



Looking Ahead: IMPAACT Scientific Agenda

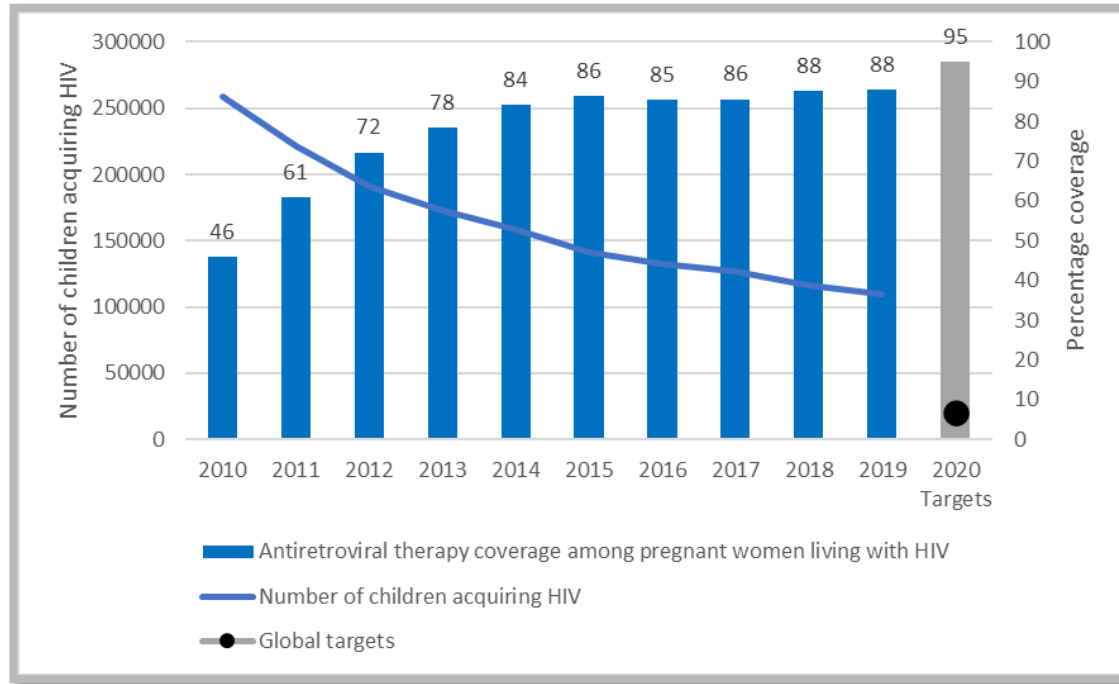
Philippa Musoke, MD, and Patricia Flynn, MD
IMPAACT Network Vice Chairs
22 June 2021

IMPAACT Annual **Meeting** 2021

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

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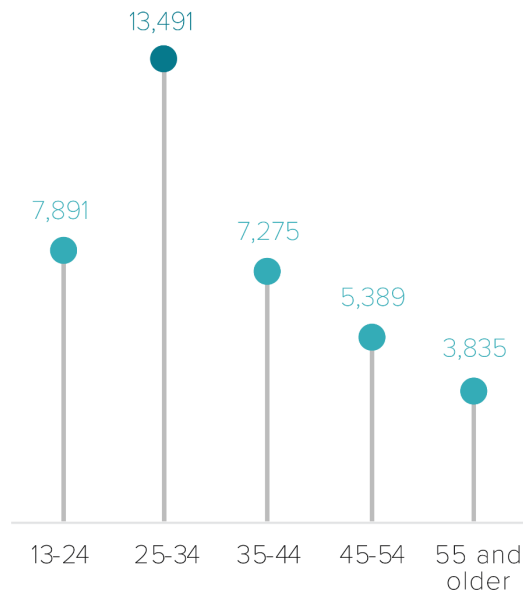
In 2019 there were 150,000 new pediatric HIV infections



New diagnoses disproportionately affect adolescents and young adults

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

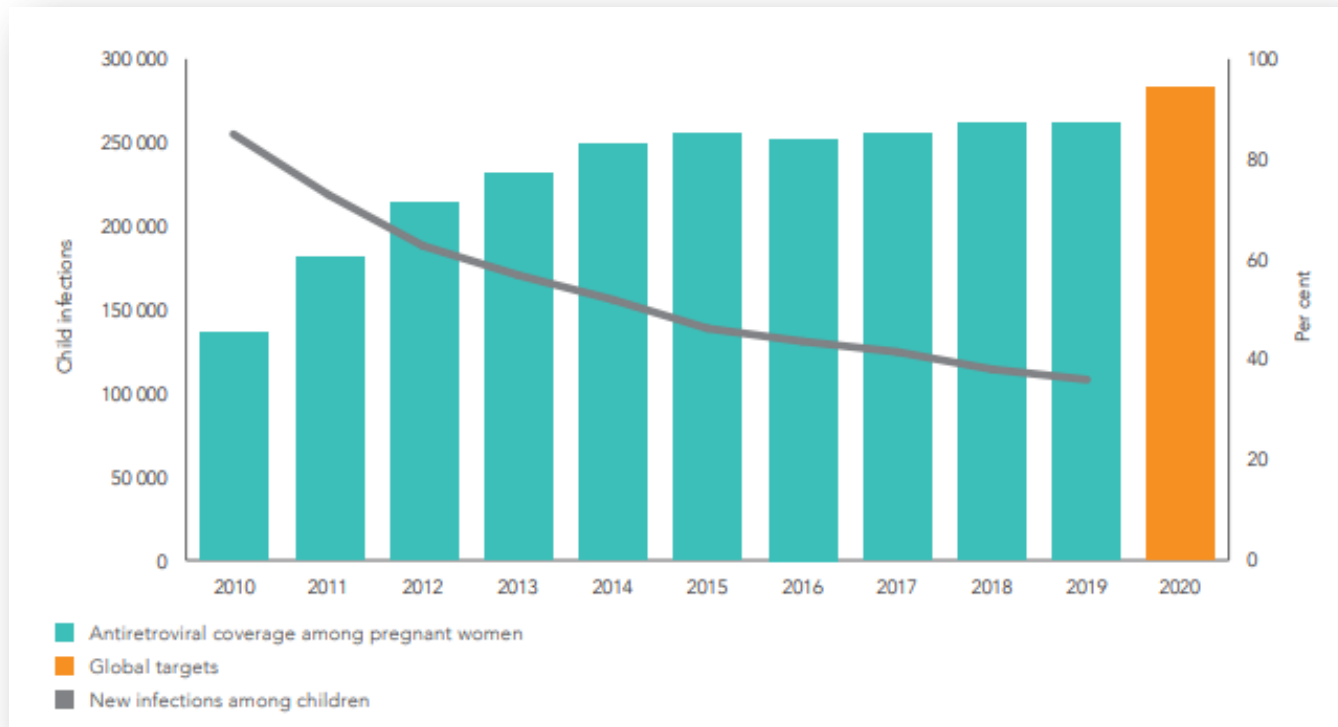
The number of new HIV diagnoses was highest among people aged 25 to 34.



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



Ethical Obligation for Inclusion

< ADVANCES IN PREVENTION AND MANAGEMENT OF COVID-19

From Medscape Education Clinical Briefs

CME / CE

Are Pregnant Women Being Excluded From Clinical Trials?

Authors: News Author: Jyoti Madhusoodanani; CME Author: Laurie Barclay, MD Faculty and Disclosures

CME / CE Released: 1/5/2021 Valid for credit through: 1/5/2022

Opinion

VIEWPOINT

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

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and Regulatory Science
Initiative,
Computational Health
Informatics Program,
Boston Children's
Hospital, Harvard
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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 (Elmore). Global Issues.

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 disease¹; both trials were open to patients of any age and ultimately enrolled 73 (33%) and 173 children (36%) 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](https://doi.org/10.1016/S0022-3476(99)70400-2)



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

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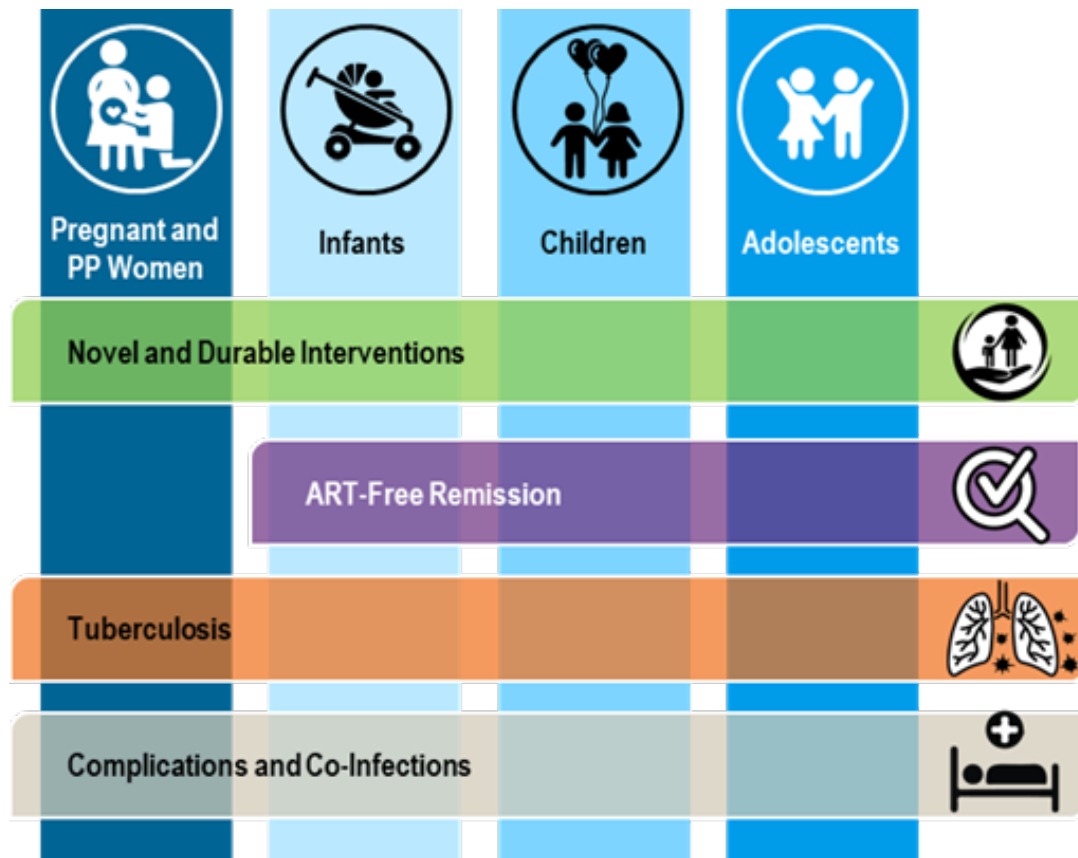
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Why Do We Need Research in Infants, Children, Adolescents and Pregnant Women?

- ▶ 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?

IMPAACT Research Agenda, 2020 – 2027

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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.



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.

IMPAACT Science Generation

June 2019 to May 2021

10 New Capsules for Review

- 3 Treatment
- 3 Complications
- 3 Tuberculosis
- 1 Cure

2 New Concept Sheets for Review

- 1 Treatment
- 1 Complications

10 New Protocols Approved for Development

- 3 Treatment
- 1 Complications
- 4 Tuberculosis
- 1 Cure
- 1 COVID-19

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HIV Treatment

Scientific Committee Chairs: Theodore Ruel and Moherndran Archary

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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)	
<u>Priority 1:</u> Characterize the PK properties and dosing of ARVs and relevant drug-drug interactions (DDIs) among women during pregnancy and lactation, and their infants				
	<u>Priority 2:</u> Evaluate novel prophylaxis regimens for infants born to women with HIV			
	<u>Priority 3:</u> 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			
	<u>Priority 4:</u> Conduct PK and clinical studies necessary to optimize use of current ARVs in achieving virologic suppression among pediatric populations with ARV experience			

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)
IMPAACT 2026 IMPAACT 2010 P1026s			
	IMPAACT 2023		
		P1093	
		IMPAACT 2036 IMPAACT 2029 IMPAACT 2019	IMPAACT 2022 IMPAACT 2017 IMPAACT 2014

Nine Protocols Currently in Development

Four within the Treatment Research Area

2036	Phase I/II Study of the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of Oral and Long-Acting Injectable Cabotegravir and Rilpivirine in Virologically Suppressed Children with HIV >2 to <12 years of age and weighing >10 kgs and <50 kgs
2029	Phase I/II Study of Switching to Fixed Dose Combination Dolutegravir/ Rilpivirine among Virologically Suppressed Children and Adolescents Living with HIV
2023	Phase I Study of the Safety, Tolerability, and Pharmacokinetics of Dolutegravir in Neonates Exposed to HIV-1
2022	Phase II Study of the Virologic Efficacy and Feasibility of Long-Acting Injectable Antiretroviral Medications in Non-Adherent Youth with HIV

Study Highlight: IMPAACT 2023

Safety & PK of Dolutegravir in Neonates Exposed to HIV

- ▶ Study to determine DTG dosing for children from birth through the first 6 weeks of life
- ▶ Planned sites in Brazil, South Africa, Thailand, and the US

Anticipate protocol to sites
by July 2021



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Study Highlight: IMPAACT 2036

Safety & PK of Oral and Long-Acting Injectable Cabotegravir and Rilpivirine in Virologically Suppressed Children with HIV

- ▶ Continued successful collaboration from IMPAACT 2017 with ViiV/Janssen to study long-acting, injectable regimens in children
- ▶ Anticipate participation of sites in the US and internationally



Anticipate protocol to sites
by November 2021

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Planned Studies

- ▶ Evaluate novel prophylaxis regimens for infants born to women with HIV
 - Compounds of interest include broadly neutralizing antibodies (bNABs) and long-acting injectables (LAI).
 - Can these strategies reduce reliance on daily medications? One dose for non-breastfeeding infants and few for breastfeeding.
- ▶ Evaluate ARVs and regimens that address the specific needs of adolescents with HIV.
 - Can LAIs play a role in non-adherent youth?
- ▶ Continue to investigate other new ARV agents

IMPAACT Collaboration with WHO

- ▶ IMPAACT and the WHO are leading the discussion around the next questions that need to be addressed to *optimize maternal health and prevent new pediatric infections*
 - Approaches to Enhance and Accelerate the Study of New Drugs for HIV and Associated Infections in Pregnant Women
 - Postnatal Prophylaxis to Reach Elimination of Vertical Transmission: Optimizing Research and Accelerating Access to Innovation
- ▶ ***New aspirational objective to not just prevent all new pediatric infections but to provide safe and effective agents for maternal treatment and postnatal prophylaxis so that all women living with HIV can safely breastfeed their babies***

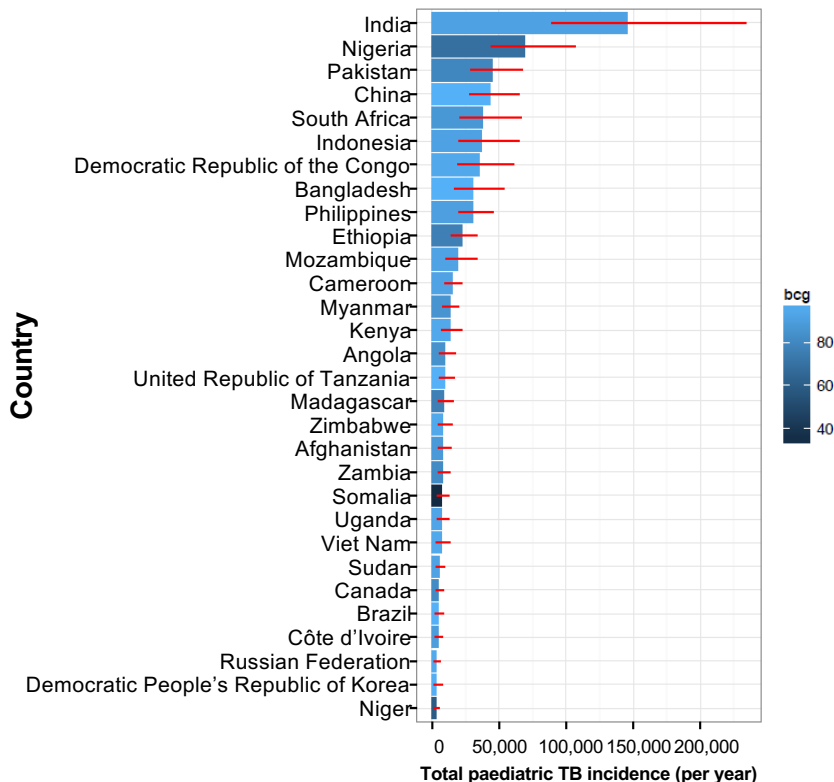
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Tuberculosis

Scientific Committee Chairs: Anneke Hesselning and Amita Gupta

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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

Tuberculosis

Pregnant and Postpartum women	Infants (Birth – 1,000 days of life)	Children (1,000 days of life to 13 years)	Adolescents (13-24 years)
<u>Priority 1:</u> Evaluate the efficacy, PK and safety of new and shorter drug regimens to prevent drug-susceptible and drug-resistant TB in infants, children, adolescents and pregnant and postpartum women with and without HIV			
<u>Priority 2:</u> Evaluate the efficacy, PK, safety and acceptability of new drug regimens, optimize existing drug dosing and evaluate novel drugs for the treatment of drug-susceptible and drug-resistant TB in infants, children, adolescents and pregnant and postpartum women with and without HIV			
	<u>Priority 3:</u> Evaluate novel tools for the diagnosis of active TB, correlates of TB treatment in response and markers of disease progression in infants, children, adolescents with and without HIV		
<u>Priority 4:</u> Evaluate novel TB vaccines for prevention of TB disease			

Tuberculosis

Pregnant and Postpartum women	Infants (Birth – 1,000 days of life)	Children (1,000 days of life to 13 years)	Adolescents (13-24 years)
IMPAACT 2025		IMPAACT 2035/HVTN 604	
	IMPAACT 2034 IMPAACT 2024 IMPAACT 2005 P1108		
	IMPAACT 2003B/A5300B/PHOENIX		

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Nine Protocols Currently in Development

Five within the Tuberculosis Research Area

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

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Planned 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.

Complications and Co-Occurring Conditions

Scientific Committee Chair: Allison Agwu and Jackie Hoare

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Complications

Pregnant and Postpartum women	Infants (Birth – 1,000 days of life)	Children (1,000 days of life to 13 years)	Adolescents (13-24 years)
	<u>Priority 1</u> : Investigate potential neuroprotective and neurotoxic effects of ART to preserve neurocognitive development and mental health in infants, children and adolescents		
<u>Priority 2</u> : Refine and optimize evaluation and treatment of neurocognitive and mental health disorders, particularly executive dysfunction, depression and PTSD			
<u>Priority 3</u> : Evaluate novel preventive and/or therapeutic approaches for high-priority diseases of importance to pediatric populations living with and affected by HIV, including RSV, working with NIAID and other partners			
<u>Priority 4</u> : Evaluate other co-occurring conditions and complications of importance for pediatric, adolescent and pregnant and postpartum women, with NIH and other partners			

Study Highlight: IMPAACT 2016

Group-Based Intervention to Improve Mental Health and ART Adherence among Adolescents

- ▶ Two-arm, randomized study to examine if an Indigenous Leader Outreach Model of trauma-induced cognitive behavioral therapy intervention improves mental health outcomes and ART adherence for youth living with HIV
- ▶ Team, Network leadership, and sites in discussion on appropriate timeline to initiate study



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Planned Studies

- ▶ Investigate potential neuroprotective and neurotoxic effects of ART to preserve neurocognitive development and mental health in infants, children and adolescents
- ▶ Evaluate novel preventive and/or therapeutic approaches for high-priority diseases of importance to pediatric populations with or affected by HIV, including RSV, working with NIAID and other partners
- ▶ Refine and optimize evaluation and treatment of neurocognitive and mental health disorders, particularly executive dysfunction, depression and PTSD
 - Interventions for depression in adolescents with HIV
 - Reducing postpartum depression in women with HIV
- ▶ Evaluate other co-occurring conditions and complications of importance for pediatric, adolescent and pregnant populations with HIV (Hepatitis C)

ART-free Remission (Cure)

Scientific Committee Chairs: Deborah Persaud and Elizabeth McFarland

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ART-free Remission (Cure)

NEWS RELEASES

Media Advisory

Thursday, June 6, 2019

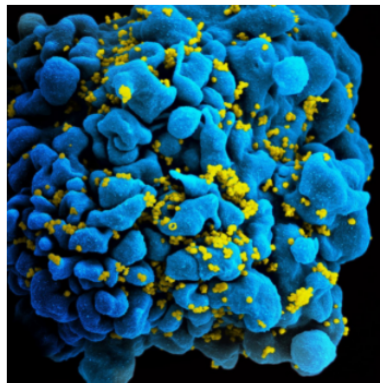
NIH HIV experts prioritize research to achieve sustained ART-free HIV remission



What

Achieving sustained remission of HIV without life-long antiretroviral therapy (ART) is a top HIV research priority, according to a new commentary in *JAMA* by experts at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

ART involves taking a combination (usually three) of drugs daily, often combined into a single pill. ART has transformed the lives of people with HIV, enabling those with access to the medications to live a near-normal lifespan. Despite this success, the side effects, pill fatigue, stigma and expense of taking daily ART for life have motivated researchers to find an alternative, write NIAID Director Anthony S. Fauci, M.D., and colleagues. Consequently, scientists are seeking ways to put HIV into full and sustained remission so daily ART is unnecessary. The authors say feasible approaches must involve minimal risk and manageable side effects for people with HIV and must be



Scanning electronmicrograph of an HIV-infected T cell. NIAID

ART-free Remission (Cure)

- ▶ Evaluate whether **very early therapy** with more potent ART, **in combination with bNAbs**, limits HIV reservoir establishment in infants and leads to ART-free remission
- ▶ Evaluate **immune-based therapies**, including therapeutic HIV vaccines and bNAbs, in children and adolescents with HIV
- ▶ Examine **combined initial therapy with ARVs plus immunotherapies**, with and without LRAs, in adolescents and young adults to rapidly induce virologic control and potentiate elicitation of a “vaccinal effect” mediated through antigen-antibody immune complexes
- ▶ Examine the role of the **CNS and T follicular helper CD4+ T cells** as sanctuary sites following perinatal HIV infection and develop studies to explore elimination of HIV reservoirs within these anatomic locations
- ▶ Identify **optimal virologic and immunological biomarkers** to detect and quantify HIV reservoirs, and predictors of reservoir size and time to viremic rebound

Study Highlight: IMPAACT 2028

Long-Term Clinical, Immunologic, and Virologic Profiles of Children who Received Early Treatment for HIV

- ▶ Enable long-term follow-up of infants who received early or very early treatment for HIV in other cure-related studies
 - IMPAACT P1115
 - IMPAACT 2008
 - TIES
 - CHER
 - LEOPARD
- ▶ Establish a biorepository for investigations related to the clinical, immunologic, and virologic effects of early treatment with priority for early career investigators

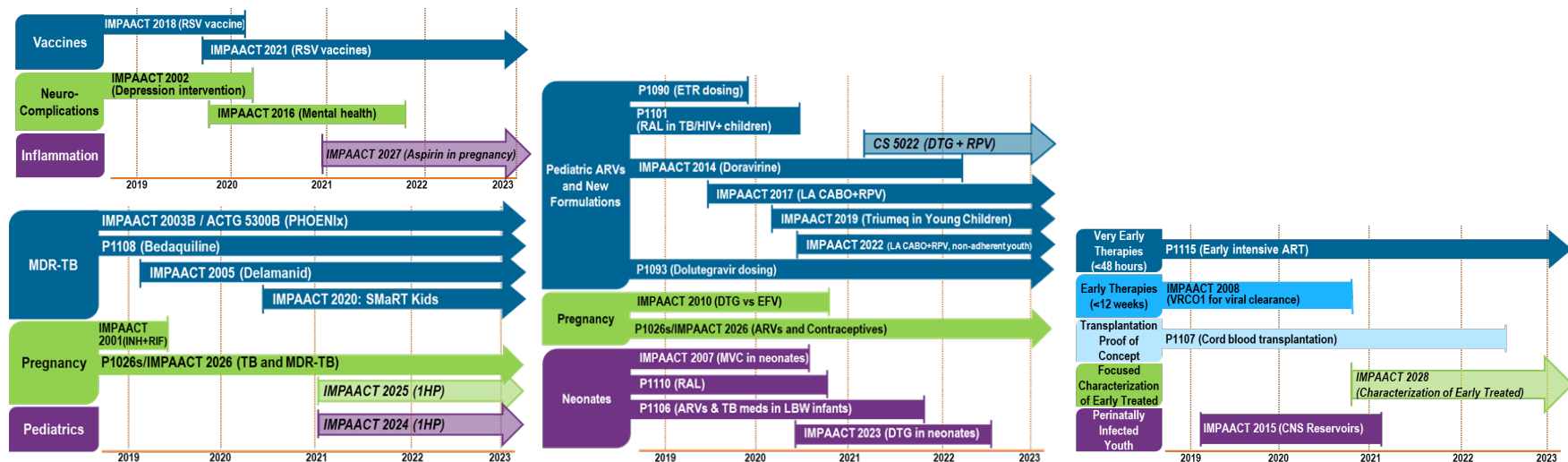
Anticipate opening to accrual
by June 2021

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Planned Studies

- ▶ Examine the potential strategies for ART-free remission following aggressive initial therapy in adolescents and young adults
 - Can you rapidly induce virologic control and potentiate elicitation of a “vaccinal effect” mediated through antigen-antibody immune complexes?
- ▶ Evaluate whether very early interventions can limit the HIV reservoir and lead to ART-free remission
 - Potent ART that blocks virus entry and/or viral integration, with or without bNAbs
- ▶ Evaluate whether these same interventions are effective in children and adolescents with HIV who have displayed long-term suppression on ART and lead to ART-free remission

The Network has a robust and growing portfolio of current studies and new proposals in the pipeline



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THANKS!



We look forward to working with all of you to meet our goals to improve health outcomes for infants, children, adolescents, pregnant and breastfeeding women impacted or living with HIV.

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