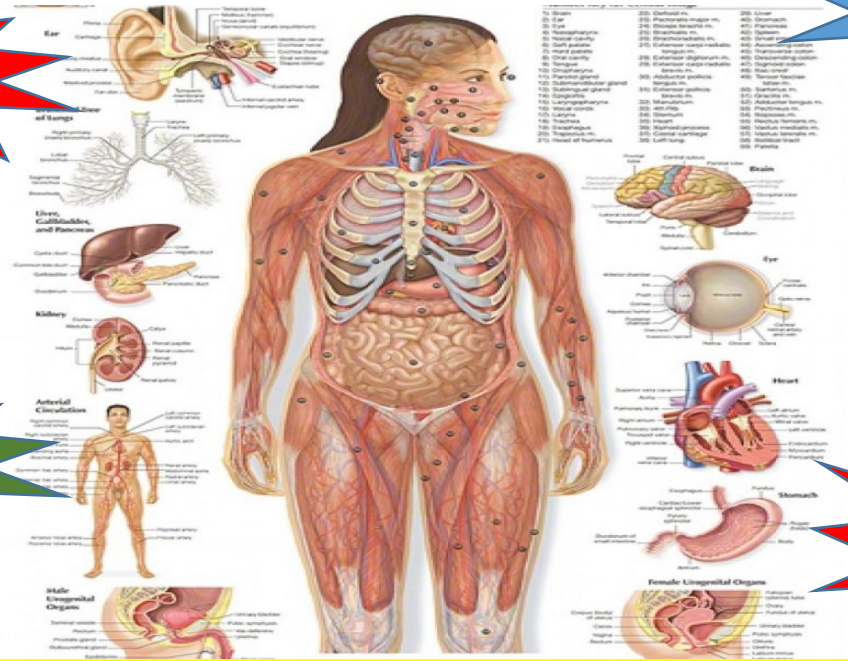
NICHD Rep: Jack Moye
NIAID Rep: Ellen Townley
NIMH Rep: Pim Brouwers
DMC Rep: Alex DiPerna
SDAC Primary Rep: Jane Lindsey
SDAC Secondary Rep: Meredith Warshaw
ICAB Rep: Gwyneth Hendricks*; Angie Partap
LC Rep: Dale Dayton
Ops Center Coordinator: Jen Libous, Rachael Jeffrey, Sarah Buisson
SLG Liaison: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

*International; ⊥PHACS

How will WICY with HIV infection be impacted?

HIV

Social determinants



Co-infections

ART

Other

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 JPIDS 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

Summary of Priorities by Region

Priorities	Asia	Africa	South America	U.S.
Cognitive impairment				
Psychiatric & mental health (depression, anxiety)				
HIV & HCV co-infection				
HIV & aging				
Long term effects of children born to women on option B+				
Lipodystrophy (prevention & resolution)				
Long term complications of HIV & ART				
Immune activation				

ICAB survey 2017

Priorities Specified in IMPAACT Proposal, Aug 2019

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- **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

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- **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

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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

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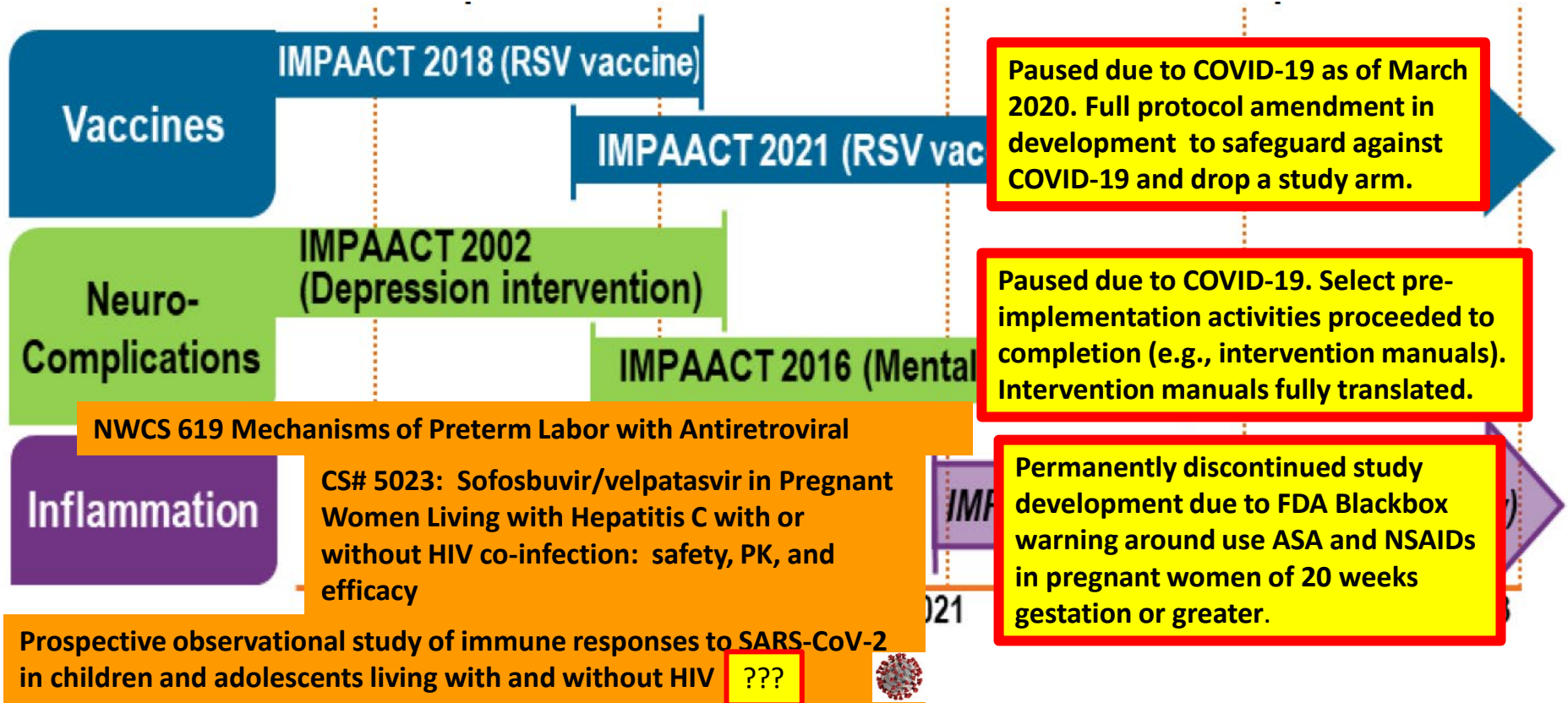
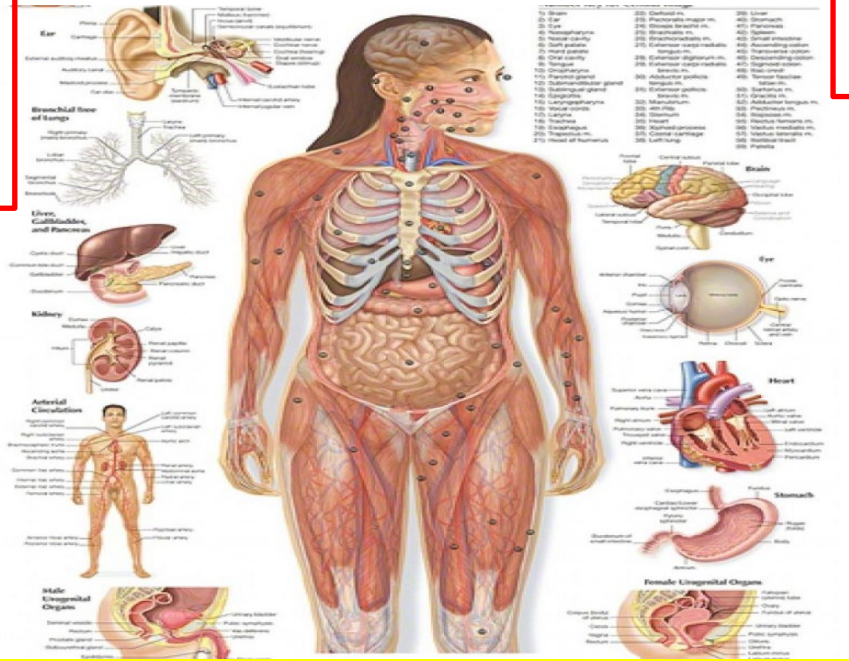


Additional Committee Proposals and Responses

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

Heart:
Pulse wave velocity*

Inflammation:
Fish oil*
Microbicides



Premature birth:
Aspirin
Factors associated with prematurity

Kidney:
TDF vs. TAF

Liver:
Hepatitis B
Hepatitis C*

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 JPIDS 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


Time
to
REFLECT

C&C Scientific Committee Survey Results, April 2021 (N=7)

The committee has put forward proposals that address the priorities.

99% AGREE

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Challenges and Opportunities

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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?

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-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

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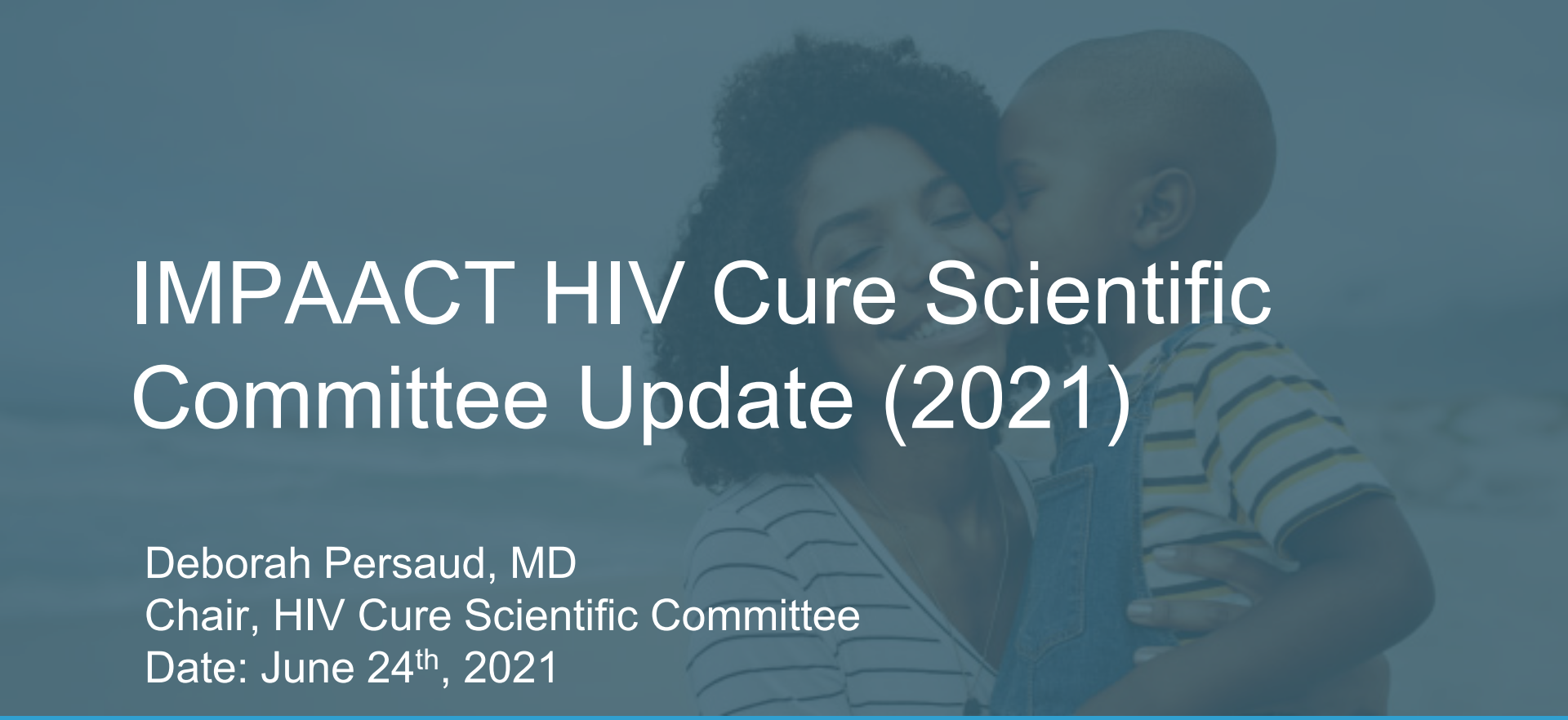
Priorities	Asia	Africa	South America	U.S.
Cognitive impairment	X	X	X	X
Psychiatric & mental health (depression, anxiety)	X	X	X	X
HIV & HCV co-infection	X			
HIV & aging	X			
Long term effects of children born to women on option B+		X		
Lipodystrophy (prevention & resolution)			X	
Long term complications of HIV & ART	X			X
Immune activation				X

ICAB survey 2017



IMPAACT HIV Cure Scientific Committee Update (2021)

Deborah Persaud, MD
Chair, HIV Cure Scientific Committee
Date: June 24th, 2021

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A Tribute

William Borkowsky, MD
(1947-2021)

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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

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NIMH: Pim Brouwers
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IMPAACT SLG Liason: John Sleasman
IMPAACT Leadership: Sharon Nachman, James McIntyre, Pat Flynn and Philippa Musoke

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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

NIH National Institute of Allergy and Infectious Diseases
NIH NICHD
NIH NIMH

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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)

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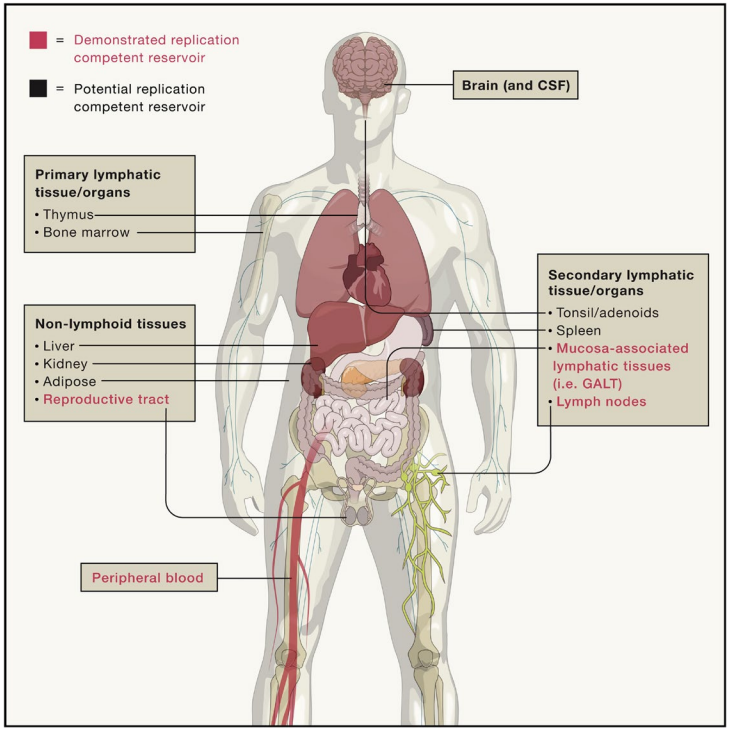
Goal: Limit the Cells that allow HIV to survive for a lifetime despite ART: Barriers to a Cure



Reviewed in: Margolis D et al. Cell 2020

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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)

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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

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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

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Cases of Sustained HIV Remission in Children

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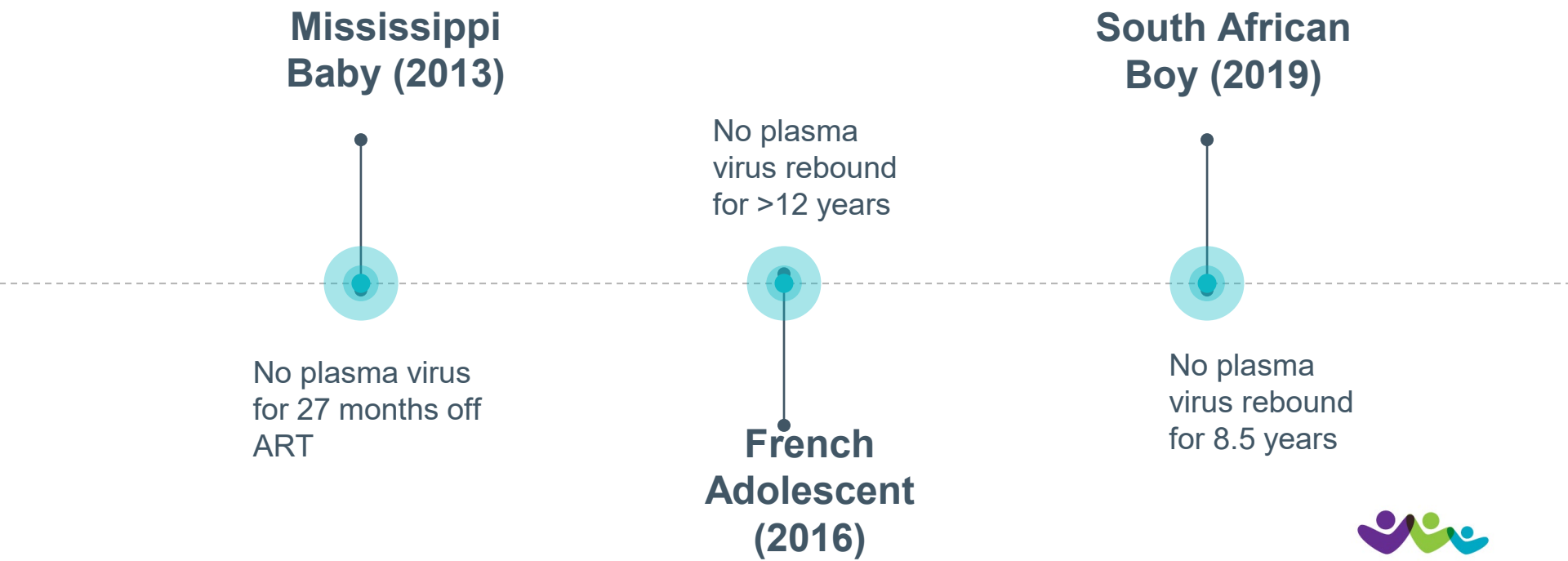
Optimism and Hope for Remission in Perinatal Infection: Very Early and Early ART



Persaud, Gay, Luzuriaga et al 2013 NEJM; Luzuriaga, Gay, Persaud et al 2015 NEJM; Frange P et al. Lancet HIV 2016; Violai A et al. Nature Communications 2019

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IMPAACT HIV Cure Clinical Trials (2013—

Very early and early ART Plus Immunotherapeutics (broadly neutralizing antibodies-IMPAACT P1115 and P2008

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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)

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P1115

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

clincialtrials.gov NCT02140255

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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**

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What have we learned from IMPAACT P1115 (V 1.0)

- Early infant testing is feasible in resource-constrained settings
- Very early ART can be successfully implemented at IMPAACT 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

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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

Protocol Chairs: Betsy McFarland, Alka Khaitan and William Borkowsky

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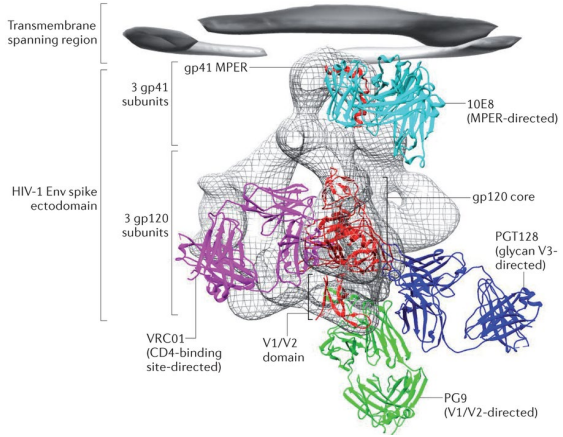
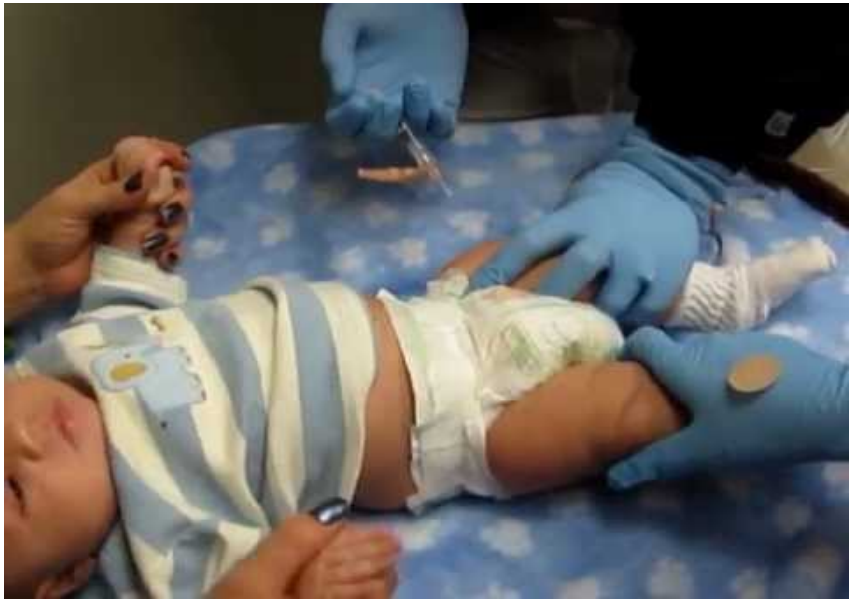
IMPAACT 2008



Kwong PD et al. Nature Reviews/Immunology 2013

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



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)

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IMPAACT 2008

- 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

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What have we learned from IMPAACT 2008

- Accrual was feasible
- Subcutaneous infusion of multiple doses of broadly neutralizing antibodies are feasible and well tolerated

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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

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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.

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Participating Sites and Study Update

5013 Jacobi Medical Center
5092 Johns Hopkins
5030 Emory
5017 Seattle
5048 Southern LA
5114 Bronx Lebanon Hospital
4001 Lurie Children's Hospital
6501 St. Jude
5112 UCLA
4601 UCSD
6601 Puerto Rico
5052 Colorado

- 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**

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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

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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

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International Maternal Pediatric Adolescent AIDS Clinical Trials Network

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NIH NIMH

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Thank you and Questions

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Acknowledgments

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), all components of the National Institutes of Health (NIH), under Award Numbers UM1AI068632-15 (IMPAACT LOC), UM1AI068616-15 (IMPAACT SDMC) and UM1AI106716-09 (IMPAACT LC), and by NICHD contract number HHSN275201800001I. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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Treatment Scientific Committee Activities

Pat Flynn, MD
CAB Session
24 June 2021

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

IMPAACT Research Agenda, 2020 – 2027

IMPAACT Annual **Meeting** 2021

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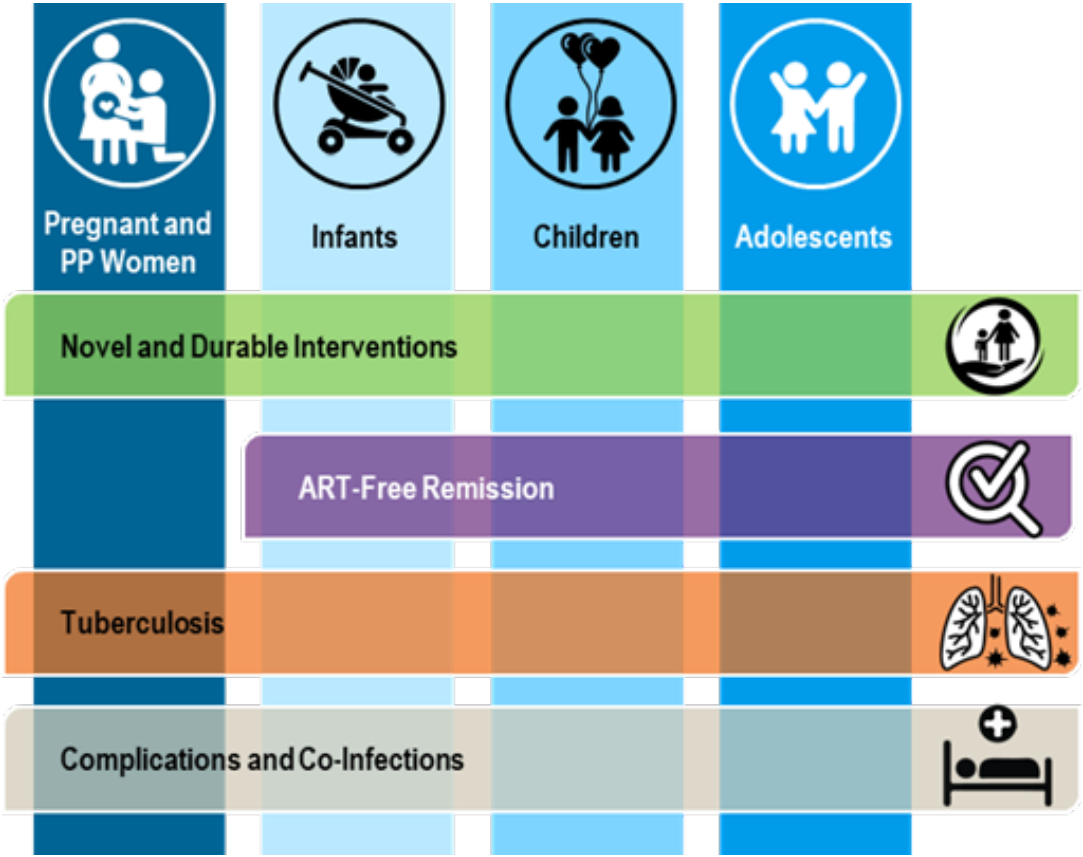

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Novel and Durable Interventions (AKA Treatment) Research Agenda

- 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.

HIV Treatment

Scientific Committee Chairs: Theodore Ruel and Moherndran Archary

IMPAACT Annual **Meeting** 2021

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HIV Treatment

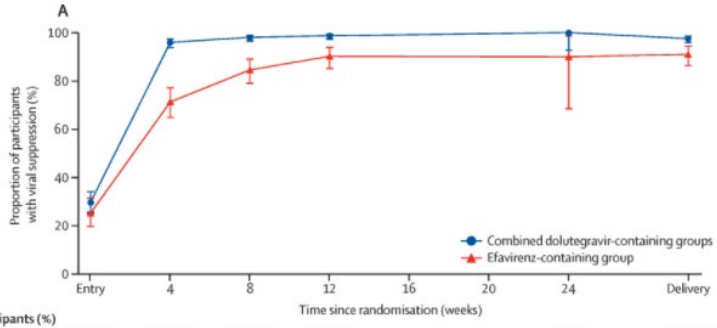
Pregnant and Postpartum women	Infants (Birth – 1,000 days of life)	Children (1,000 days of life to 13 years)	Adolescents (13-24 years)
Priority 1: Characterize the PK properties and dosing of ARVs and relevant drug-drug interactions (DDIs) among women during pregnancy and lactation, and their infants			
	Priority 2: Evaluate novel prophylaxis regimens for infants born to women with HIV		
	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		
	Priority 4: Conduct PK and clinical studies necessary to optimize use of current ARVs in achieving virologic suppression among pediatric populations with ARV experience		

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

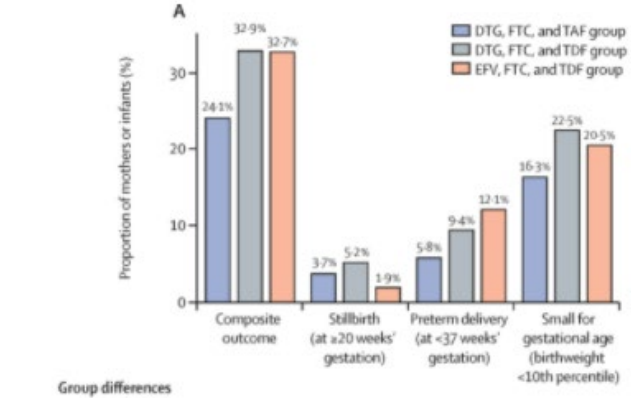
- P1026S – investigation of PK in pregnant and postpartum women receiving commercially available agent
  - 32 publications and 42 abstracts
- IMPAACT 2026 – Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum
  - Pregnant WLHIV receiving oral ARVs 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



Proportion of participants (%)						
Combined dolutegravir-containing groups	129/432 (30%)	404/421 (96%)	404/412 (98%)	382/387 (99%)	47/47 (100%)	395/405 (98%)
Efavirenz-containing group	53/209 (25%)	147/206 (71%)	170/201 (85%)	166/184 (90%)	18/20 (90%)	182/200 (91%)



Group differences (95% CI)				
DTG, FTC, and TAF group vs DTG, FTC, and TDF group	−8·8% (−17·3% to −0·3%)	−1·5% (−5·4% to 2·4%)	−3·6% (−8·8% to 1·5%)	−6·2% (−13·9% to 1·5%)
DTG, FTC, and TDF group vs EFV, FTC, and TDF group	0·2% (−8·8% to 9·1%)	3·3% (−0·2% to 6·8%)	−2·7% (−8·7% to 3·3%)	2·0% (−6·0% to 10·0%)
DTG, FTC, and TAF group vs EFV, FTC, and TDF group	−8·6% (−17·1% to −0·1%)	1·8% (−1·3% to 4·9%)	−6·3% (−11·8% to −0·9%)	−4·2% (−11·7% to 3·4%)

Lockman S et al. Lancet: 397, 1276, 2021

Priority 2: Evaluate novel prophylaxis regimens for infants born to women with HIV

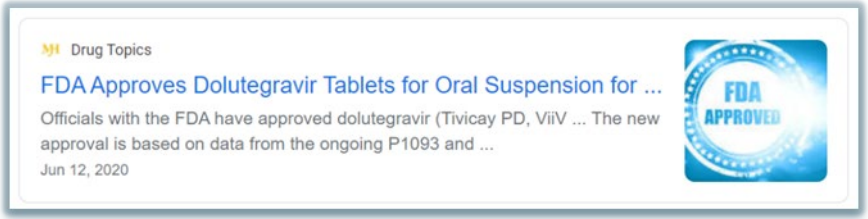
- Building on IMPAACT 1097 and 1110 studies of raltegravir
- IMPAACT 2023 - A Phase I Study of the Safety, Tolerability, and Pharmacokinetics of Dolutegravir in Neonates Exposed to HIV-1
- Awaiting final version, June 2021
- Trial sites in US, South Africa, Thailand, Brazil

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



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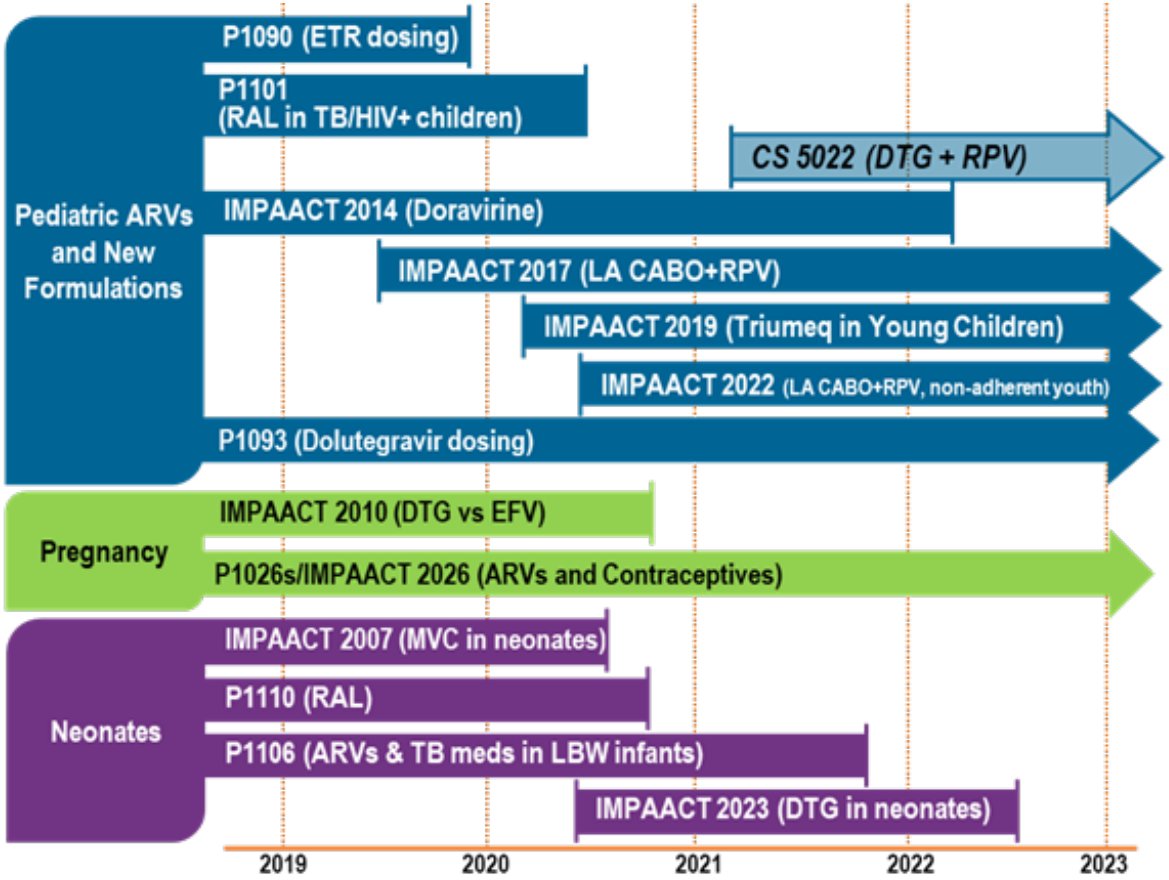
Priority 4: Conduct PK and clinical studies necessary to optimize use of current ARVs in achieving virologic suppression among pediatric populations with ARV experience

- 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

We will be busy! 2020-2027



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Thank you!

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

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