



William Shearer
1937-2018



International Maternal Pediatric AIDS Clinical Trials (IMPAACT) Network

State of the Network
2019 Annual Meeting

Sharon Nachman, MD

Overview

- IMPAACT in the current context of HIV
- Scientific committee updates and drivers of each scientific agenda
 - What are the priorities?
 - What is ongoing?
 - What is planned for future study?
- IMPAACT activities and achievements in the past year

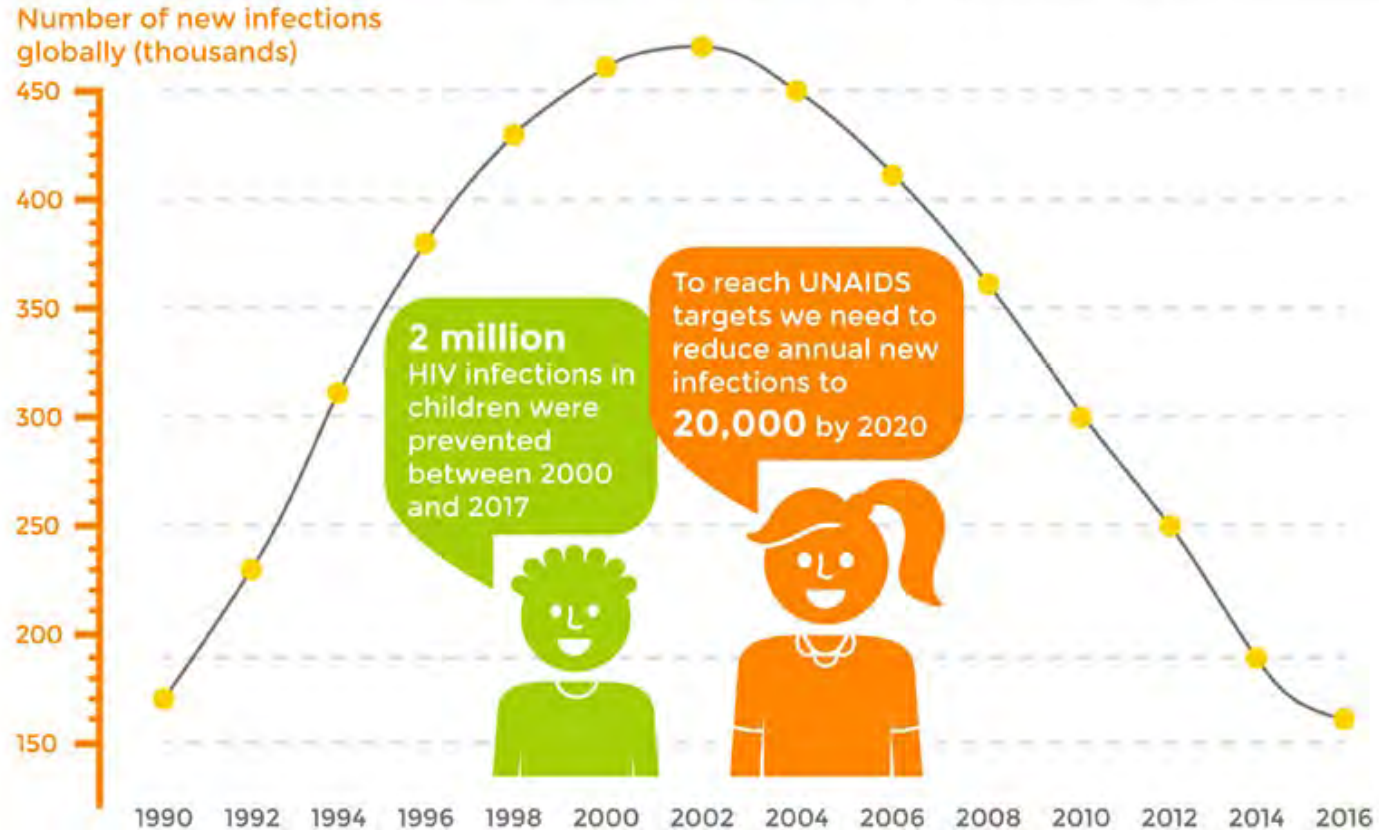
Real question: What is our scientific agenda for the next 10 years?



How do we really end the epidemic?

“New HIV infections among children globally has declined from 270,000 in 2010 to 180,000 in 2017 (35%), reports indicate that there is far less progress being made than previously thought.”

New HIV infections in children aged 0-14 years old.



Source: World Bank - accessed 5th December 2017 and UNICEF analysis of UNAIDS 2017 data

In 2017, there were roughly 1.8 million new HIV infections worldwide,
180,000 of which were among children.

Most of these children live in sub-Saharan Africa
and were infected via their HIV-positive mothers during pregnancy,
childbirth or breastfeeding.



36.9 MILLION

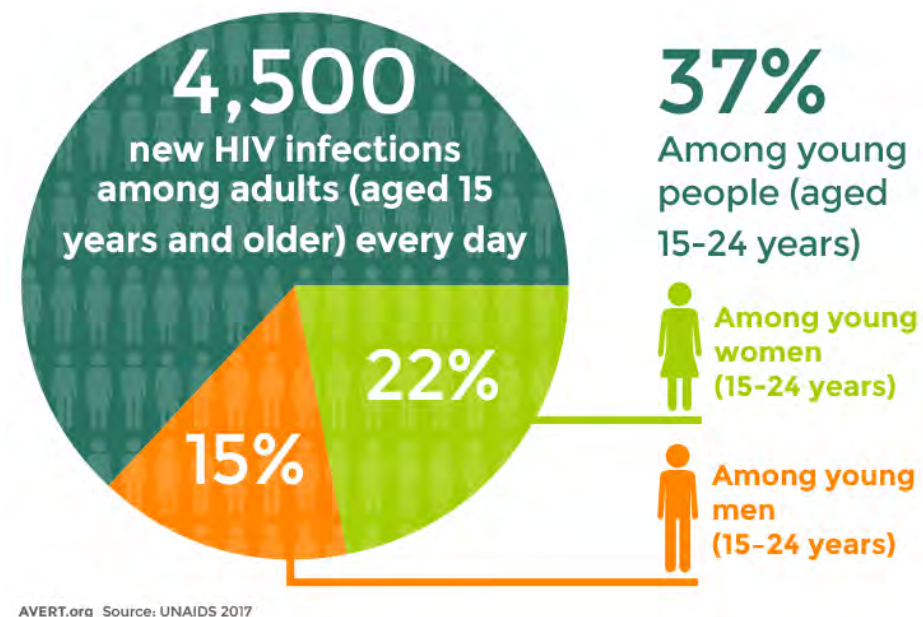
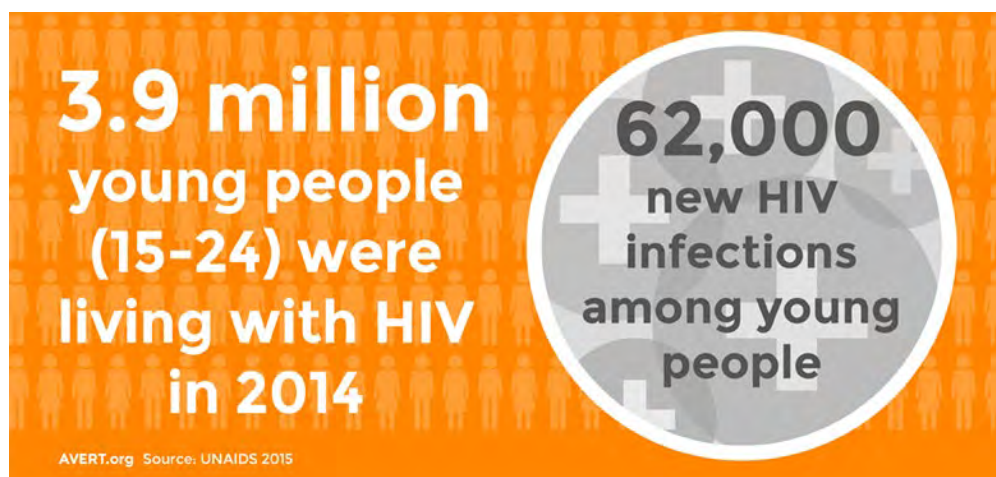
people worldwide are currently living
with HIV/AIDS.

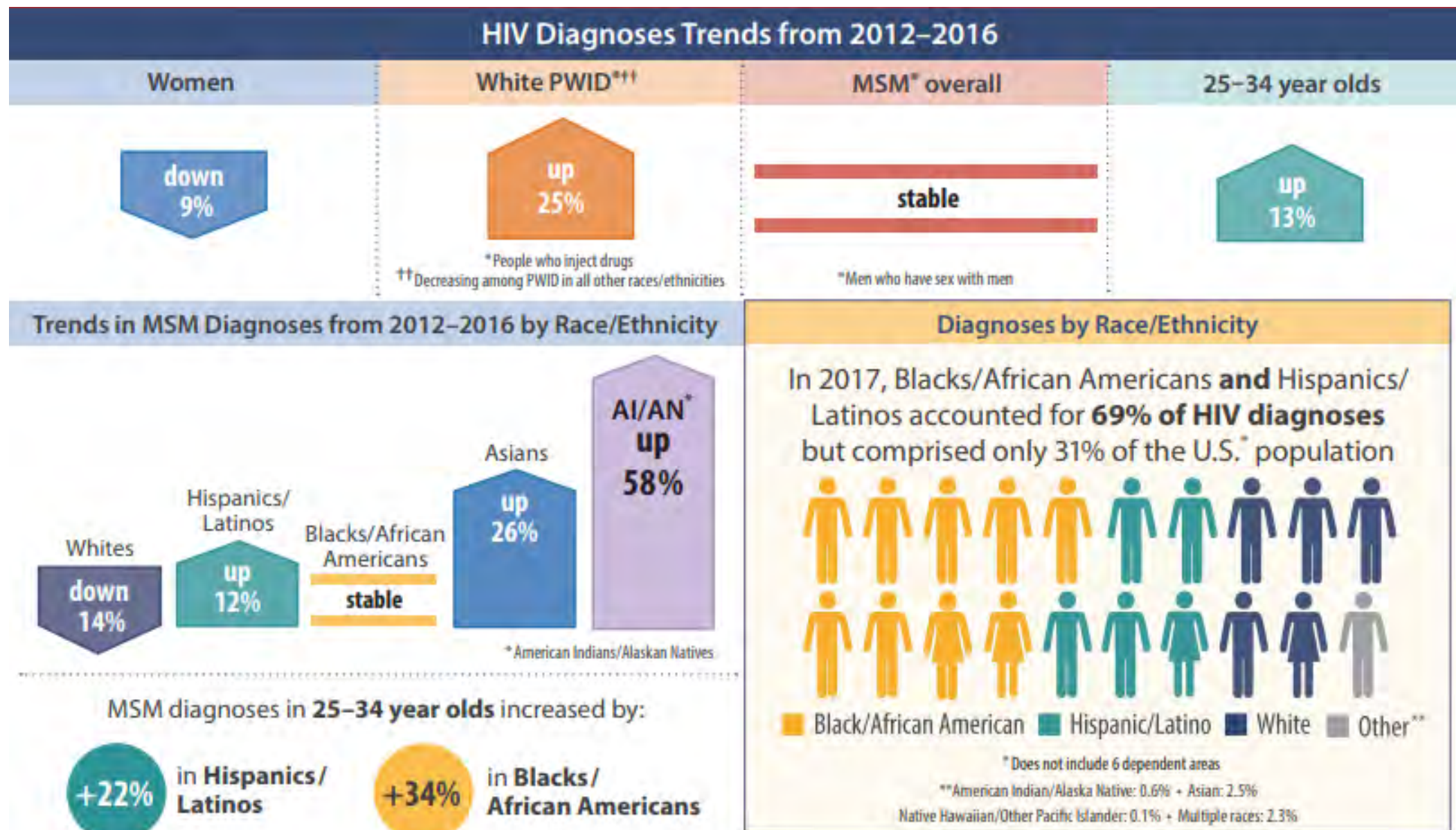
**1.8 MILLION
CHILDREN**

worldwide are living
with HIV. Most of these
children were infected
by their HIV-positive
mothers during
pregnancy,
childbirth or
breastfeeding.

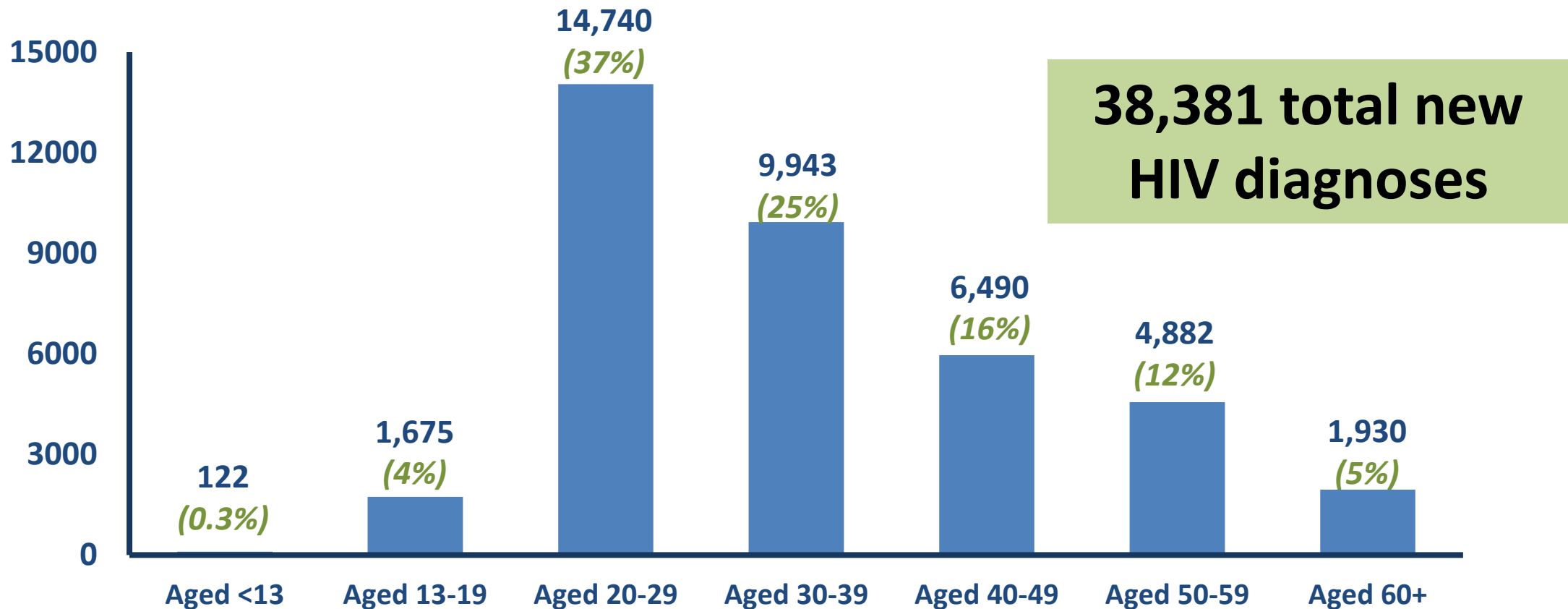


“The number of adolescents dying due to AIDS-related illnesses tripled between 2000 and 2015, the only age group to have experienced this rise.”





New HIV Diagnoses in the U.S. By Age, 2017

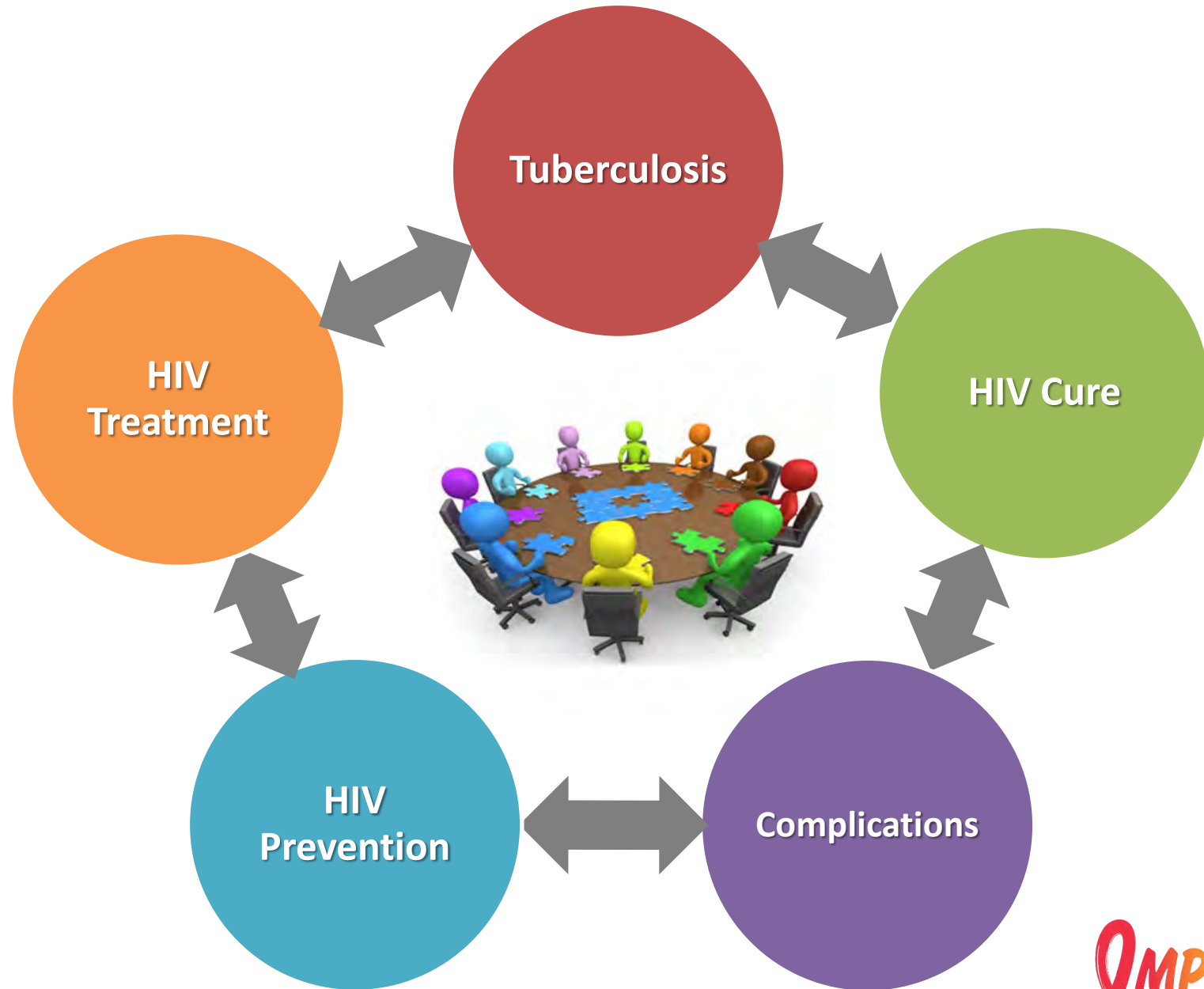


IMPAACT's Mission

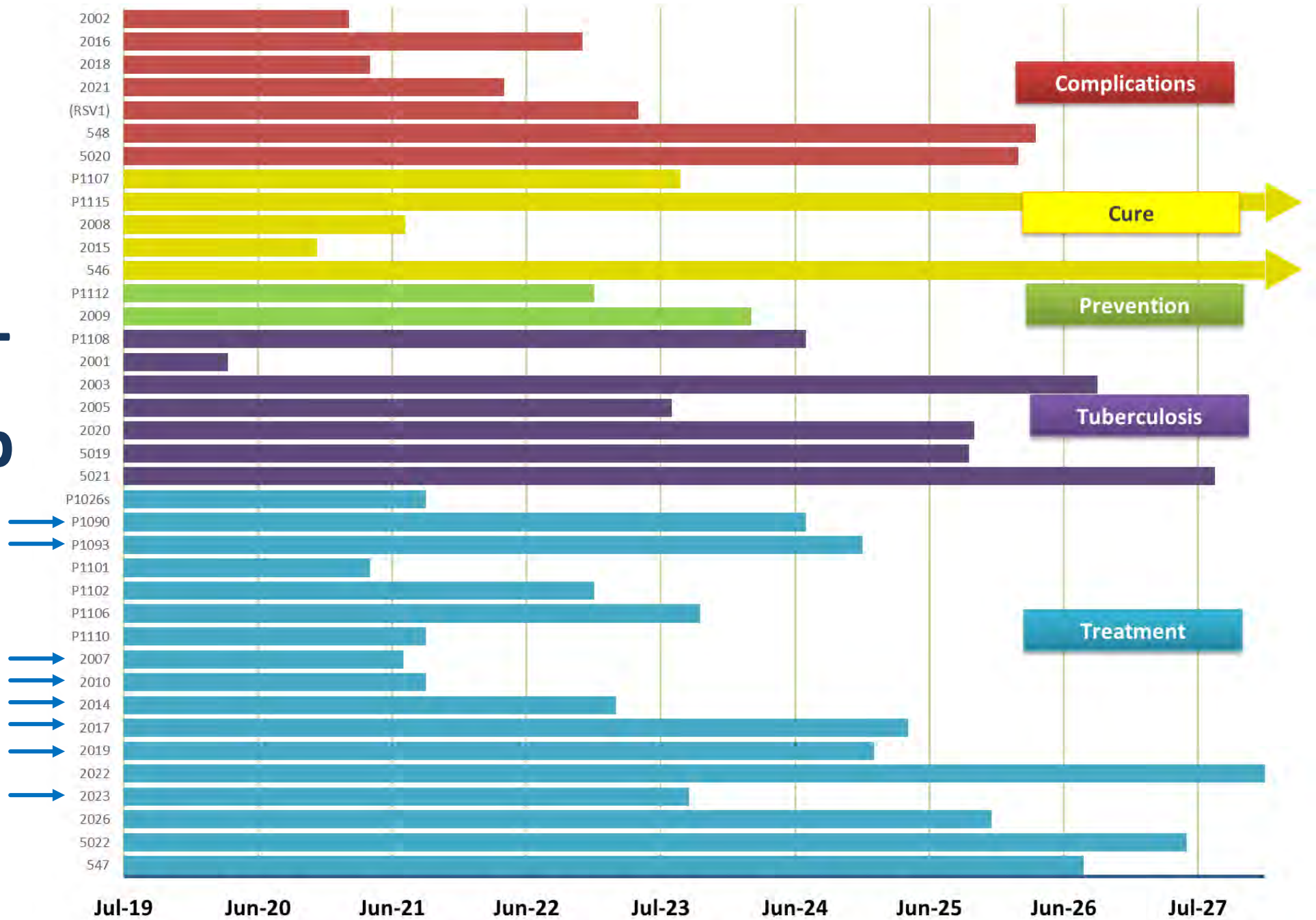
- To decrease incident HIV and HIV-associated infections, including mother-to-child transmission among infants, children, youth, and pregnant/postpartum women
- To decrease HIV-associated mortality and morbidity among these populations



**What are the
scientific
questions for
the next 10
years?
How do we
end HIV?**



IMPAACT Roadmap





**What is driving
the Cure agenda?**

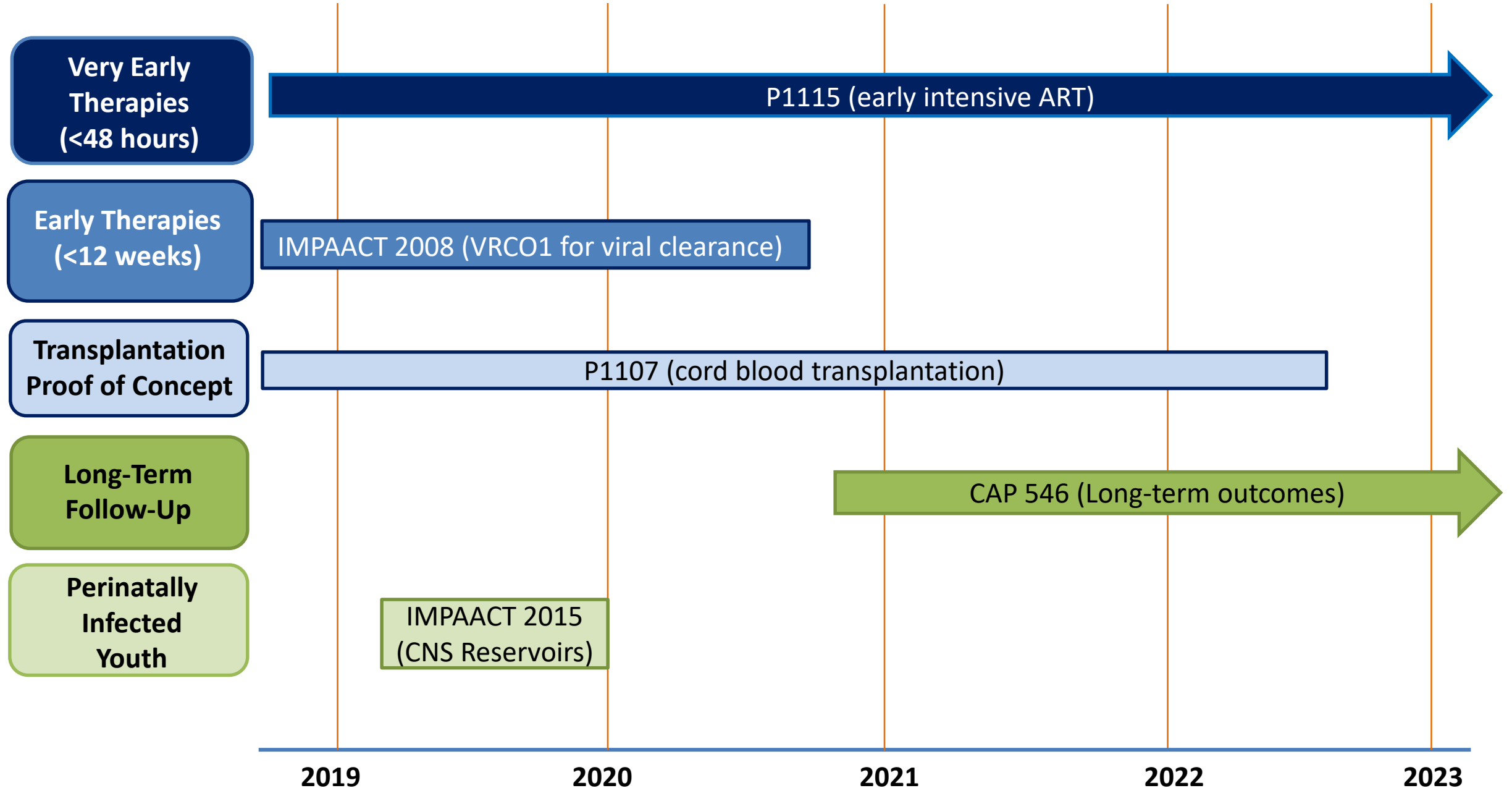
Cure Scientific Agenda

- **Functional Cure:** Evaluate early aggressive ART to reduce viral reservoir in neonates
- **Reservoirs:** Evaluate specific interventions in chronically infected-youth



- Antiretroviral treatment
- HIV vaccines
- Immunomodulatory agents
- Out of the box molecules

IMPAACT HIV Cure Roadmap



Study Highlight: P1115

Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission

- Accrual of 460 mother-infant pairs completed in 2017
- Version 1.0 manuscripts in progress
- Version 2.0 issued to sites in September 2018
- Sites are working to complete V2 transition requirements
- Many are protocol registered for V2
 - 17 US sites
 - 4 international sites

Anticipate enrollments
under Version 2
by late 2019

Focus for the Future: Cure

- We know when infants get infected:
 - Elucidate relationship between reservoirs (GI, lymphoid, CNS), treatments, and possibility of sterilizing cure
 - Neonatal immunity is key to cure success, so understanding adaptive and innate immune responses will continue to be critical
- Optimizing HIV-1 remission and cure strategies for:
 - Older infants with immunotherapeutic agents
 - Older children and youth to reduce residual viremia



**What is driving
the Tuberculosis agenda?**

Tuberculosis and Children

- Children represent about 10-11% of all TB cases
- Most children tolerate treatment very well
- Need for simple, child-friendly fixed-dose formulations that are easy to administer and align with WHO dosage recommendations

Burden

1 Million

At least 1 million children become ill with TB each year. Children represent about 10% of all TB cases

Global TB report 2018

Mortality

233 000

children die from this preventable and curable diseases

Childhood TB Roadmap

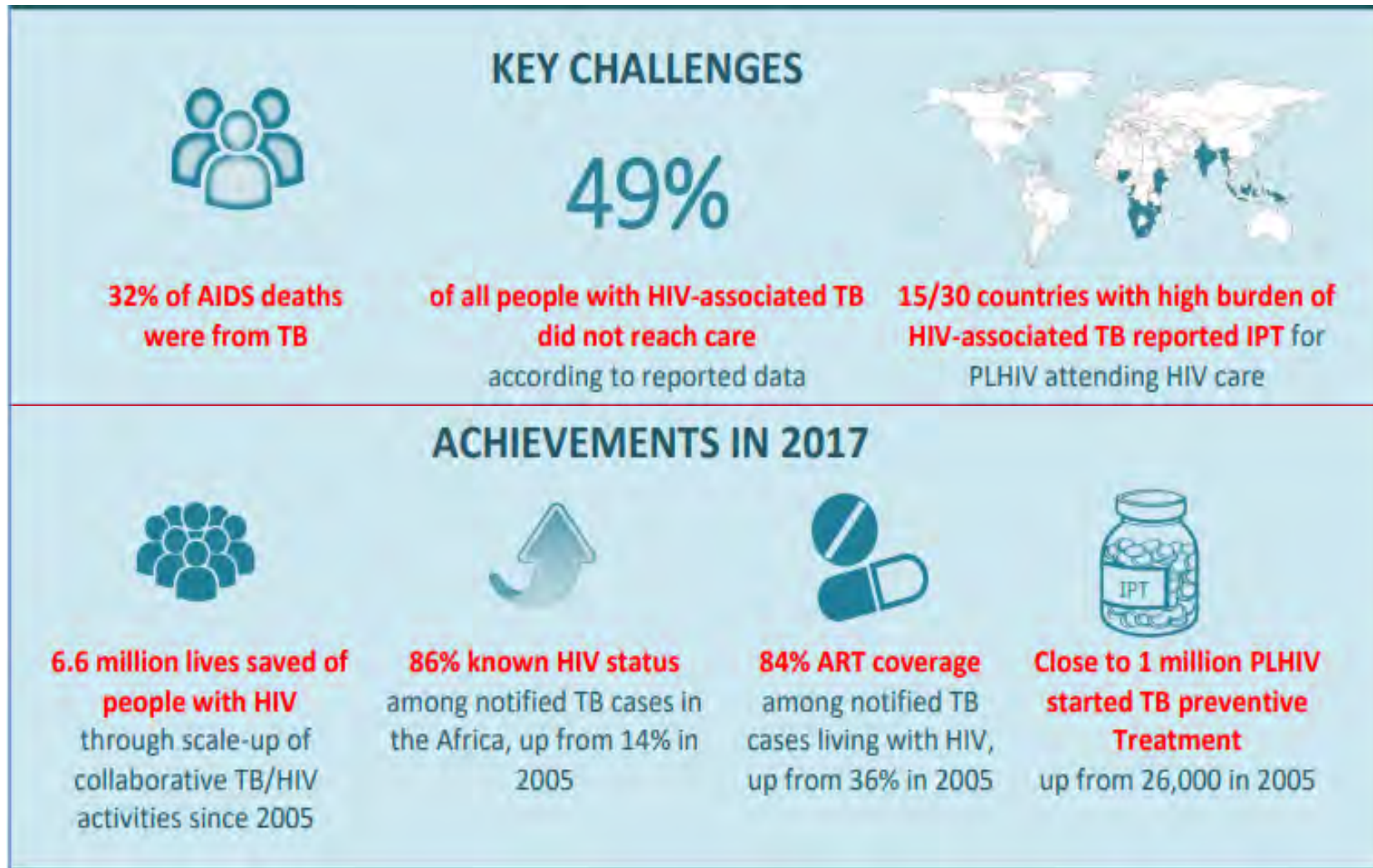
Preventive TB treatment

292 182

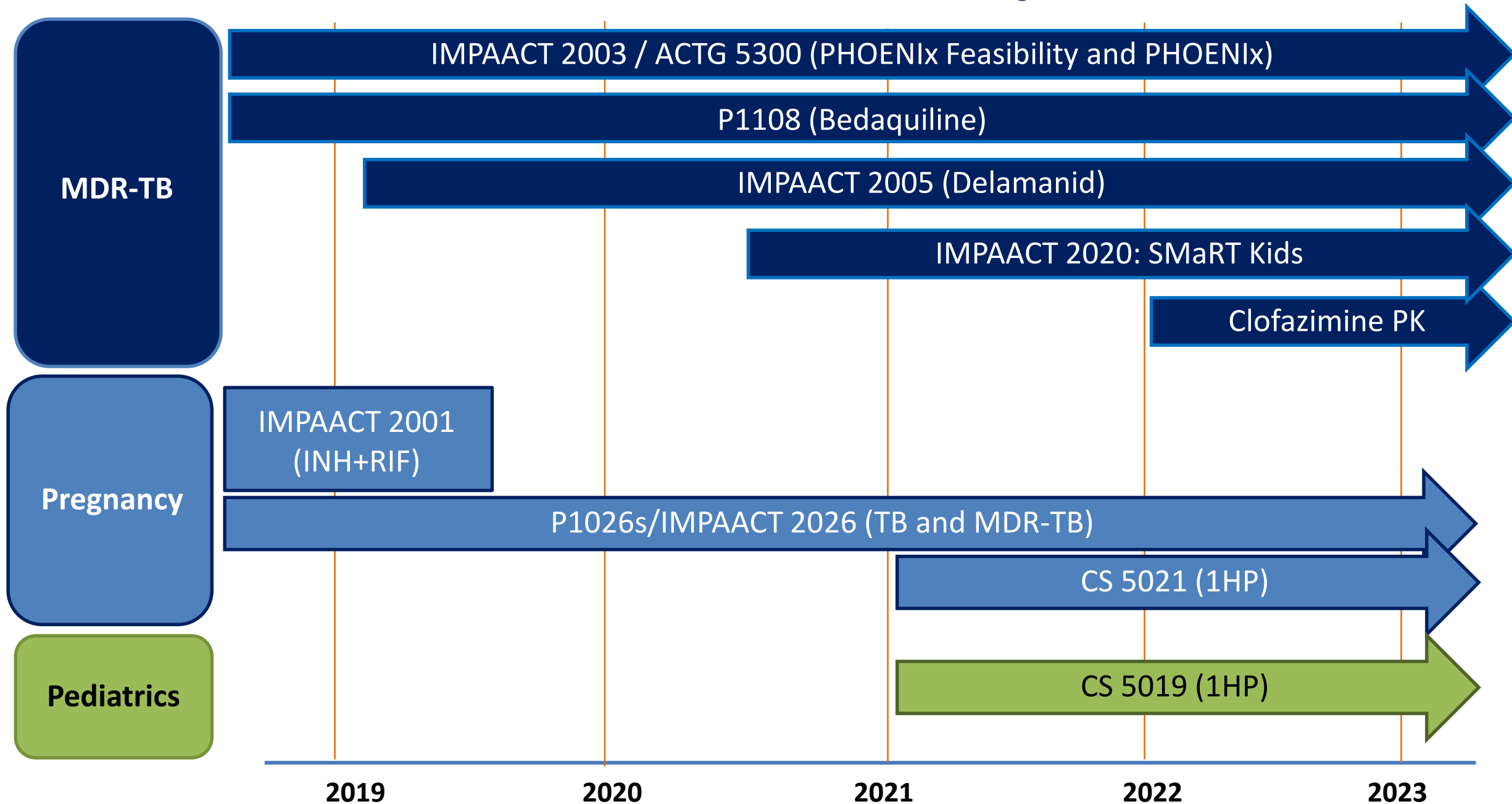
Children accessed TB preventive therapy in 2017. Only 23% of the estimated 1.3 million children under 5 years of age eligible for preventive therapy in TB households received this in 2017

Global TB report 2018

Tuberculosis and HIV



IMPAACT TB Roadmap



Study Highlight: IMPAACT 2020

Shortened Oral Treatment for Multidrug-Resistant Tuberculosis in Children (SMaRT Kids)

- Phase II study among ~169 children with MDR-TB
- Primary objective: characterize safety and tolerability of all-oral, short-course regimen



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

Anticipate Version 1.0
to sites by Q4 2019

Focus for the Future: Tuberculosis

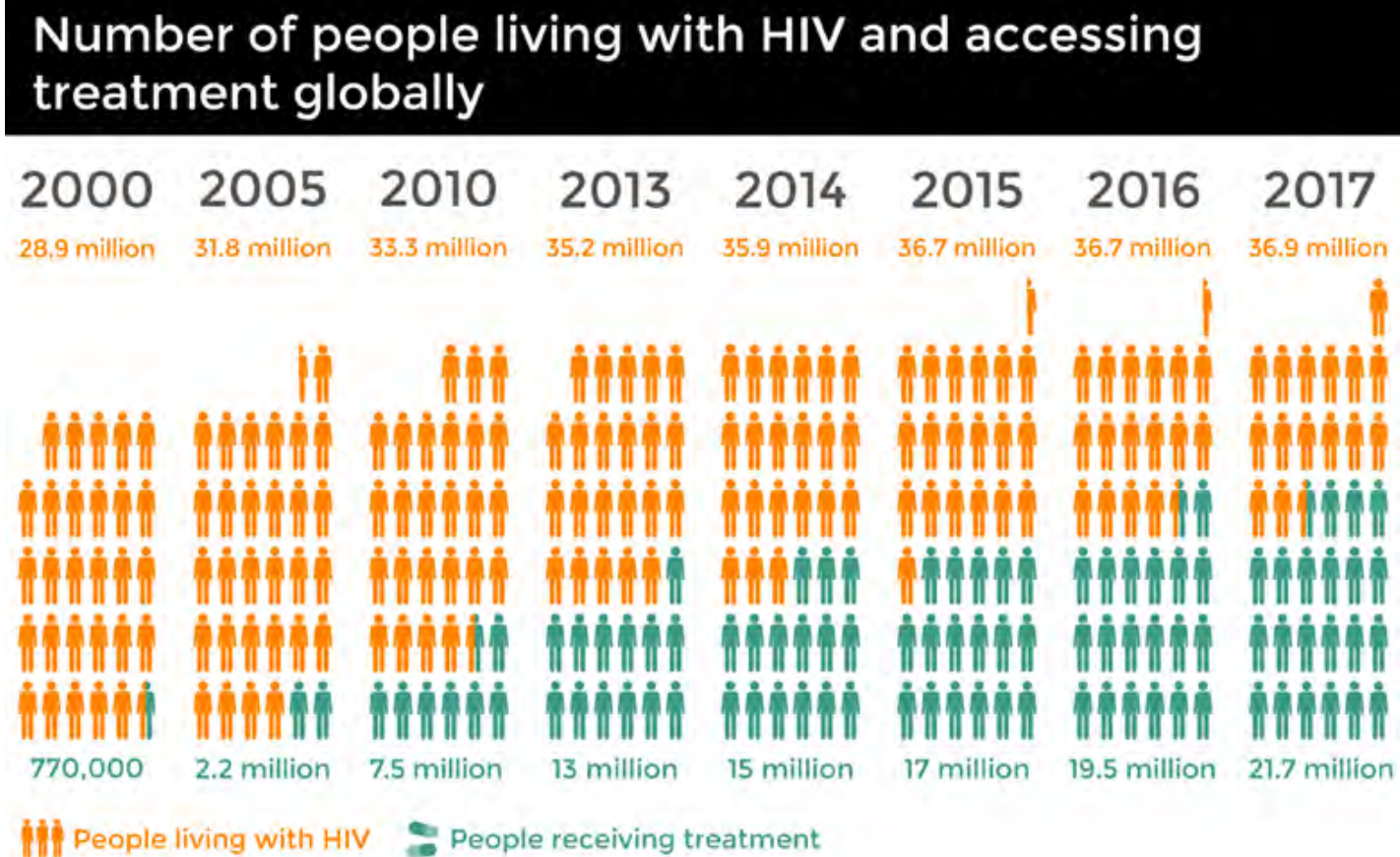
- Prevent TB
 - New vaccines
- Diagnose TB
 - Infants
 - Alternate samples
 - PCR facile
 - Imaging tools
- Treat drug susceptible TB
 - New drugs
 - Shorter regimens
 - Optimize: Better tasting drugs, FDCs
- Treat MDR-TB
 - New drugs
 - Shorter regimens
 - Fewer toxicities





**What is driving
the Treatment agenda?**

21.7 million people living with HIV were receiving antiretroviral treatment in 2017, up from 17 million in 2015 and 7.5 million in 2010.



Source: UNAIDS Data 2018

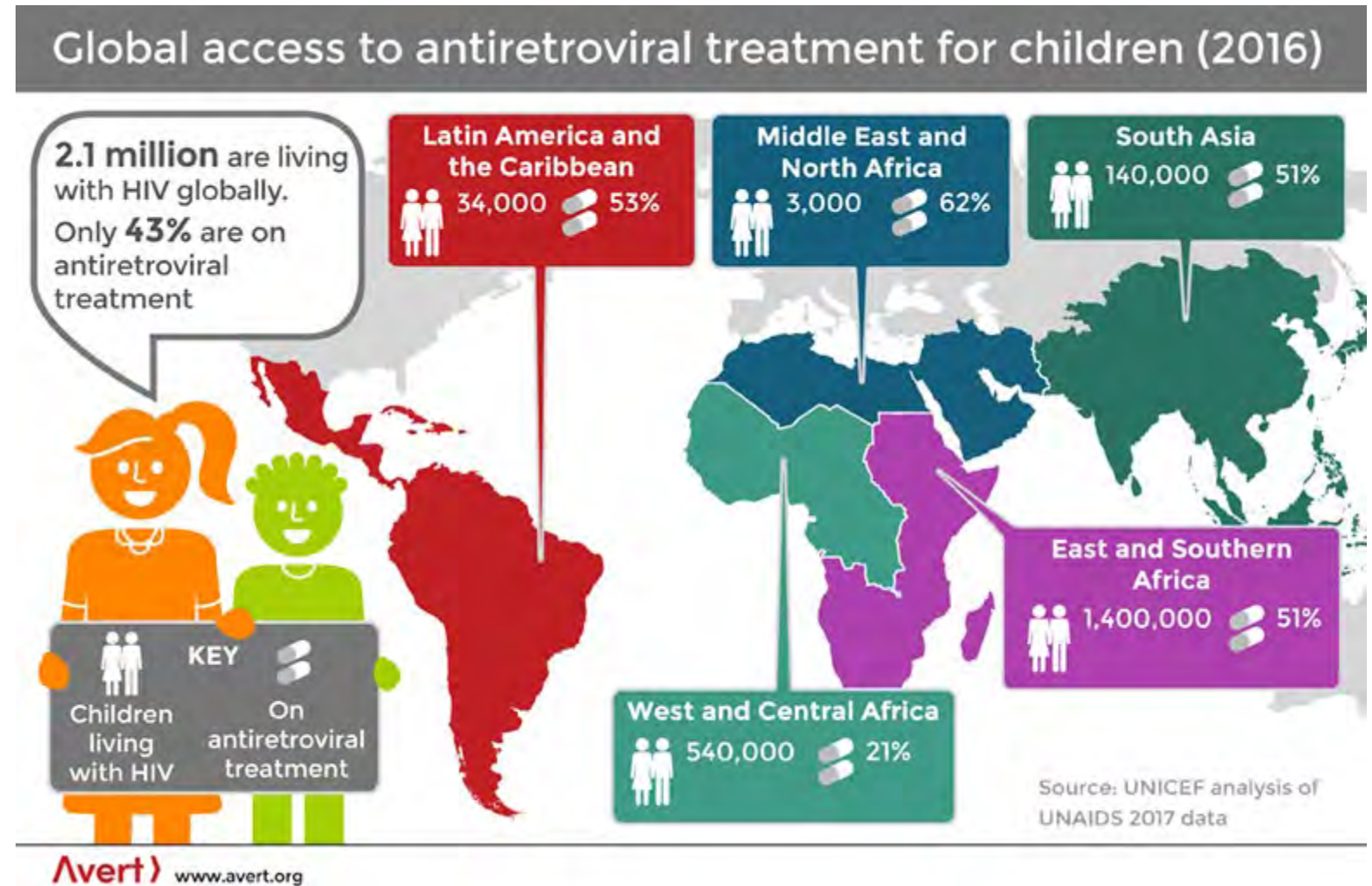
More than half of all people living with HIV (59%) now have access to life-saving treatment.

80% of all pregnant women living with HIV accessed treatment to prevent HIV transmission to their babies.

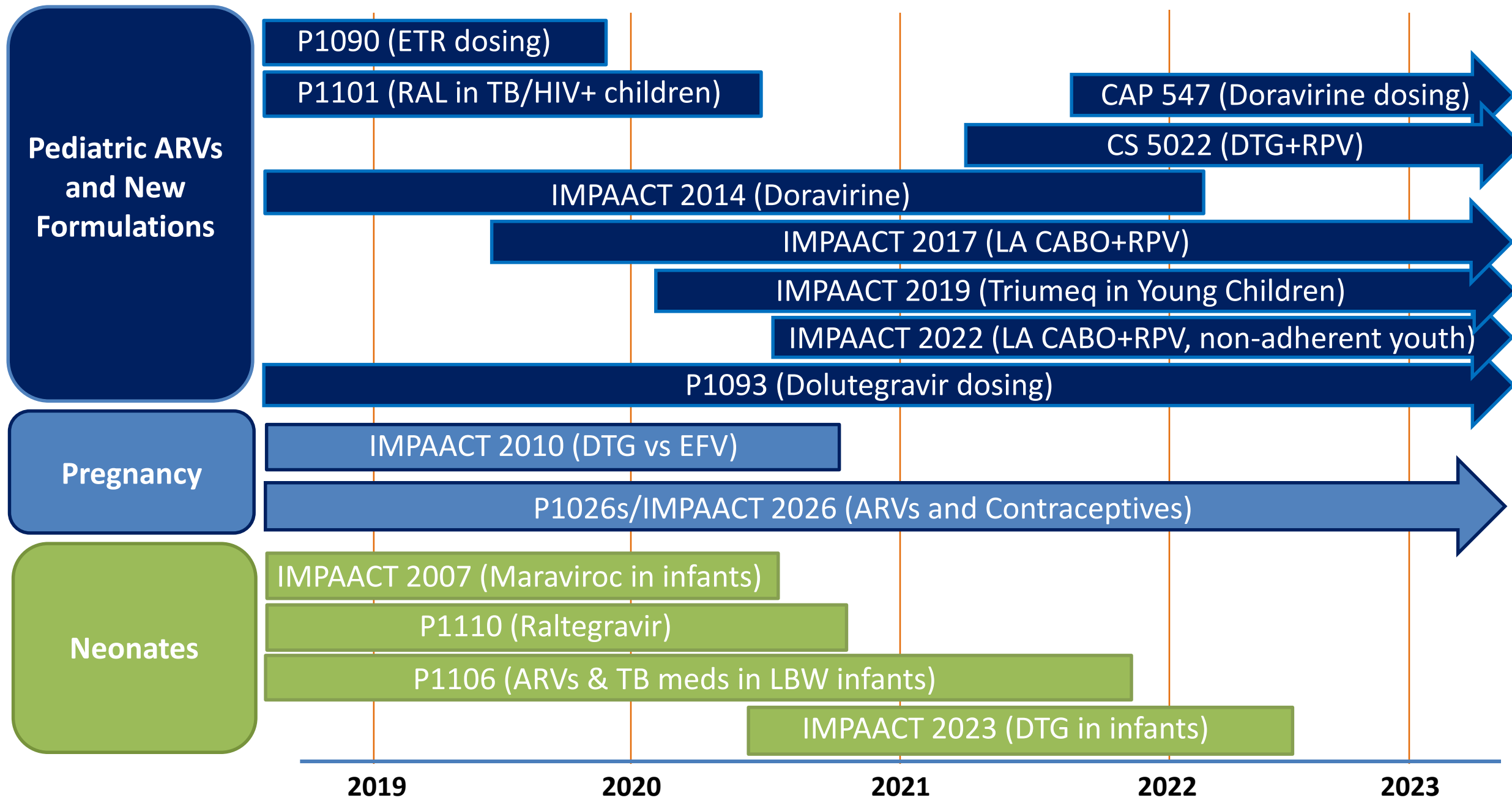
There were 180,000 new HIV infections among children (from 300,000 in 2010); young women are especially at risk.

HIV treatments for children work. But there continue to be challenges.

- ? Limited range of age-appropriate ARVs in pediatric formulations
- ? Drug palatability (tricky to swallow or taste unpleasant)
- ? Medicine volumes
- ? Keeping medications stored properly



IMPAACT Treatment Roadmap



Study Highlight: IMPAACT 2023

Safety and PK of DTG in Neonates Exposed to HIV

- Phase I study among HIV-1 exposed neonates at risk of acquiring HIV-1 infection
- Purpose: Evaluate safety, tolerability, and PK of dolutegravir solution given in the first 6 weeks of life



Anticipate
protocol to sites by
January 2020

Study Highlight: IMPAACT 2026

PK of ARVs, Anti-TB Meds, Contraceptive and Related Drugs During Pregnancy and Postpartum

- Phase IV prospective PK study of selected ARVs, anti-TB medications, hormonal contraceptives, and other related drugs
- Follow-on to P1026s



Anticipate Version 1.0
by August 2019

Focus for the Future: Treatment

■ Our populations

- Neonates and infants
- At risk and newly infected youth
- Pregnant women



■ Our research areas

- Safety
- Long-acting injectables
- Pharmacokinetics
- Implantables
- Drug interactions
- Adherence
- Microbiome



**What is driving
the Complications agenda?**

HIV/ARV Complications & Co-Morbidities

Scientific Agenda

- Prevent and **treat** cognitive impairment
 - Evaluate long-term neurocognitive outcomes with focus on prevention and early treatment; drug-drug interactions, and relationship to specific ARV therapies
 - If early therapy prevents neurocognitive impairment, what other adjuvants can we use? Other therapies?
- Role of inflammation in:
 - General and specific organ disease progression
 - Interplay between specific reservoirs, immune dysregulation, and developing complications



HIV/ARV Complications & Co-Morbidities

Scientific Agenda

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



IMPAACT Complications & Co-Morbidities Roadmap

Vaccines

IMPAACT 2018 (RSV vaccine)

IMPAACT 2021 (RSV vaccines)

RSV Capsule

Neuro-Complications

IMPAACT 2002 (depression intervention)

IMPAACT 2016 (mental health)

CAP 548 (Computer cognitive games)

Inflammation

CS 5020 (Aspirin in Pregnancy)

2019

2020

2021

2022

2023

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



Anticipate open to
accrual by July 2019

Focus for the Future: Complications & Comorbidities

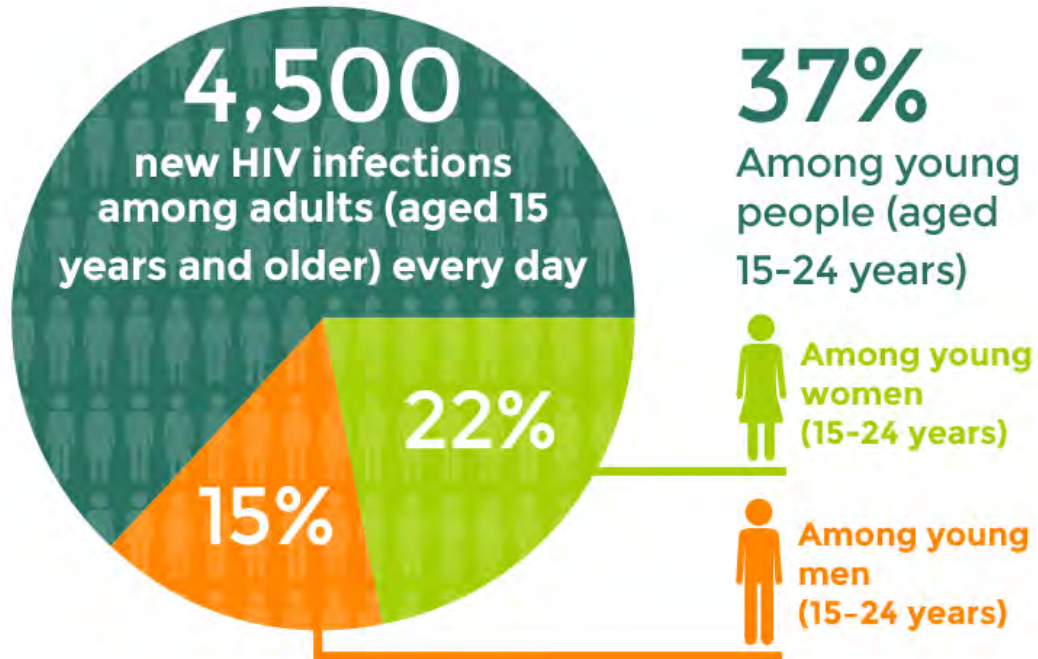
- Revisit the hepatitis treatment and prevention questions
 - New drugs
 - New data sets
- Non-HIV, infectious diseases
- Preserve neurocognitive development
- Treat neuropsychiatric issues
- Current and emerging pathogens?
 - RSV
 - Others



**What is driving
the Prevention agenda?**

Young Women at High Risk for HIV

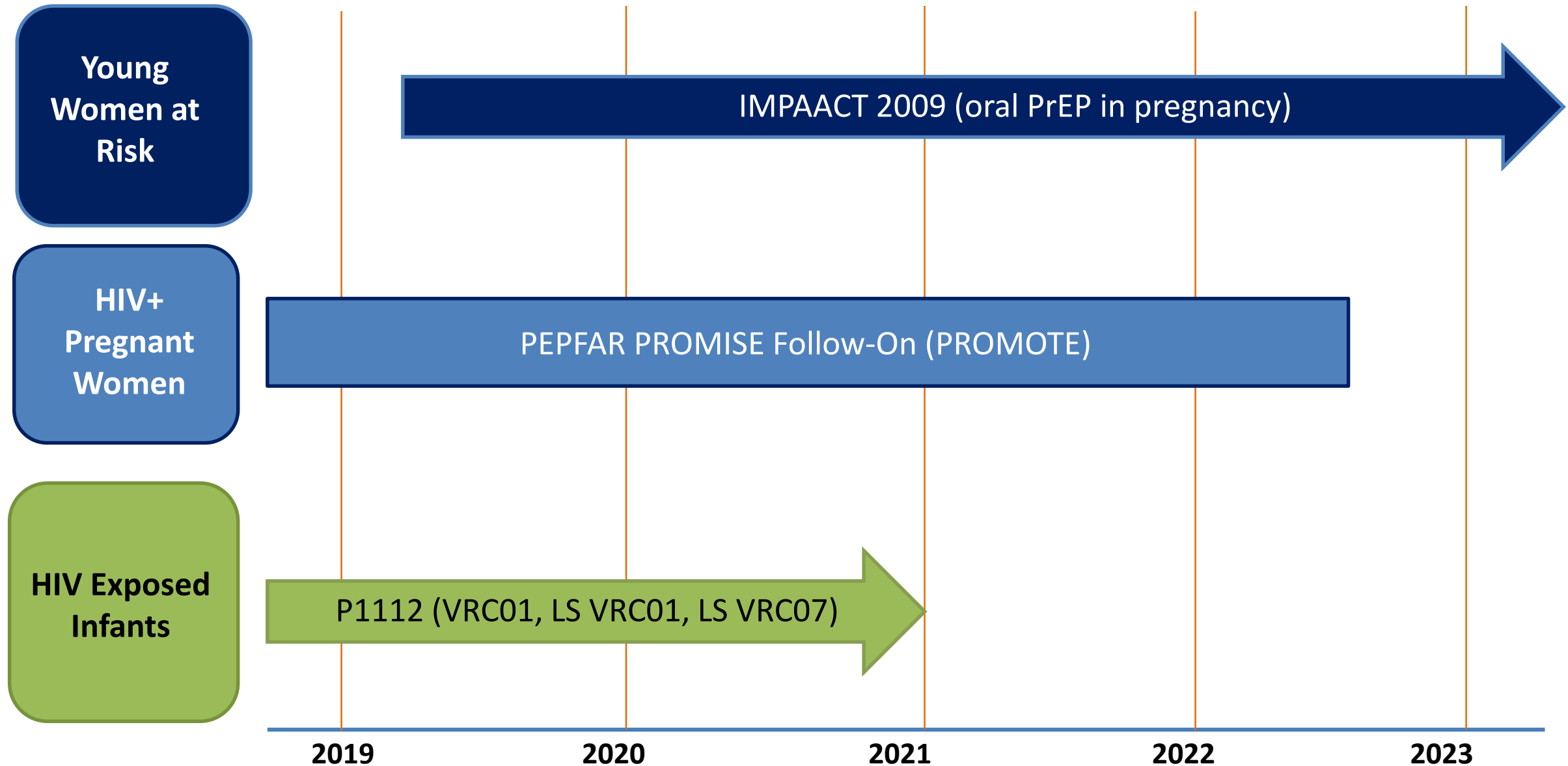
More Pronounced in Sub-Saharan Africa



- **Structural issues:** access to education, sexual and reproductive health services, poverty, food insecurity and violence
- **Female centered HIV prevention strategies** are needed to protect this vulnerable population

IMPAACT's agenda is aligned with other networks to address this need (HPTN).

IMPAACT Prevention Roadmap



Gaps in Prevention

■ Key Populations

- Adolescent/young MSM in the U.S. and elsewhere
- Adolescent girls/young women in Africa

■ Age de-escalation does not work!

- New tools are need among at-risk youth
 - Injectables
 - Implantables
 - Interventions to maximize adherence

Focus for the Future: Prevention

- Prevention in pregnant women
 - High rates of pregnancy in under 20 year olds in African settings: at age of highest HIV risk
- Long-acting prophylaxis in pregnant and postpartum women
 - Consequences for infants
 - Dealing with “the tail” of LA drugs in women at high risk of infection
- How best to use implantable devices across the ages
- U.S. adolescent agenda?

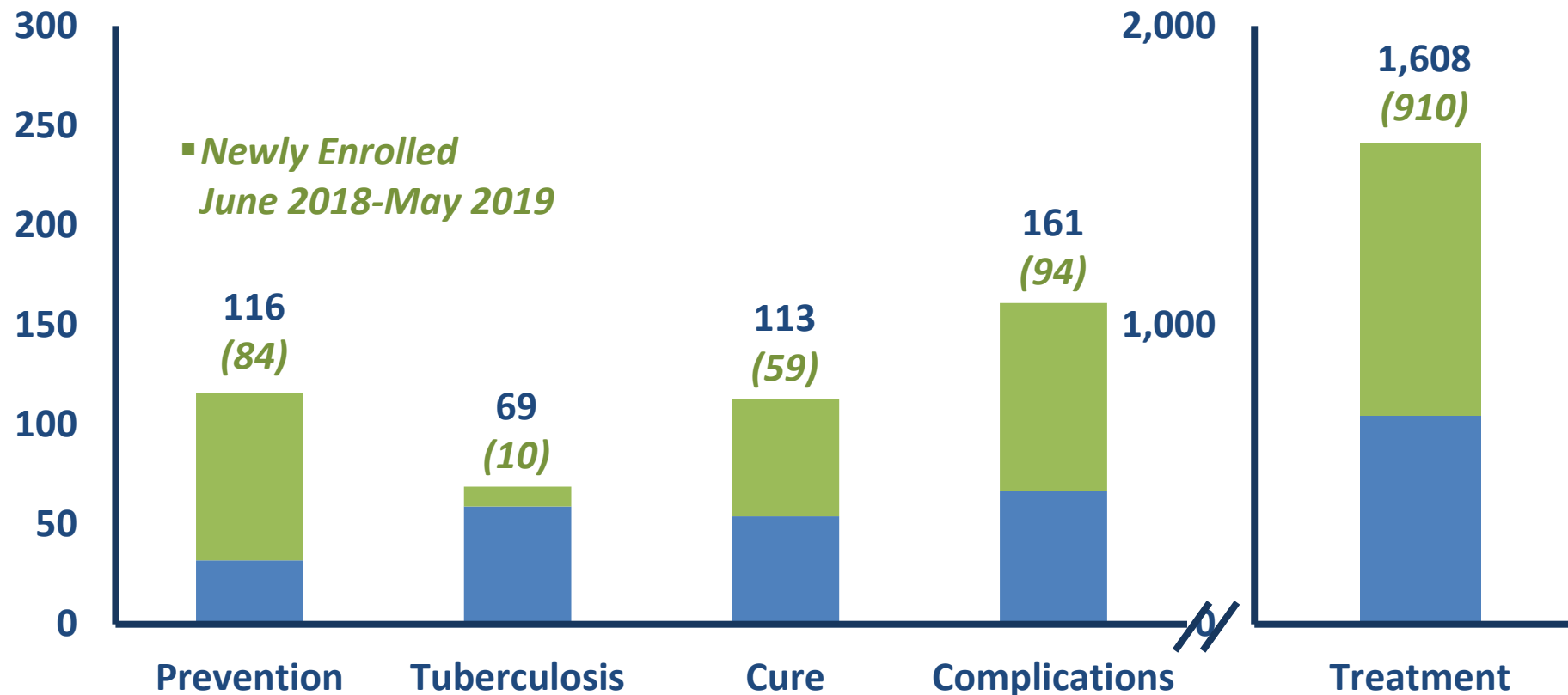




Activities in the Past Year

IMPAACT Participants on Study

June 2018 to May 2019



Total On Study = 2,067 participants

Newly Enrolled = 1,157 participants

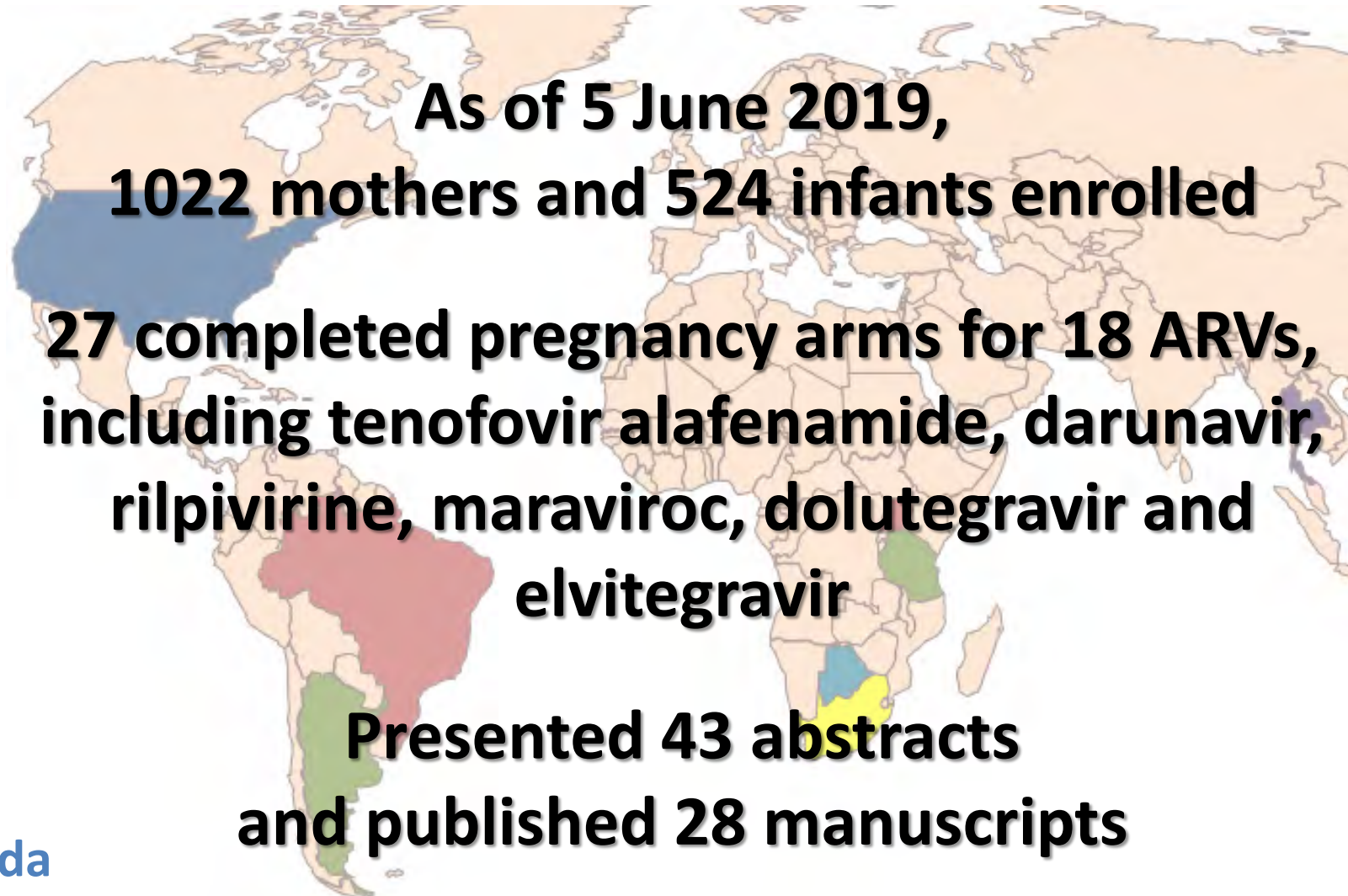
Annual Enrollment

June 2018 to May 2019

- **1,157** participants enrolled onto IMPAACT studies
- **487** participants were enrolled while pregnant or early postpartum (P1026s, P1112, 2001, 2007, 2008, 2009, 2010/VESTED)
- **372** infant participants less than one year of age
- **103** children ages 1-18 years of age

Study Highlight: P1026s

PK Properties of ARVs during Pregnancy



Study Highlight: P1026s

Contributions to Perinatal HHS Guidelines

- 30 ARV drugs in the current published HHS perinatal guidelines – PK data from P1026s cited for 20 (67%)
- 97 PK in pregnancy studies cited in perinatal guidelines for all ARVs – P1026s responsible for 32 (33%)
- P1026s data are the only cited source of PK data from studies in pregnant women for 2 drugs (maraviroc and tenofovir alafenamide)

Class	P1026s Citations/Total # of PK studies in Pregnancy* Citations	Percent of Data from P1026s
NRTI	4/20	20%
NNRTI	5/12	42%
PI	14/49	29%
INSTI	3/8	38%
Entry/Fusion	1/1	100%
PK Enhancers	5/7	71%

*Excludes case reports

Study Highlight: IMPAACT P1093

PK, Safety, and Tolerability of Dolutegravir in Infants, Children and Adolescents with HIV

- Evaluating age-based and weight-band cohorts
- 163 participants enrolled, including 78 to the pediatric dispersible tablet formulation
- Full accrual expected by April 2020



Regulatory submission
targeted for the
end of 2019

Study Highlight: IMPAACT 2017

Safety and PK of Oral and Long-Acting Injectable CAB and RPV

- Phase I/II study among virologically suppressed children and adolescents to evaluate long-acting ARV regimens
- First participant enrolled in April 2019, with 7 enrolled to date
- 4 are now receiving the injectable formulation (Cohort 1, Step 2)



Study Highlight: P1112

Safety and PK Parameters of Potent Anti-HIV Neutralizing Monoclonal Antibodies

- Phase I study among HIV-exposed infants
- Successfully completed enrollment of Dose Groups 1-4
- Dose Group 5 includes evaluation of a new bNAb called VRC07-523LS and opened to accrual in January 2019

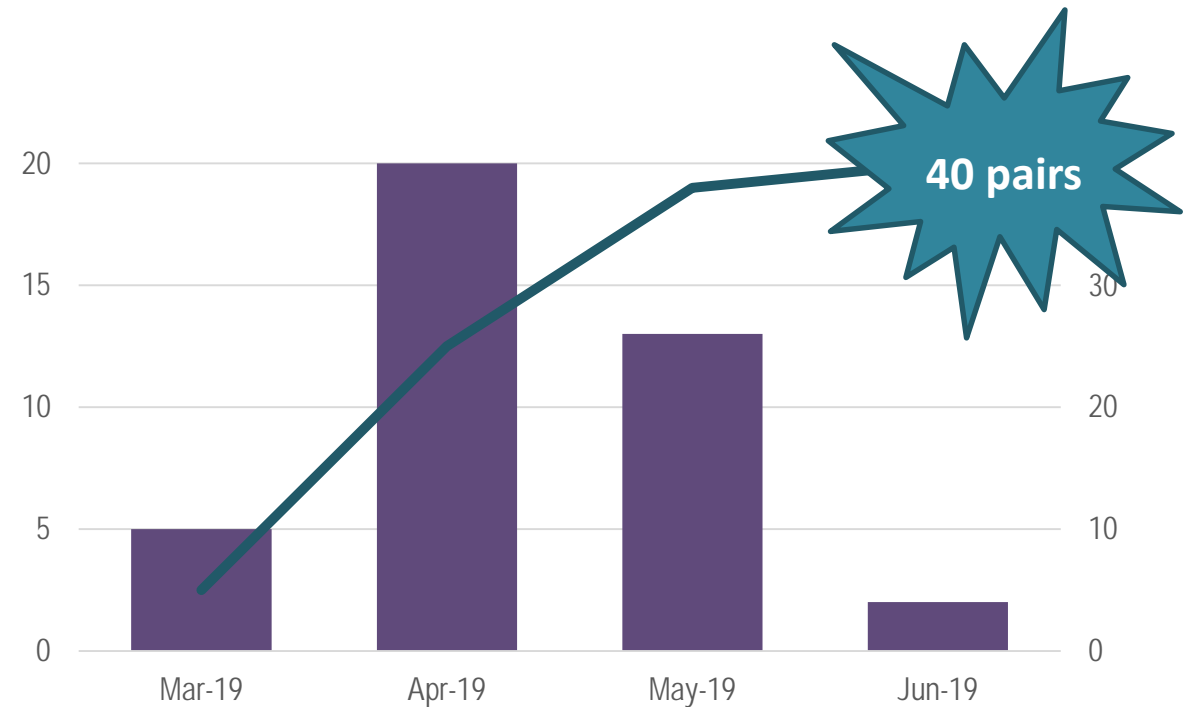


Anticipate completion
of accrual by
December 2019

Study Highlight: IMPAACT 2009

PrEP in Pregnant Women

- Completed enrollment of PK component with 5 sites enrolling 40 women!!
- Up Next: PrEP comparison component to determine feasibility, acceptability, and safety of PrEP (n=350 pairs)



Anticipate PrEP
Comparison to begin
enrolling in early 2020

Study Highlight: IMPAACT 2001

PK, Tolerability, & Safety of RIF and INH in HIV-infected and -uninfected Pregnant Women

- 50 of 50 mother-infant pairs were enrolled with follow-up completed in April 2019!



Anticipate results by
December 2019

Study Highlight: IMPAACT P1108

PK and Safety of Bedaquiline in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease

- Four of five sites activated
- 15 participants enrolled in Cohort 1 (age ≥ 6 to 18 years)
- Study target accrual = 72 participants



Study Highlight: IMPAACT 2005

Delamanid in Infants, Children and Adolescents with MDR-TB Disease

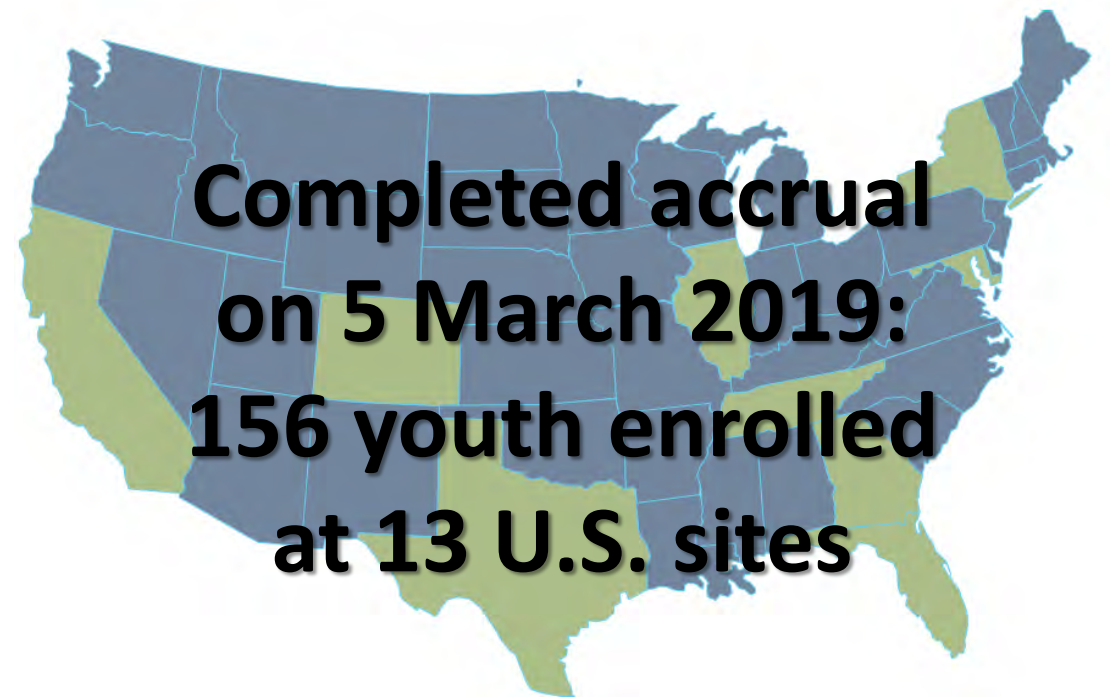
- Phase I/II study to evaluate the PK and safety among participants <18 years with MDR-TB
- Six of seven sites activated
- 2 of 48 participants enrolled in Cohort 1 (age 12 to <18 years)



Study Highlight: IMPAACT 2002

Combined Cognitive Behavioral Therapy & Medication Management Algorithm for Treatment of Depression

- Sites randomized to COMB-R or Enhanced Standard of Care arms to determine if the intervention for depression demonstrates improved outcomes for HIV-infected youth
- **Successfully completed accrual as projected in March 2019!**

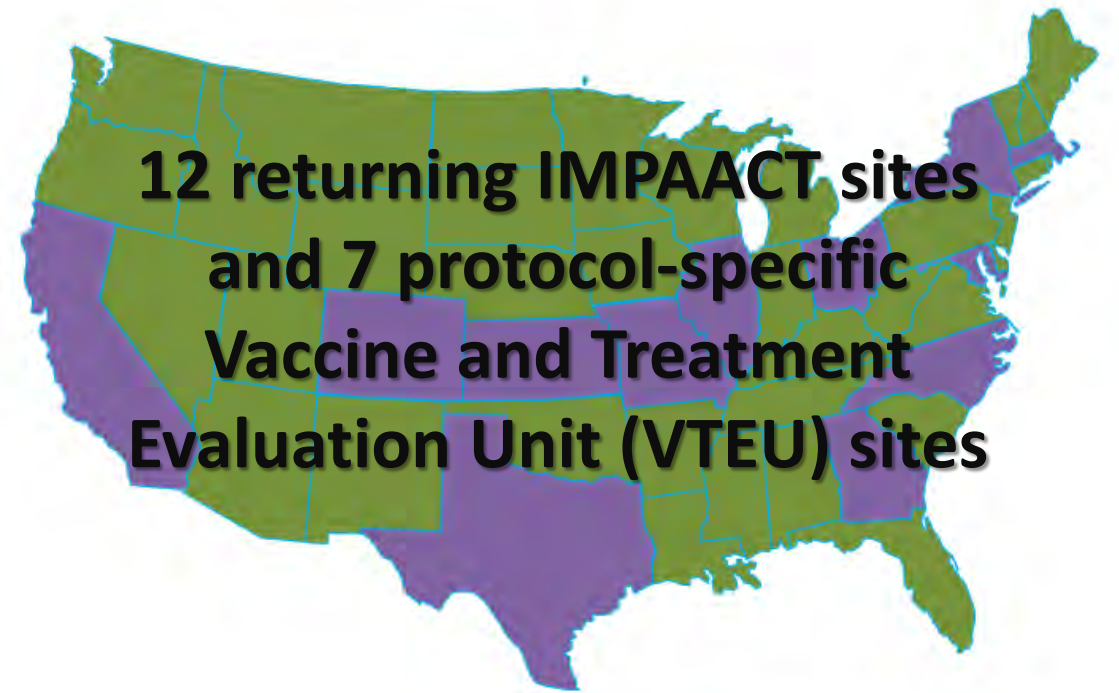


Study Highlight: IMPAACT 2021

RSV Candidate Vaccine Study

- Randomized, Phase I/II placebo-controlled study among healthy RSV-seronegative children 6-24 months of age to assess safety and immunogenicity of 3 candidate vaccines:

- RSV Δ NS2/ Δ 1313/I13134L
- RSV 276
- RSV 6120/ Δ NS2/1030s

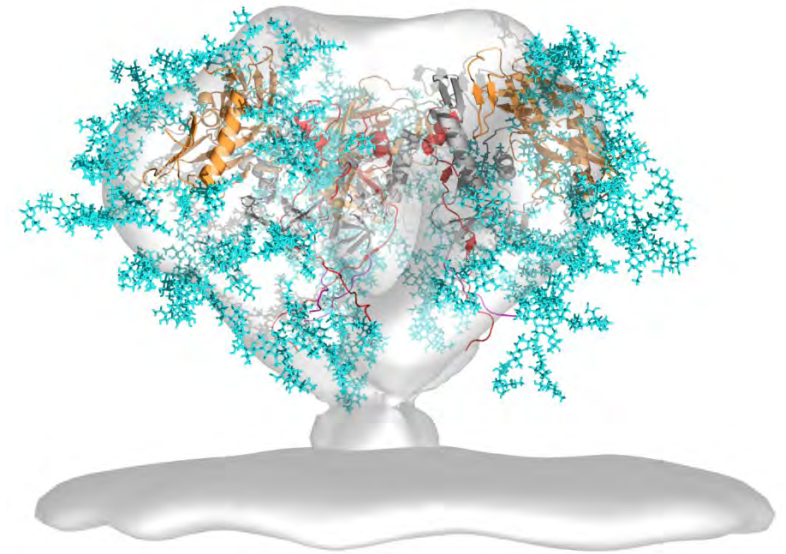


Anticipate first
enrollment in June 2019

Study Highlight: IMPAACT 2008

Study of Monoclonal Antibody Combined with ART

- Phase I/II study to assess safety of monoclonal antibody and effect on HIV DNA concentrations in infants infected with HIV
- Ten of 18 sites activated
- 26 of 68 participants enrolled in Botswana, Brazil, Malawi, and Zimbabwe

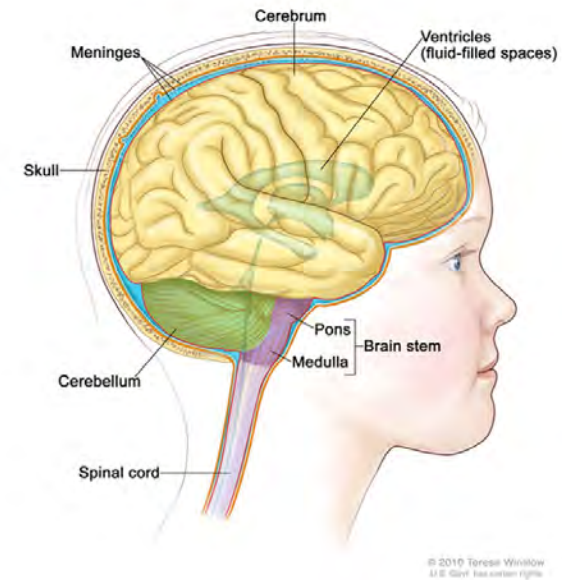


Anticipate completing
enrollment in August 2019

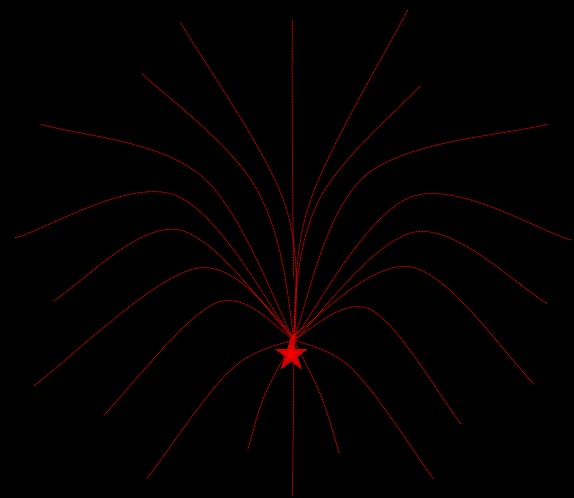
Study Highlight: IMPAACT 2015

Evaluating the HIV Reservoir in the CNS in Perinatally-Infected Individuals on ART

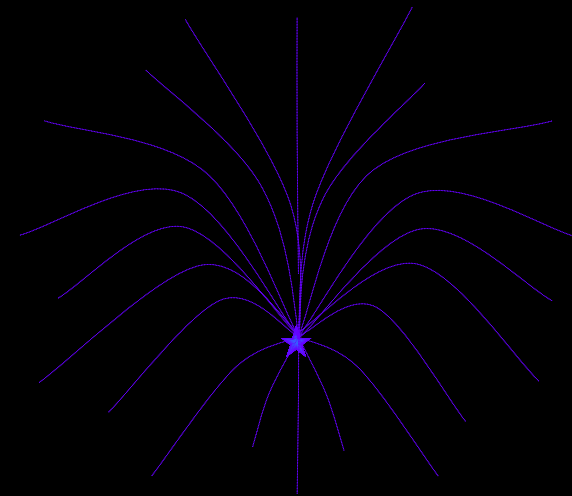
- Cross-sectional study of perinatally-infected youth and young adults on ART with neurocognitive impairment
- 7 of 12 sites activated
- First participant enrolled in February, with 4 of 45 participants enrolled to date



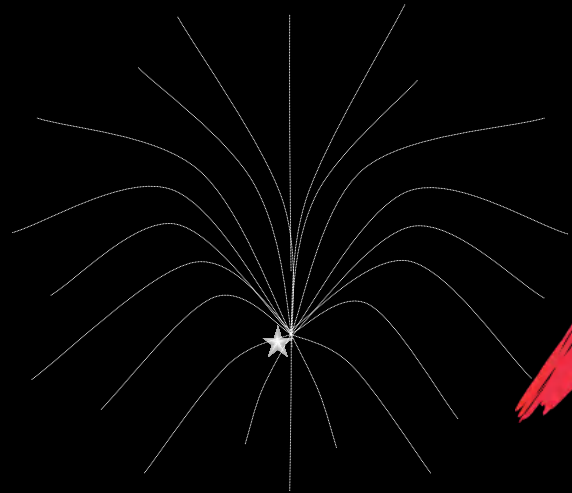
Anticipate completing
accrual by November 2019



IMPAACT 2010
completed accrual!



VESTED

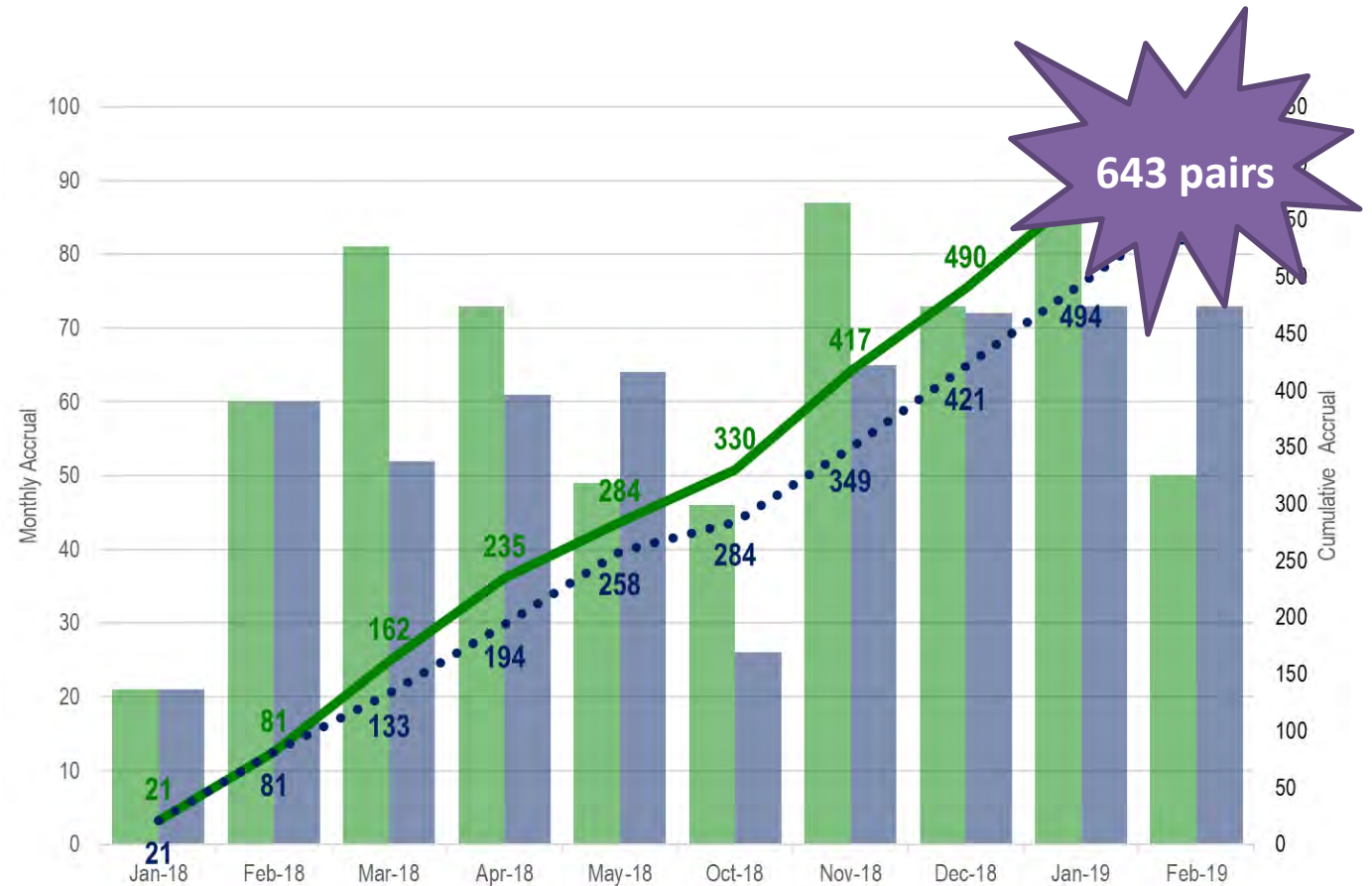


*International Maternal Pediatric
Adolescent AIDS Clinical Trials Network*

Study Highlight: IMPAACT 2010

Efficacy & Safety of DTG-Containing vs. EFV-containing ART Regimens in HIV-Infected Pregnant Women & Their Infants

- Phase III study among HIV-infected pregnant women and their infants
- 22 sites enrolled in Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, the United States, and Zimbabwe



30 Active Studies

June 2018 to May 2019

	4 In Development	4 Pending and Open	17 Enrolling	4 In Follow-up	1 Closed to Follow-up*
Treatment	2026, 2023, 2022	2019	2017, 2014, 2007, P1110, P1106, P1101, P1093, P1026s	2010, P1102, P1090	
Prevention			2009, P1112		
Complications		2021, 2016	2018	2002	
Tuberculosis	2020	2003b	2005, P1108		2001
Cure			2015, 2008, P1115, P1107		

*closed to follow-up in the last year

IMPAACT Science Generation

June 2018 to May 2019

7 New Capsules for Review

- 1 Treatment
- 1 Prevention
- 2 Complications
- 2 Tuberculosis
- 1 Cure

4 New Concept Sheets for Review

- 1 Treatment
- 1 Complications
- 2 Tuberculosis

2 New Protocols Approved for Development

- 2 Treatment

Four Protocols Currently in Development

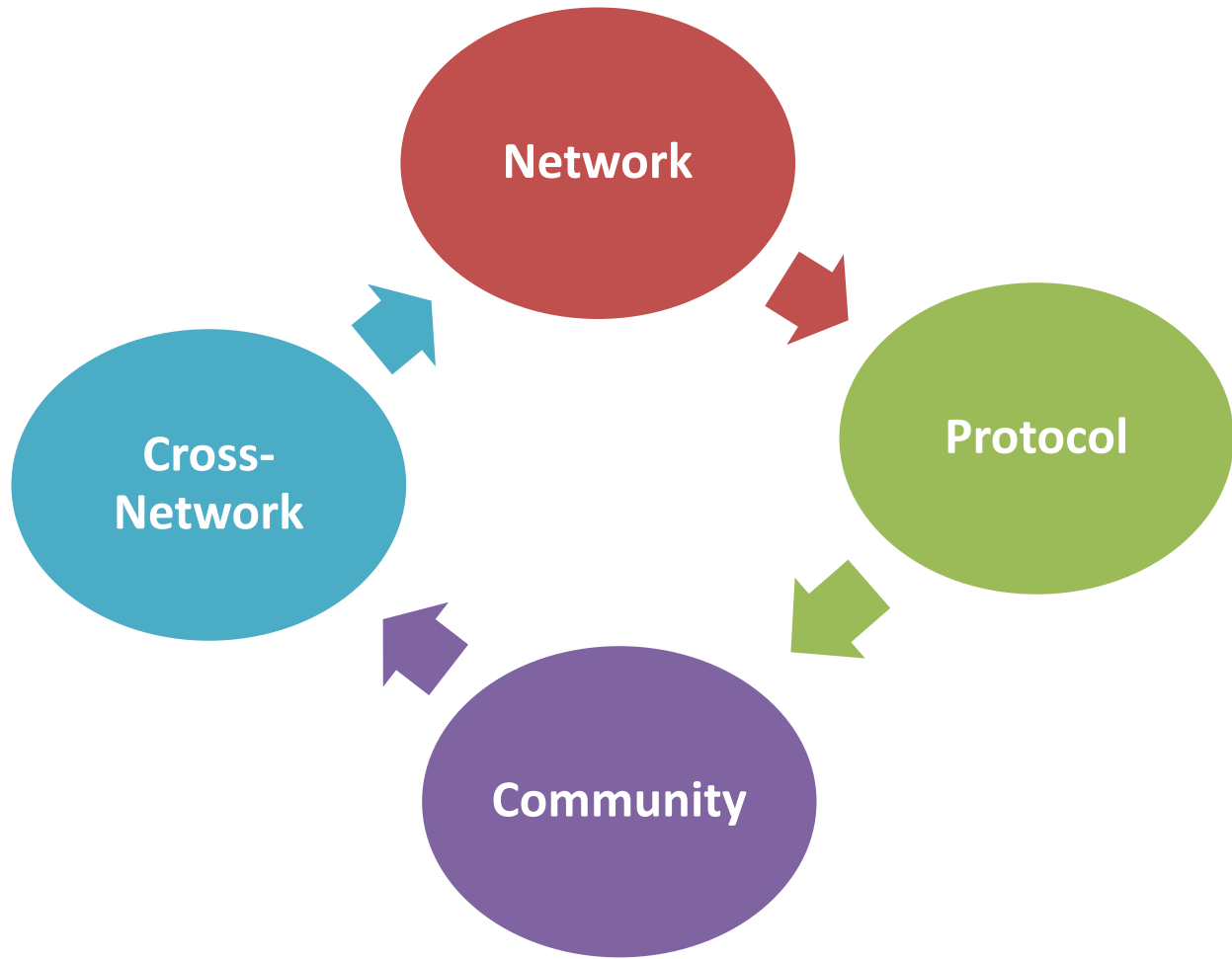
2026	Pharmacokinetic Properties of Antiretroviral, Anti-Tuberculosis, Contraceptive and Related Drugs During Pregnancy and Postpartum
2023	A Phase I Trial to Evaluate the Safety and Pharmacokinetics of Dolutegravir in Neonates Exposed to HIV-1 Infection
2022	Phase II Study of the Virologic Efficacy and Feasibility of Long Acting Injectable Antiretroviral Medications in Non-Adherent Youth with HIV
2020	Phase II Study of Shortened Oral Treatment for Multidrug-Resistant Tuberculosis in Children (SMaRT Kids)

Community Engagement Achievements

- Community representatives serve on groups across the Network, including on the scientific leadership group, scientific committees, and on each protocol team
- Comprehensive community reviews in the past year:
 - 2 protocols in development
 - 3 protocol modifications
 - 18 capsules
 - 7 concept sheets
 - 1 DACS and 1 NWCS



Community Engagement Achievements



- Engagement across network levels and groups
 - ✓ Reviewed drafts of IMPAACT 2021 and IMPAACT 2026
 - ✓ Participated in HANC Community Partners and working group within DAIDS OCSO

Publications

- **71** publications submitted for IMPAACT review in past 12 months
- **36** manuscripts published in NEJM, JAIDS, AIDS, Lancet HIV, HIV Clinical Trials, Journal of Clinical Pharmacology, PIDJ, CID, among others

THE NEW ENGLAND JOURNAL of MEDICINE

Birth Outcomes for Pregnant Women with HIV Using Tenofovir–Emtricitabine

Kathryn Rough, Sc.D., George R. Seage, III, D.Sc., M.P.H.,
Paige L. Williams, Ph.D., Sonia Hernandez-Diaz, M.D., Dr.P.H.,
Yanling Huo, M.S., Ellen G. Chadwick, M.D., Judith S. Currier, M.D.

Safety and efficacy at 240 weeks of different raltegravir formulations in children with HIV-1: a phase 1/2 open label, non-randomised, multicentre trial

Sharon Nachman, Carmelita Alvero, Hedy Teppler, Brenda Homony, Anthony J Rodgers, Bobbie L Graham, Terence Fenton, Lisa M Frenkel, Renee S Browning, Rohan Hazra, et al.

JOURNAL OF THE
Pediatric Infectious Diseases Society



Long-Term Safety and Efficacy of Dolutegravir in Treatment-Experienced Adolescents With Human Immunodeficiency Virus Infection: Results of the IMPAACT P1093 Study

Rolando M Viani, Theodore Ruel ✉, Carmelita Alvero, Terry Fenton, Edward P Acosta, Rohan Hazra, Ellen Teppler, Paul Dumbo, Ann M Burchanan, Cindy Veyre, Rajendra Singh, et al.

AIDS

Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV

Momper, Jeremiah D.^a; Best, Brookie M.^a; Wang, Jiajia^b; Capparelli, Edmund V.^a; Stek, Alice^c; Barr, Emily^d; Badell, Martina L.^e; Acosta, Edward P.^f; Purswani, Murti^g; Smith, Elizabeth^h; Chakhtoura, Nahidaⁱ; Park, Kyunghun^a; Burchett, Sandra^j; Shapiro, David E.^b; Mirochnick, Mark^k for the IMPAACT P1026s Protocol Team

- 4 abstracts from PROMISE
- 4 abstracts related to laboratory evaluations
- Primary results from NICHD P1081
- Secondary and other results from P1078, P1115, P1112, P1093, and P1072

Additional abstracts accepted to
upcoming meetings at IAS 2019 and
the HIV Pediatrics Workshop

[illegible]

Cross Network Study Initiatives



- Pregnancy Studies (IMPAACT 2026)



- MDR-TB Prevention (PHOENIx)



- TB and HIV Vaccine Studies (Aeras/P1113)



- RSV and VRC01 Studies (IMPAACT 2011/2012/2013, IMPAACT 2018, IMPAACT 2021, and P1112)



Pharma Collaborations: New Formulations/Products



Annual Meeting, by the Numbers

- 295 attendees (~71%) have downloaded and logged into the Smartphone App to help guide their schedules
- 418 people have checked into the meeting, with about half representing IMPAACT sites
- At least 54 meetings, drop-in sessions, trainings, and breakouts



IMPAACT Mobile App

Find agendas, speaker bios, maps, and more on the IMPAACT mobile app!

Search for "IMPAACT" in the iOS App Store or Google Play Store

Download the app

Select "2019 IMPAACT Annual Meeting"



Plans for the Upcoming Year...

Publish
P1092, P1078,
IMPAACT 2001,
& PROMISE

Complete
IMPAACT 2018,
2015, 2007,
2002 & P1090

Continue
IMPAACT
2014 & 2005

Complete
enrolling
IMPAACT 2008
2018, P1026s,
P1101 & P1112

Complete PK &
begin PrEP
Comparison in
IMPAACT 2009

Finalize
IMPAACT
2026, 2023 &
2020

Finalize
Amendments
for IMPAACT
2019, P1106 &
P1110

Publish
IMPAACT
2011, 2012,
& 2013

Begin
Version 2 of
P1115

Begin
IMPAACT
2021 & 2016

Continue
MOCHA &
P1108

Continue
follow-up in
VESTED &
P1093



**Thank you to site staff,
to the community, and to all the individuals and
families engaged in clinical research!**



Let's continue to move the science forward!