



International Maternal Pediatric AIDS Clinical Trials (IMPAACT) Network

State of the Network
2018 Annual Meeting

Sharon Nachman, MD

Overview

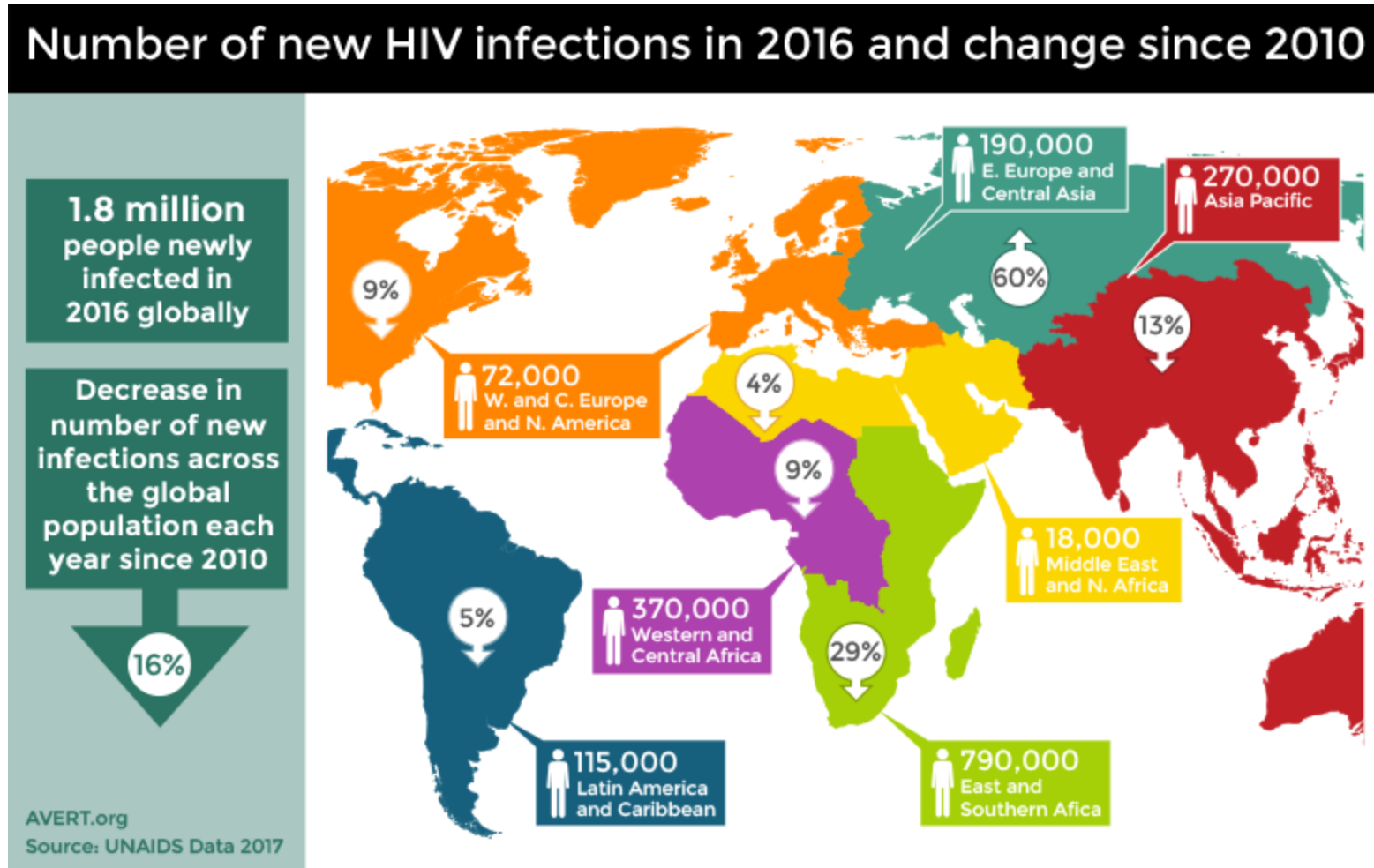
- IMPAACT in the current context of HIV
- Scientific committee updates and drivers of each scientific agenda
 - What are the priorities?
 - What is ongoing?
 - What is planned for future study?
- IMPAACT activities and achievements in the past year

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



How do we really end the epidemic?

There are large discrepancies in efforts to slow the spread of new infections in adults and children: some countries have declined by 50% or more, while many have no measurable progress



In 2016, there were roughly 1.8 million new HIV infections worldwide,
160,000 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.**



36.7 MILLION

people worldwide are currently living
with HIV/AIDS.

**2.1 MILLION
CHILDREN**

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



The vast majority of people living
with HIV are in low- to middle-income
countries, particularly in
Sub-Saharan Africa.

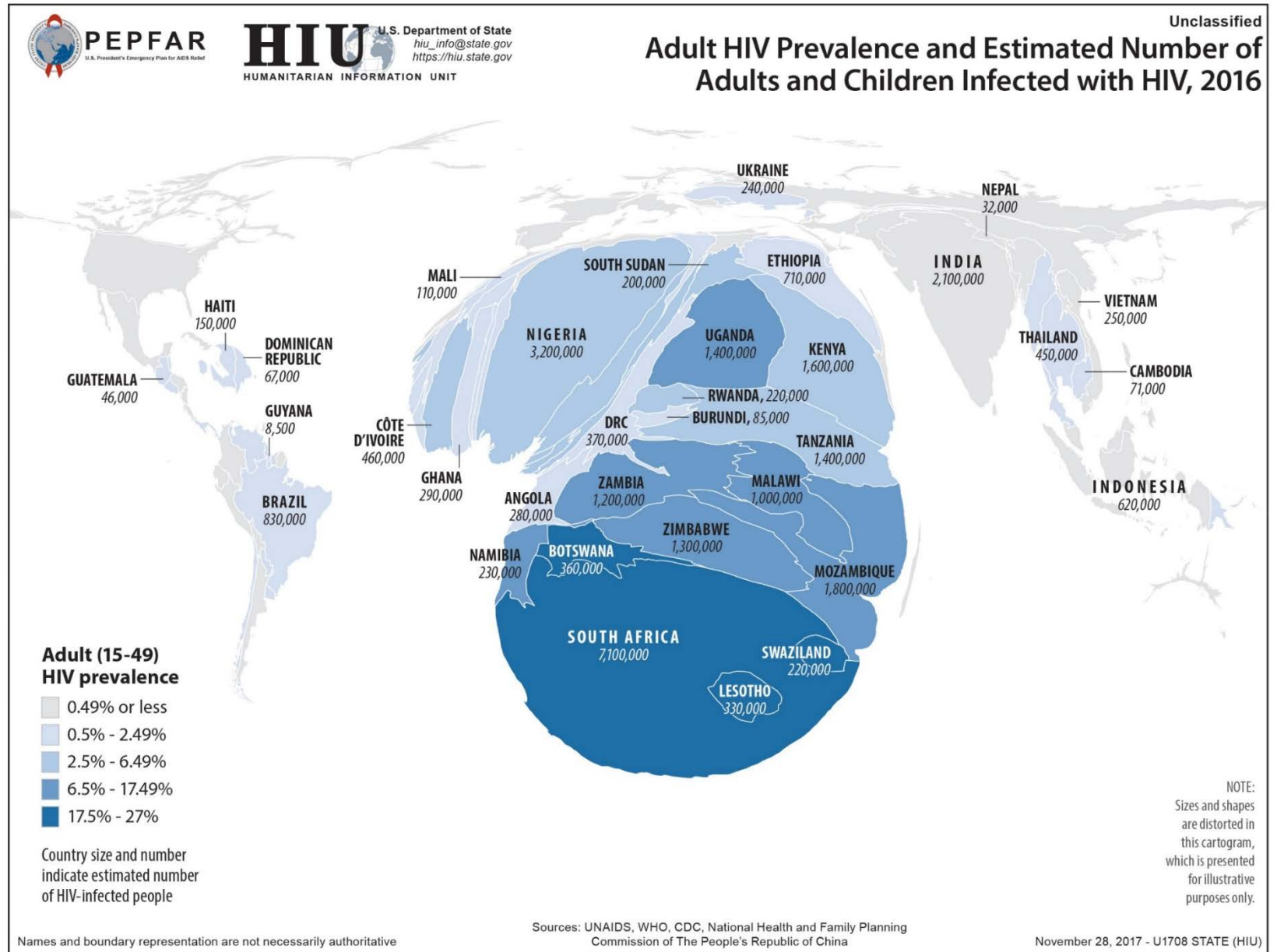


The youth bulge in many African countries represents obstacles and opportunities for prevent and treatment HIV responses

- In South Sudan, 51% of the population is less than 18 years of age
- The number of 10-24 years old in Africa will rise by more than 750 million by 2060

AIDS is the leading cause of death among young people (aged 10-24) in Africa, and second leading cause globally

A youth bulge threatens to increase new HIV infections further

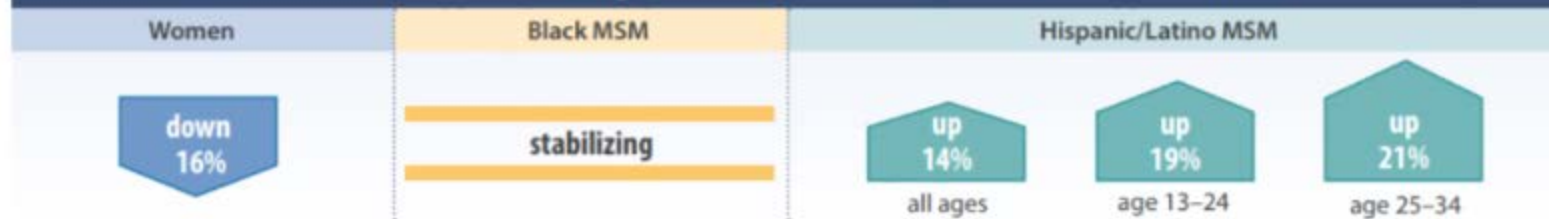


HIV Surveillance Report

Between 2011 and 2015 there was a **decrease** in HIV diagnoses, however progress is **uneven**

39,782 • Total HIV Diagnoses in 2016

HIV Diagnoses Trends from 2011–2015



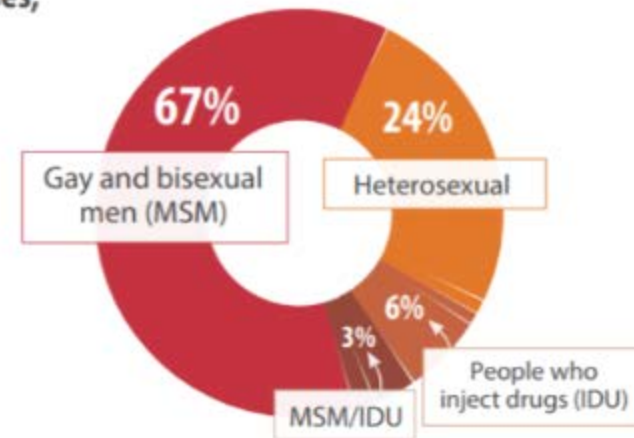
Percentage HIV Diagnoses in 2016

Blacks/African Americans accounted for **44%** of HIV diagnoses, though they comprise only **12%** of the US population

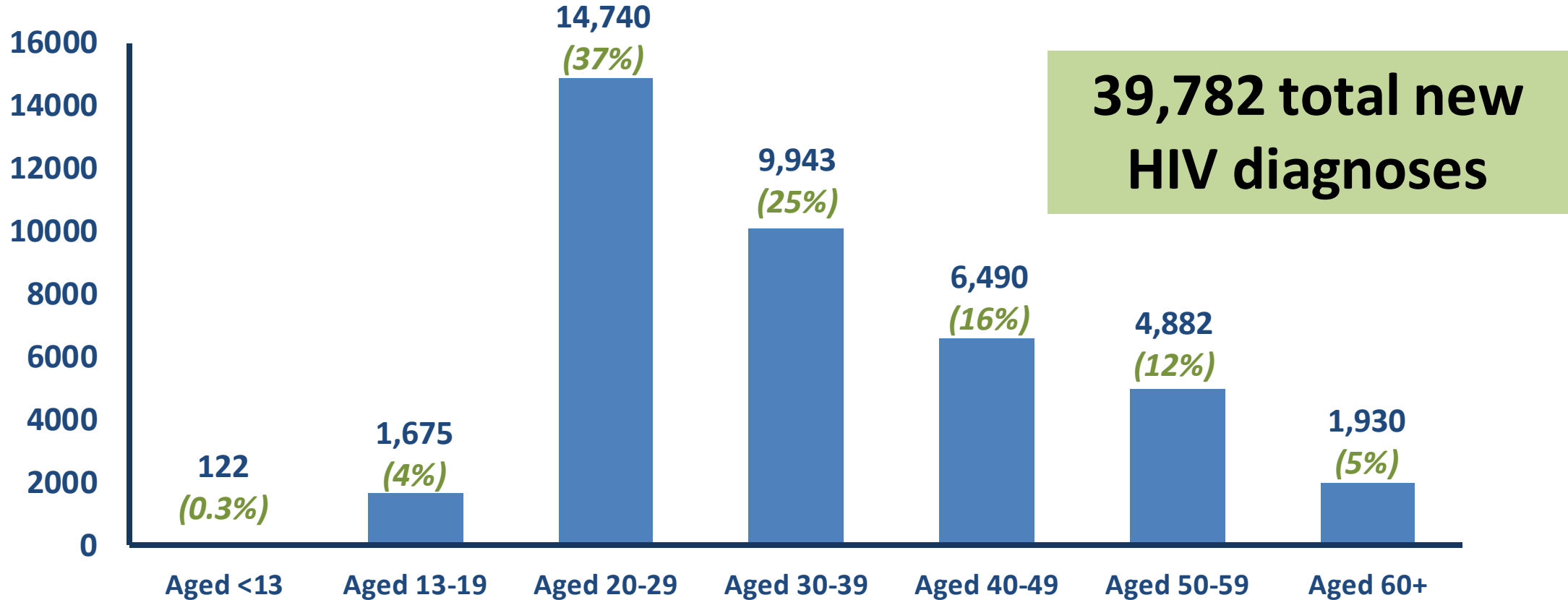


■ black/African American ■ White ■ Hispanic/Latino ■ Other*

*American Indian/Alaska Native: 0.6% • Asian: 2.5% • Native Hawaiian/Other Pacific Islander: 0.1% • Multiple races: 2.2%



New HIV Diagnoses in the U.S. By Age, 2016

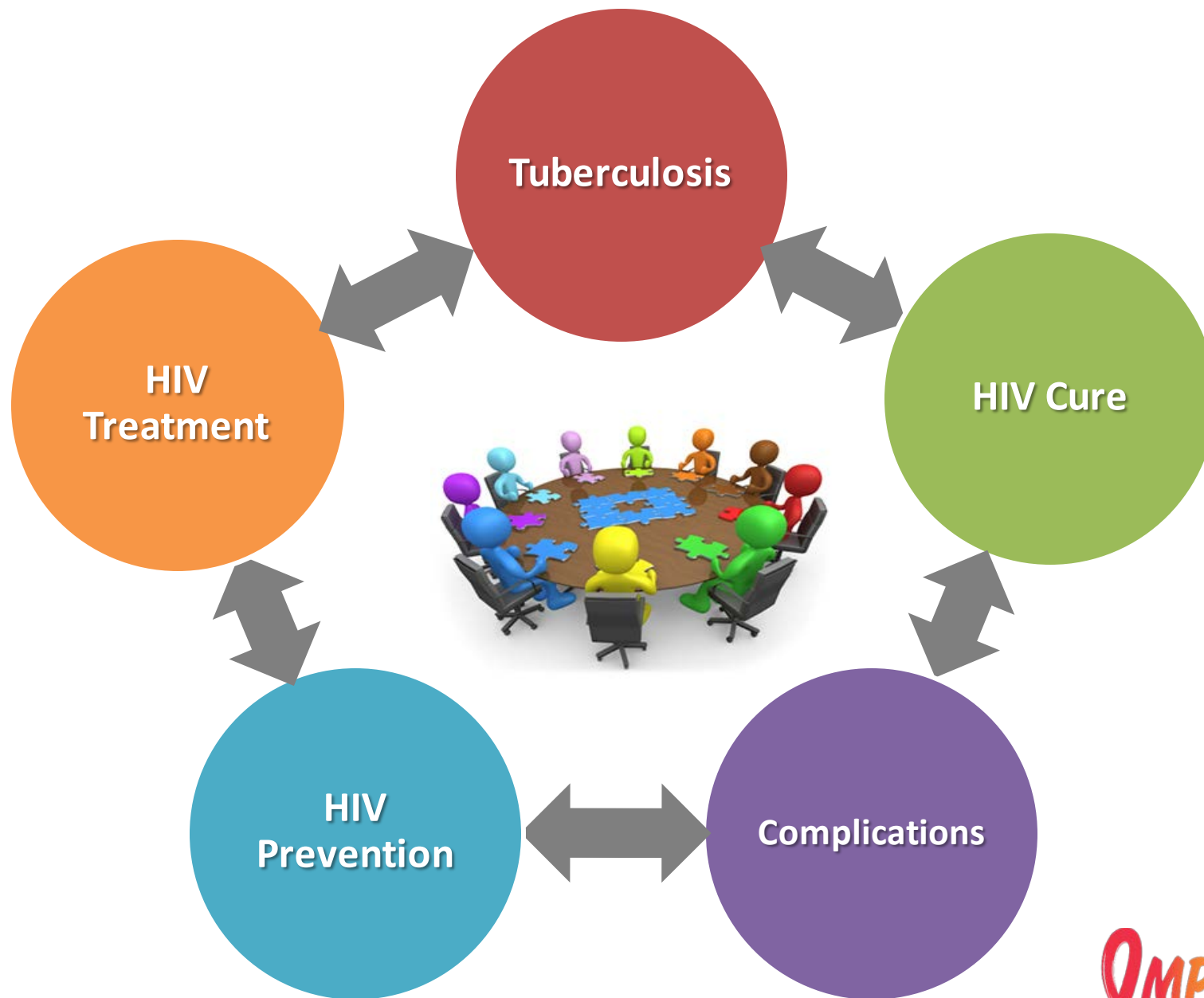


IMPAACT's Mission

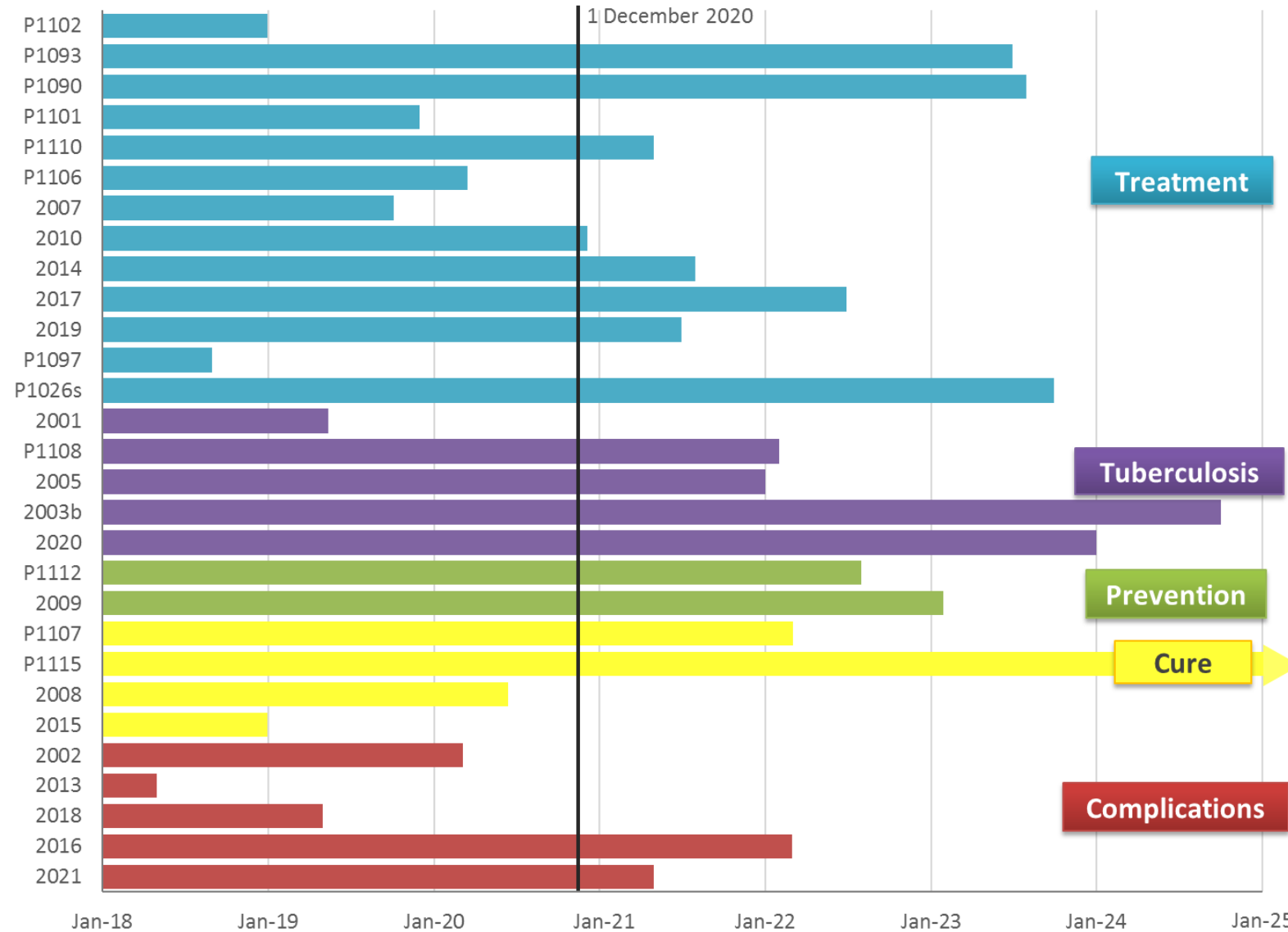
- To decrease incident HIV and HIV-associated infections, including mother-to-child transmission among infants, children, youth, and pregnant/postpartum women
- To decrease HIV-associated mortality and morbidity among these populations



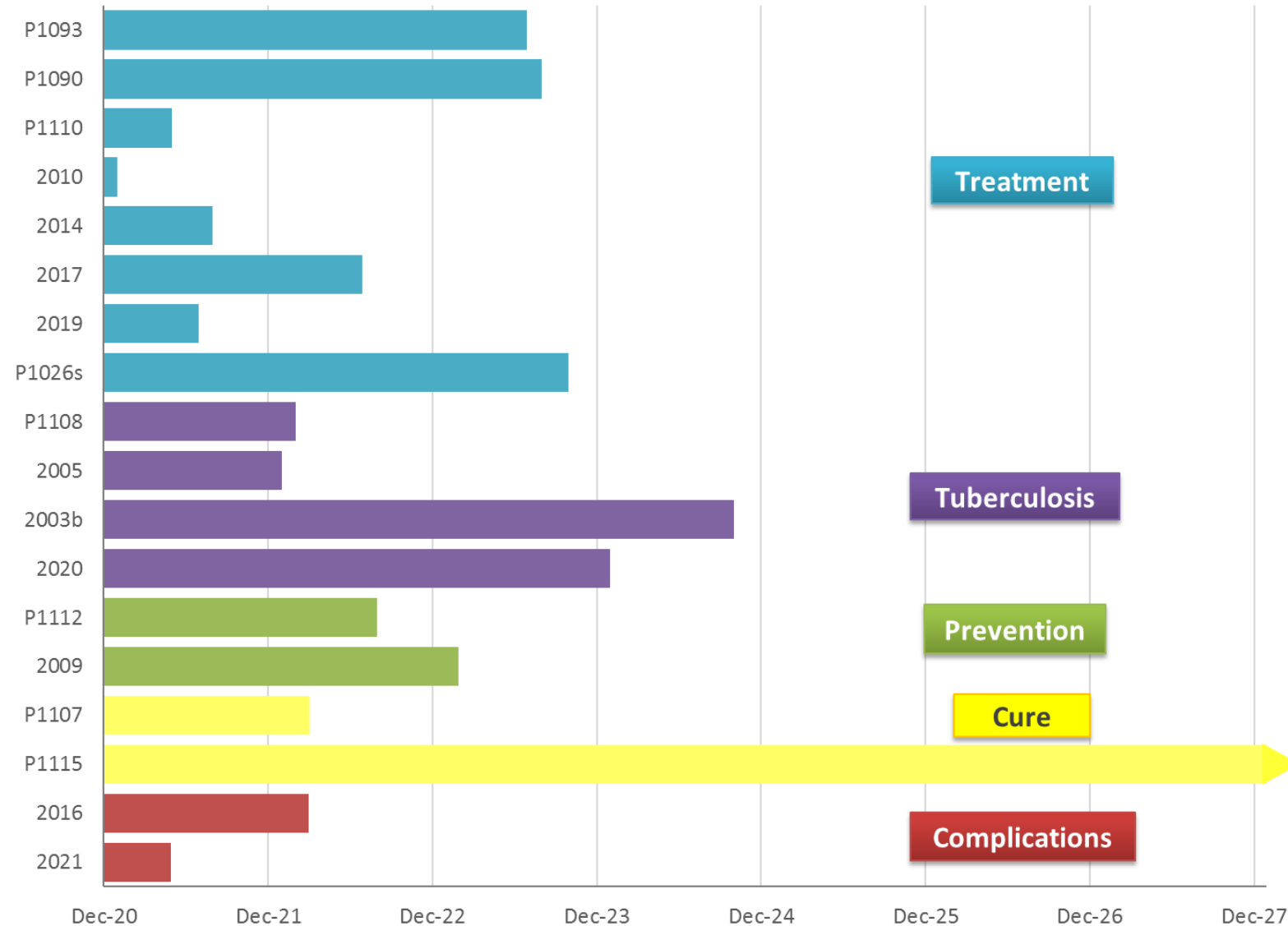
**What are the
scientific
questions for
the next 10
years?
How do we
end HIV?**



IMPAACT Roadmap



IMPAACT Roadmap – Beyond 2020





**What is driving
the Cure agenda?**

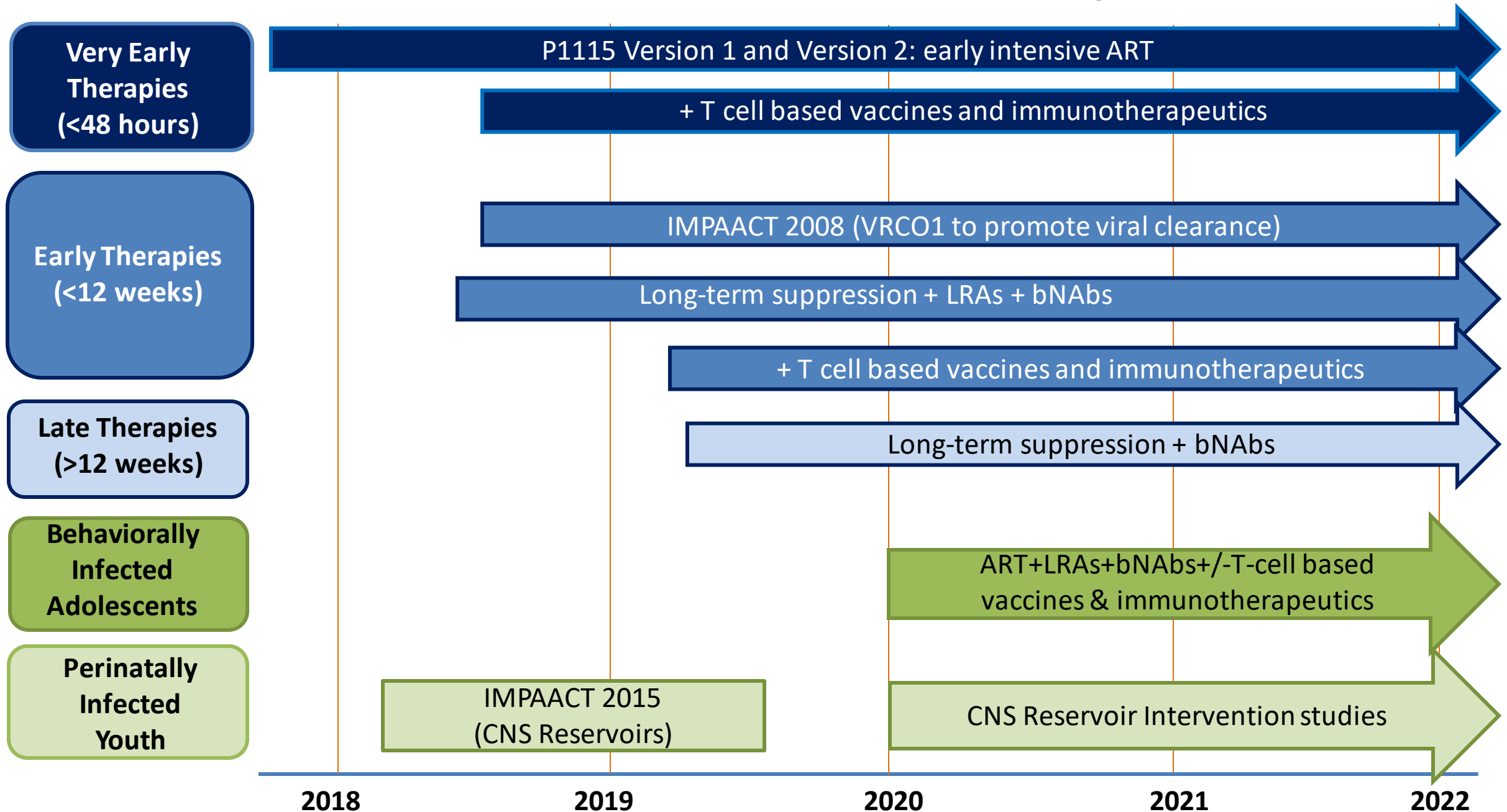
Cure Scientific Agenda

- **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

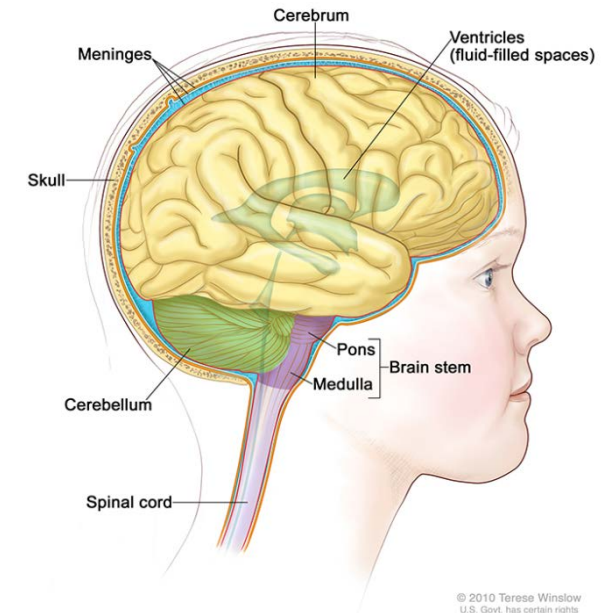
IMPAACT HIV Cure Roadmap



Study Highlight: 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 (n=30)
- Primary objective: assess prevalence of detectable HIV RNA and DNA in cerebrospinal fluid (CSF)



Anticipate first enrollment
by June/July 2018

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
- Simple, child-friendly fixed-dose formulations are easy to administer and match WHO dosage recommendations for first line treatment

Burden

1 Million

At least 1 million children become ill with TB each year. Children represent about 10-11% of all TB cases

FDC Factsheet

Mortality

250 000

This includes 52 000 TB deaths among children who were HIV-positive

More on TB/HIV co-infection

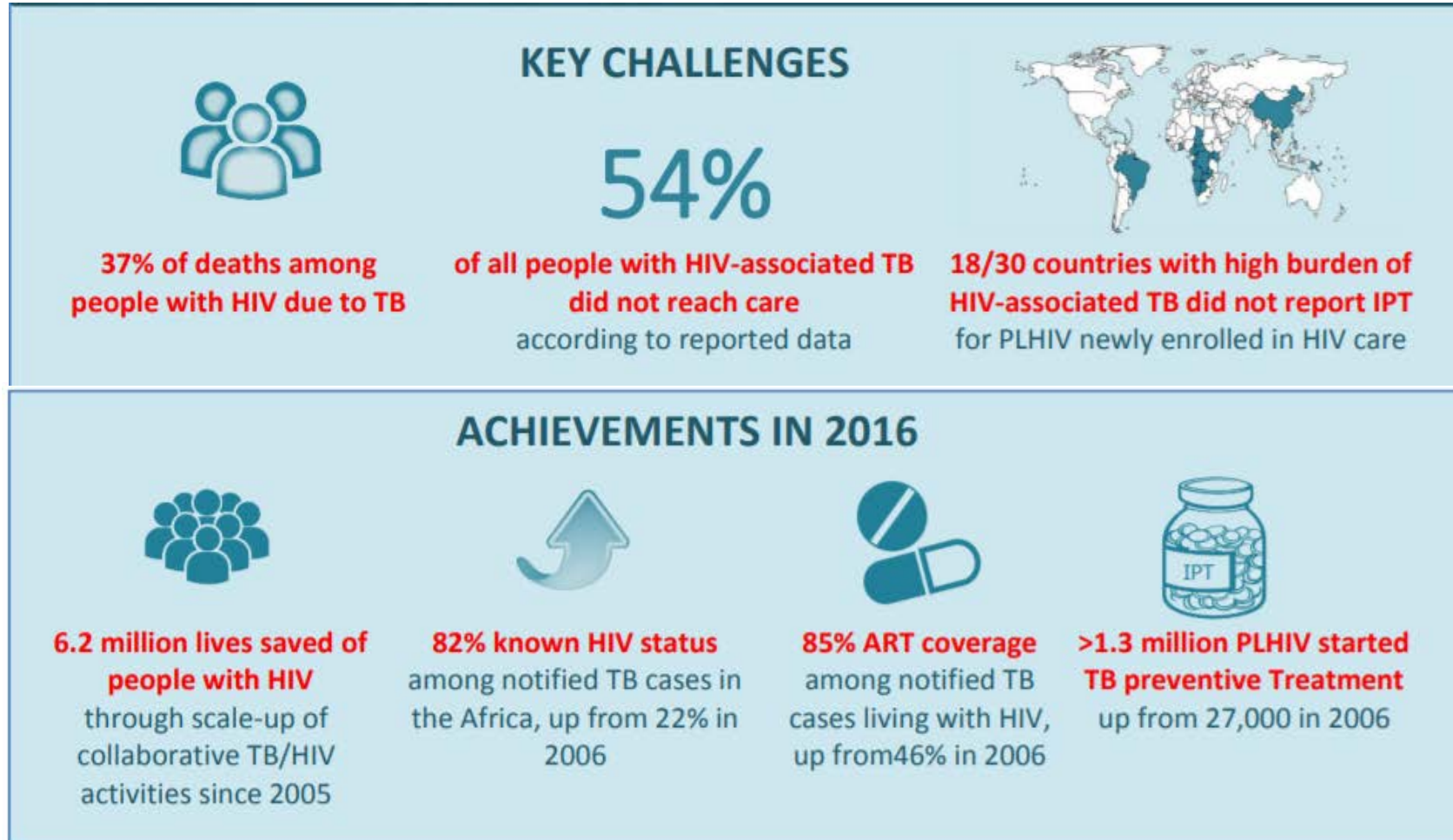
Preventive TB treatment

161 740

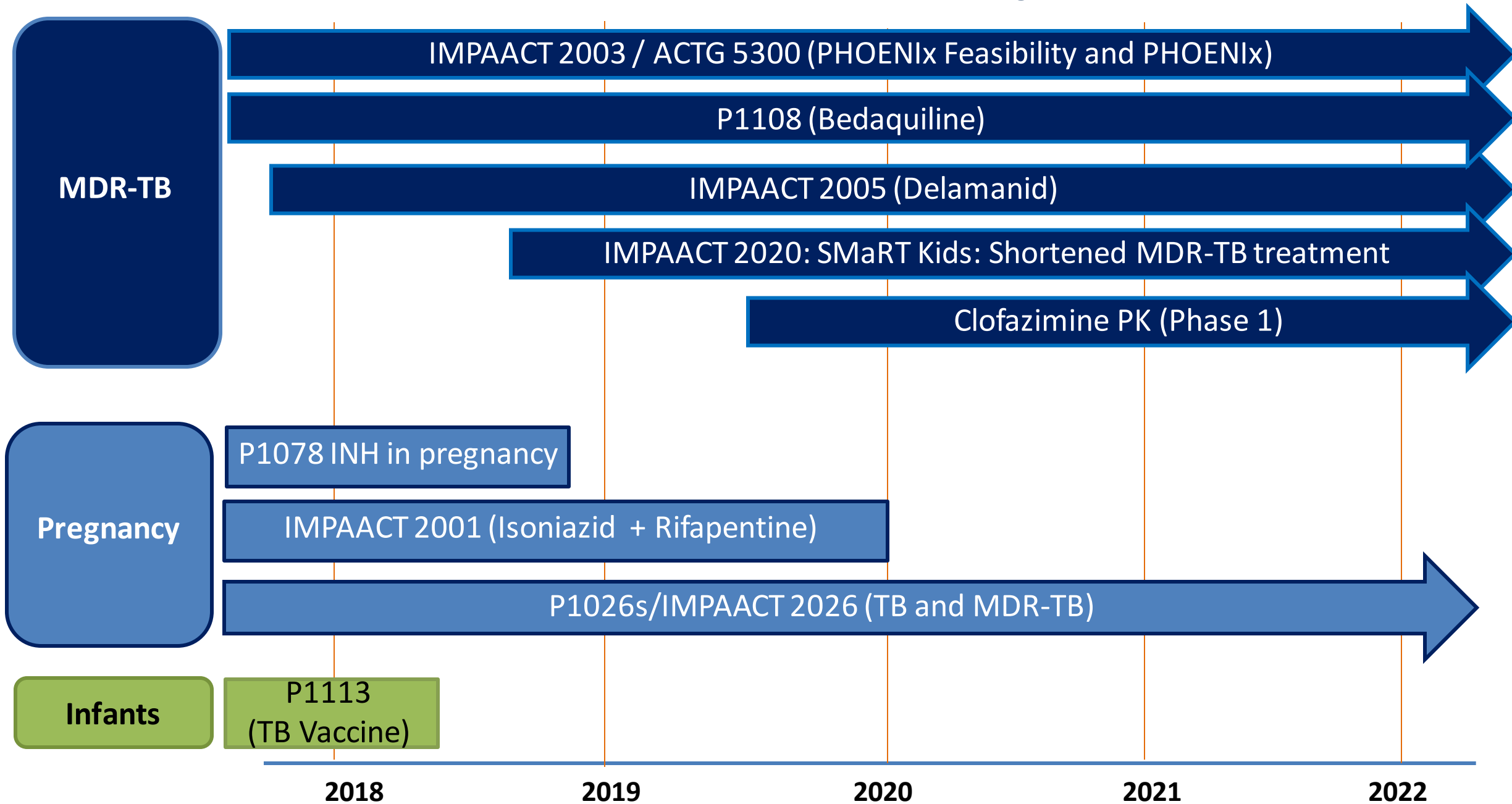
Only 13% of eligible children (1.3 million) received preventive TB treatment in 2016.

Global TB Report 2017

Tuberculosis and HIV



IMPAACT TB Roadmap



Study Highlight: IMPAACT 2020

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

- Phase III non-inferiority design study (n=438 children with MDR-TB)
- Primary objectives: compare efficacy, safety, and tolerability between WHO-recommended regimen and all-oral, short-course regimen



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

Anticipate Version 1.0
to sites by early 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

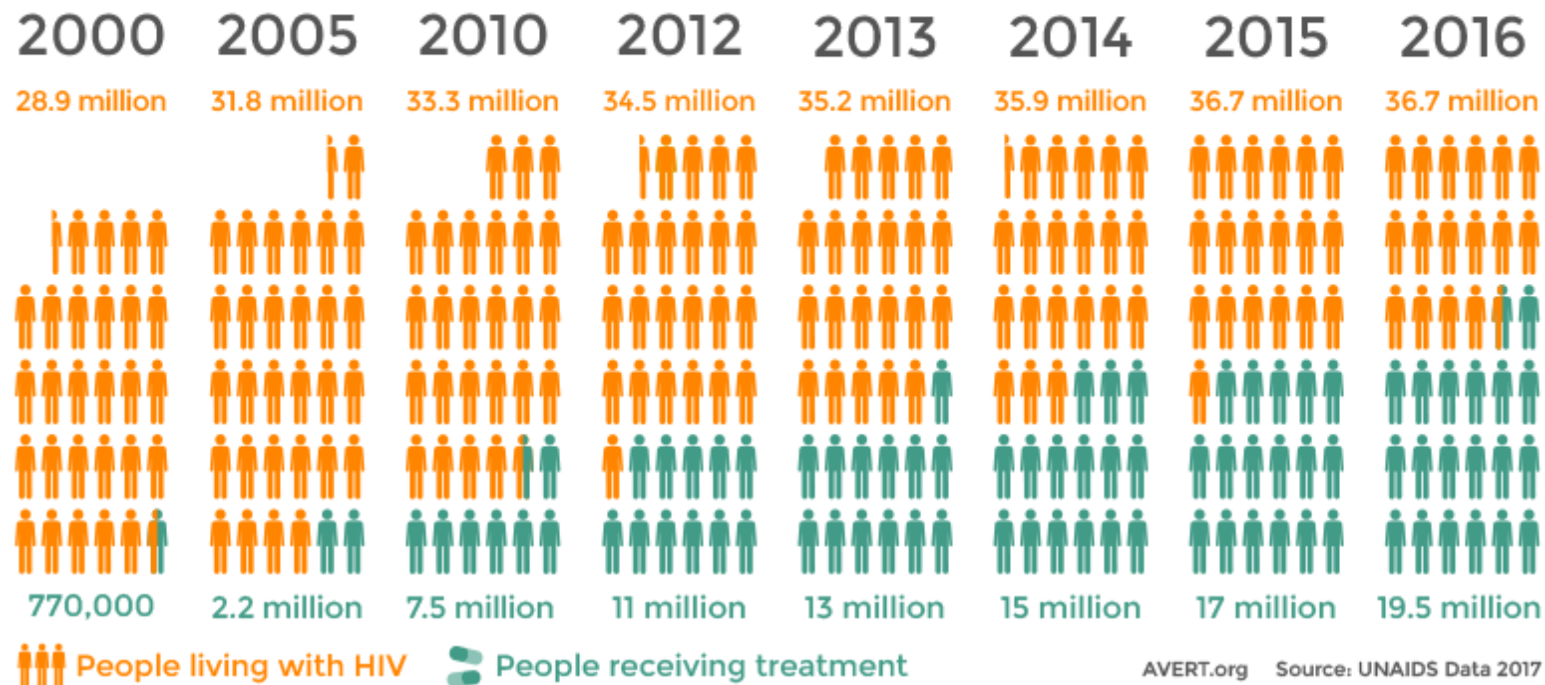




**What is driving
the Treatment agenda?**

19.5 million people living with HIV were receiving antiretroviral treatment in 2016, up from 17 million in 2015 and 7.5 million in 2010.

Number of people living with HIV and accessing treatment globally

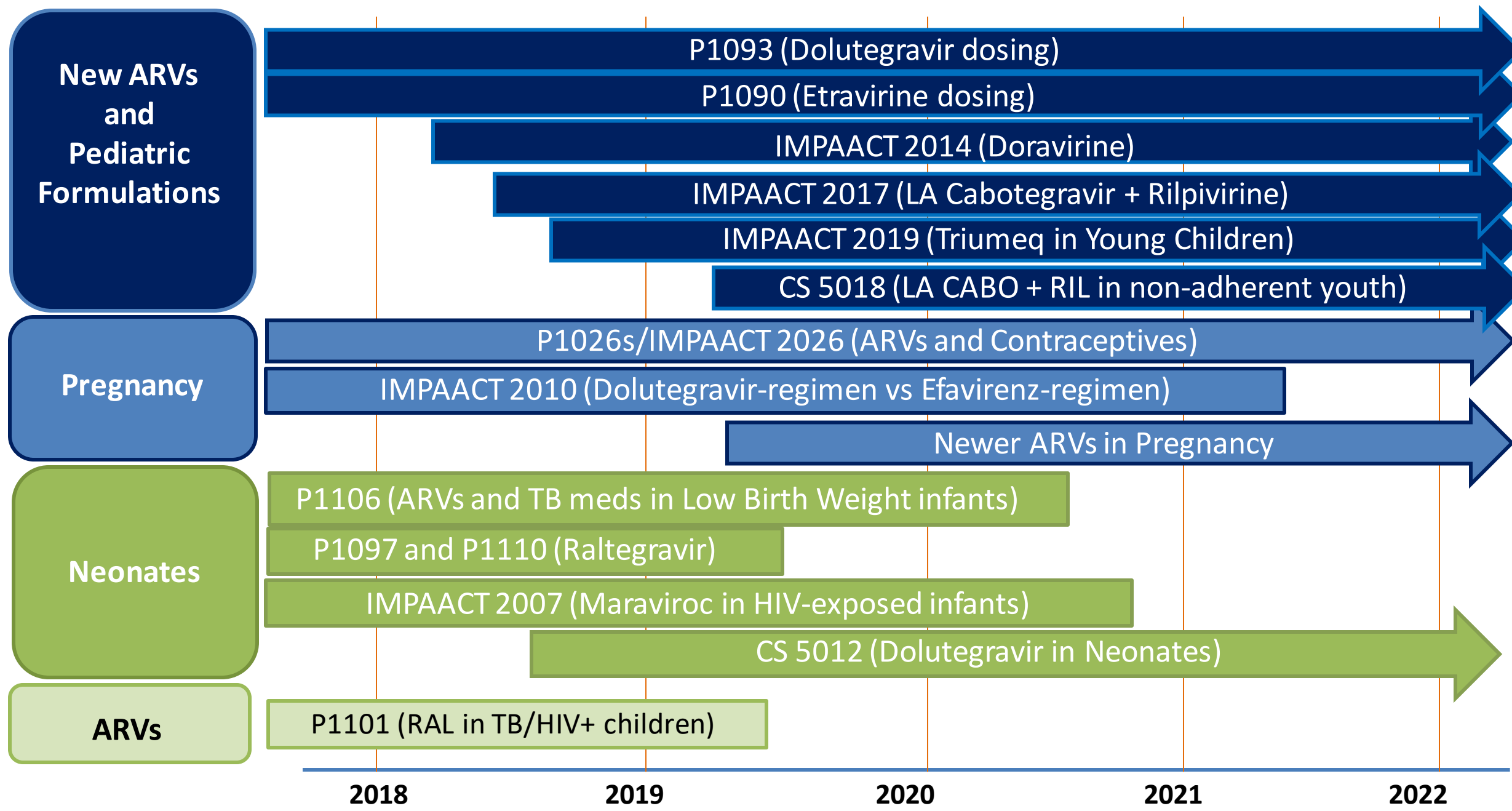


More than half of all people living with HIV (53%) now have access to life-saving treatment.

76% of all pregnant women living with HIV accessed treatment to prevent HIV transmission to their babies.

There were 160,000 new HIV infections among children (from 300,000 in 2010); young women are especially at risk.

IMPAACT Treatment Roadmap



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
- Purpose: Confirm the dose and evaluate safety, tolerability, acceptability, and PK of long-acting regimens



Anticipate
open to accrual by
September 2018

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 November 2018

DTG and Neural Tube Defects

- Recent signal related to periconception DTG use
 - How can we better understand this signal
- Studies involving dolutegravir and cabotegravir in affected populations
 - IMPAACT 2010: post delivery
 - P1093 and IMPAACT 2019: aged up youth
 - IMPAACT 2017: females of child bearing age
- Next steps are study-dependent but generally include informing site stakeholders and participants through letters and amendments

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

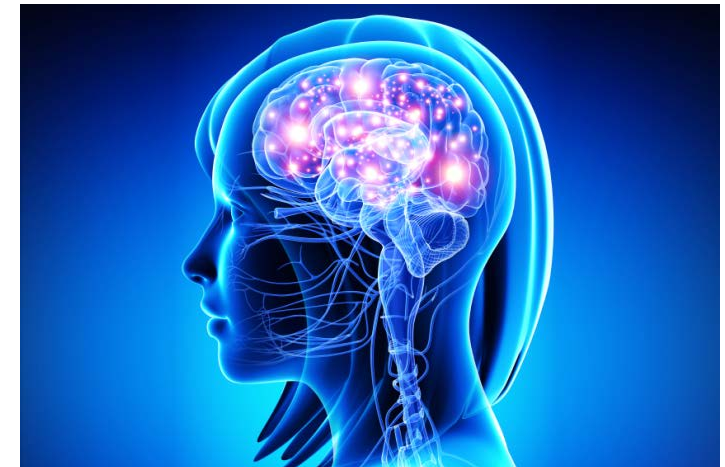


**What is driving
the Complications agenda?**

HIV/ARV Complications & Comorbidities

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



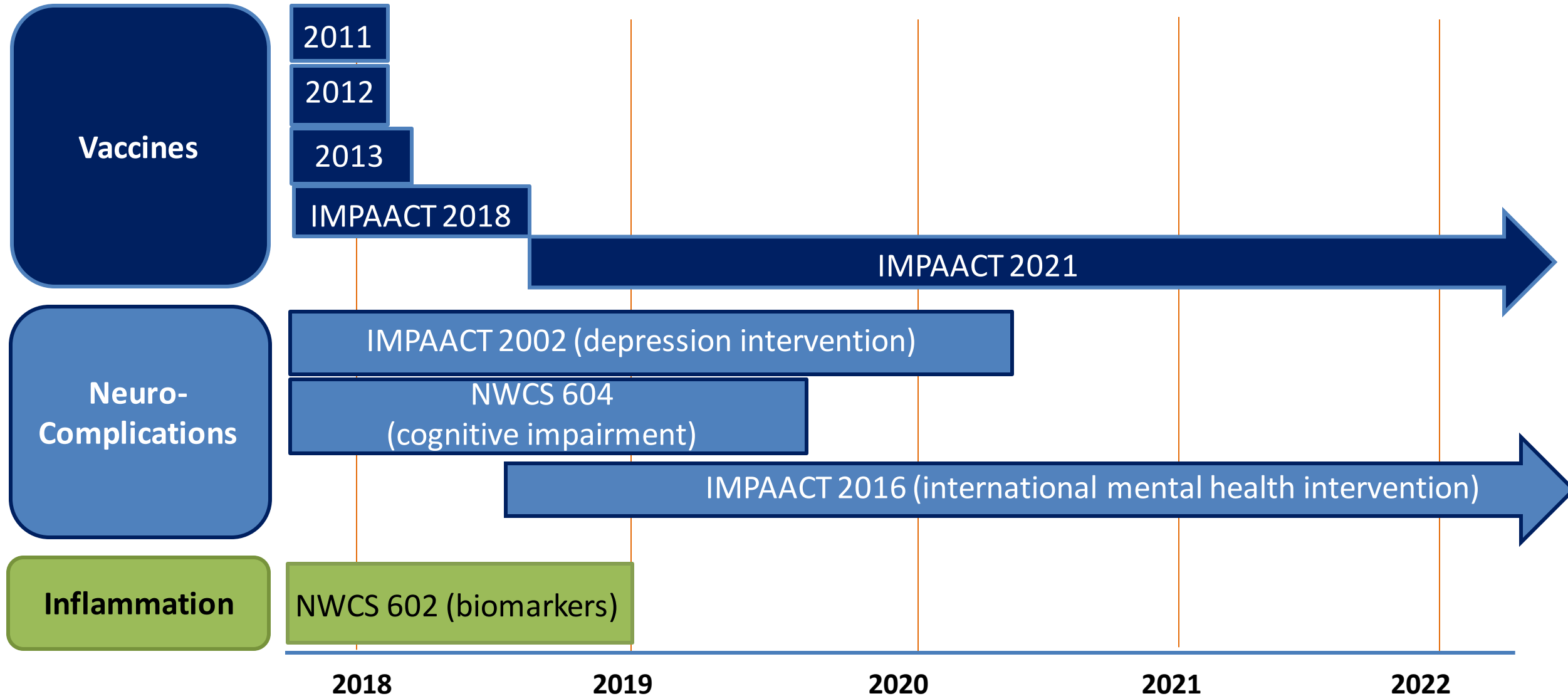
HIV/ARV Complications & Comorbidities

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)



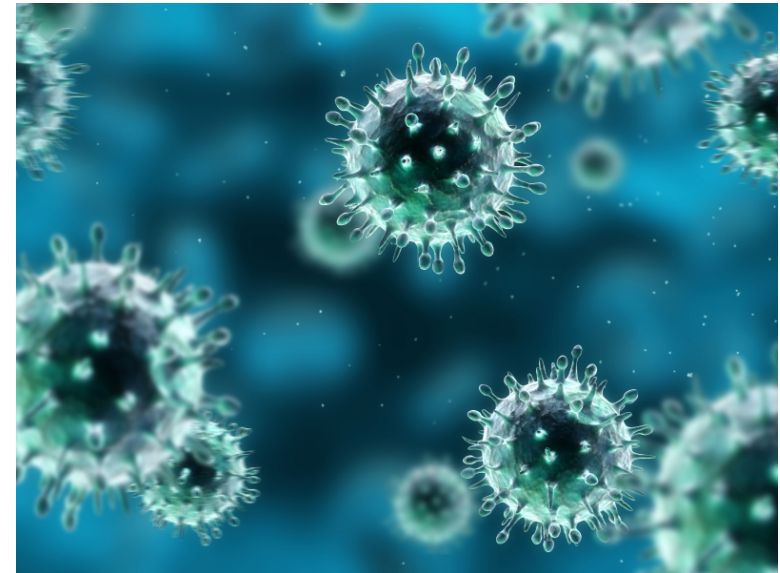
IMPAACT Complications & Comorbidities Roadmap



Study Highlight: IMPAACT 2021

RSV Candidate Vaccine Study

- Randomized phase Ib placebo-controlled study among healthy RSV-seronegative children 6-24 months of age
- Purpose: assess Δ NS2/ Δ 1313/I1314L or RSV 276 vaccines



Anticipate Version 1.0
to sites in 2018

Focus for the Future: Complications & Comorbidities

- Revisit the hepatitis treatment and prevention questions
 - New drugs
 - New data sets
- Non-HIV, infectious diseases
- Treat and/or prevent neuropsychiatric issues (e.g., maraviroc)
- Current and emerging pathogens?
 - RSV
 - Others

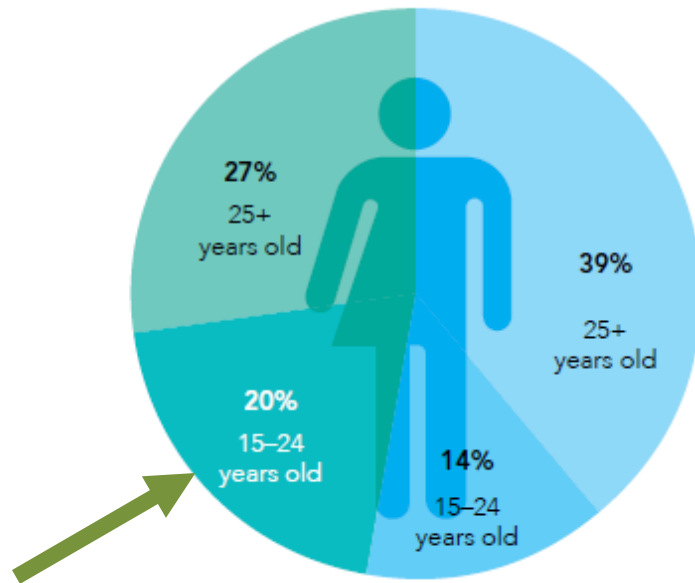


**What is driving
the Prevention agenda?**

Young Women at High Risk for HIV

More Pronounced in Sub-Saharan Africa

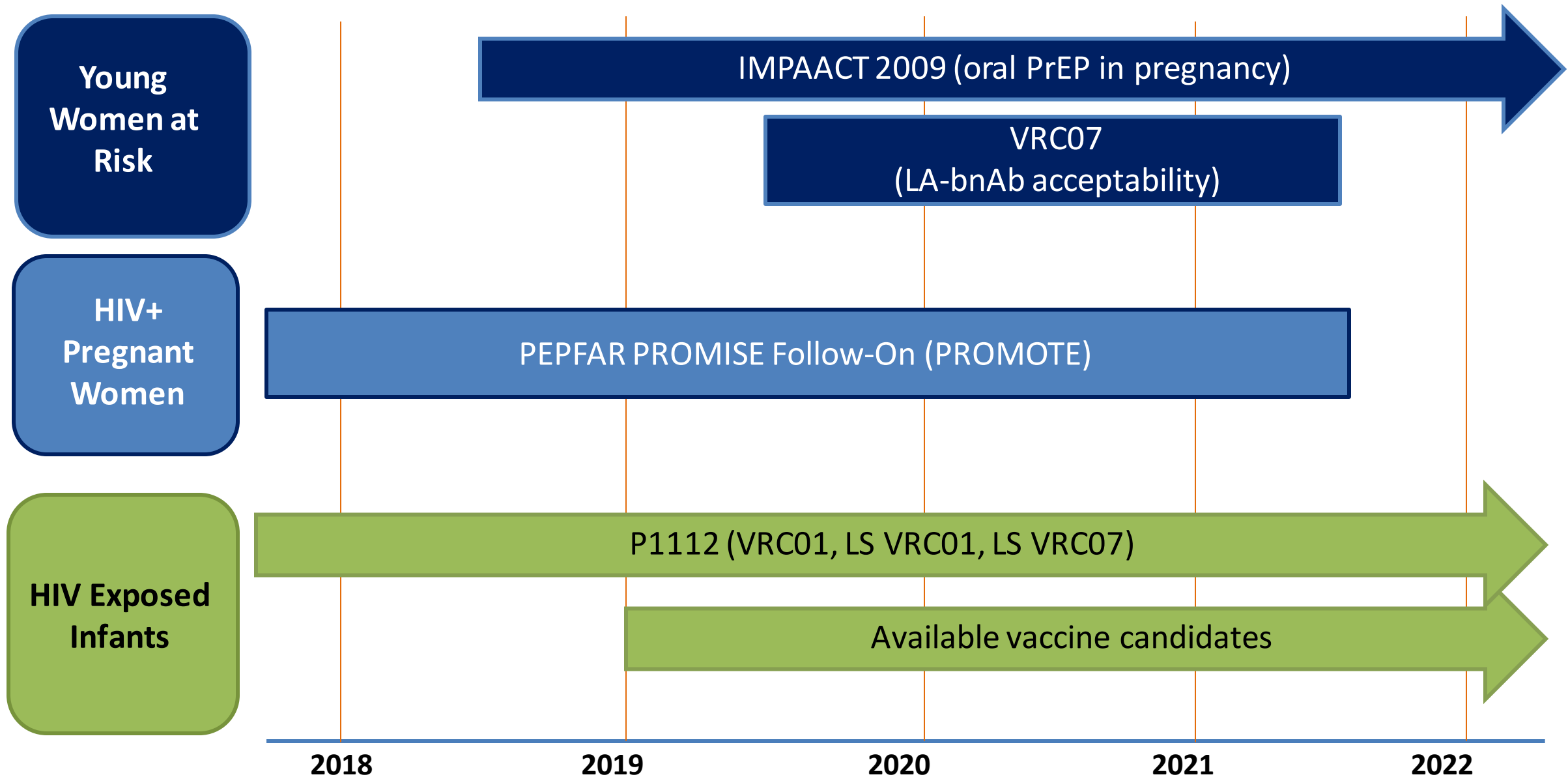
NEW HIV INFECTIONS AMONG ADULTS, BY
AGE AND SEX, GLOBAL, 2015



- **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



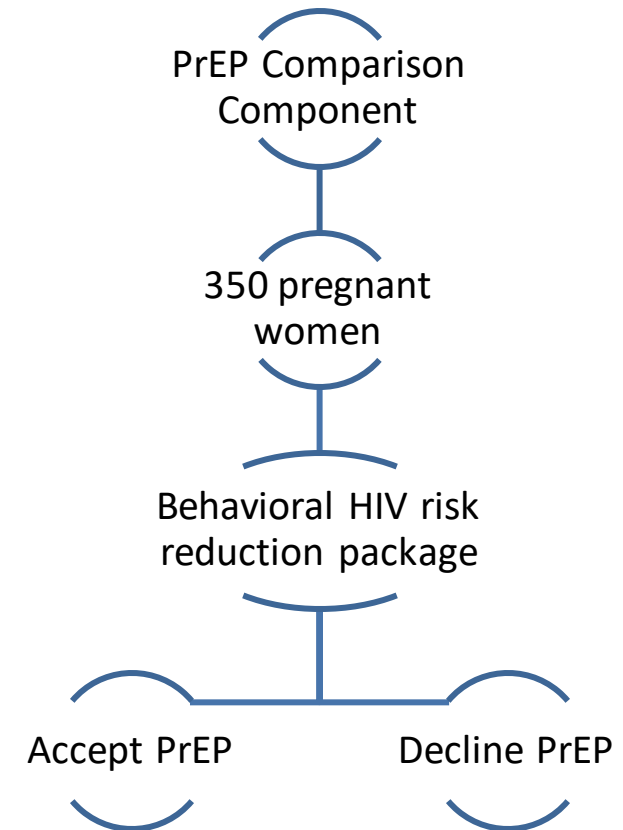
Study Highlight: IMPAACT 2009

PrEP in Pregnant Women

Among HIV-uninfected pregnant women:

- PK component to determine TFV-DP concentration with daily DOT of tenofovir PrEP (n=40 pairs)
- PrEP comparison component to determine feasibility, acceptability, and safety of PrEP (n=350 pairs)
- Exploratory evaluation of maternal and infant microbiomes

Anticipate first enrollments
in late 2018



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?

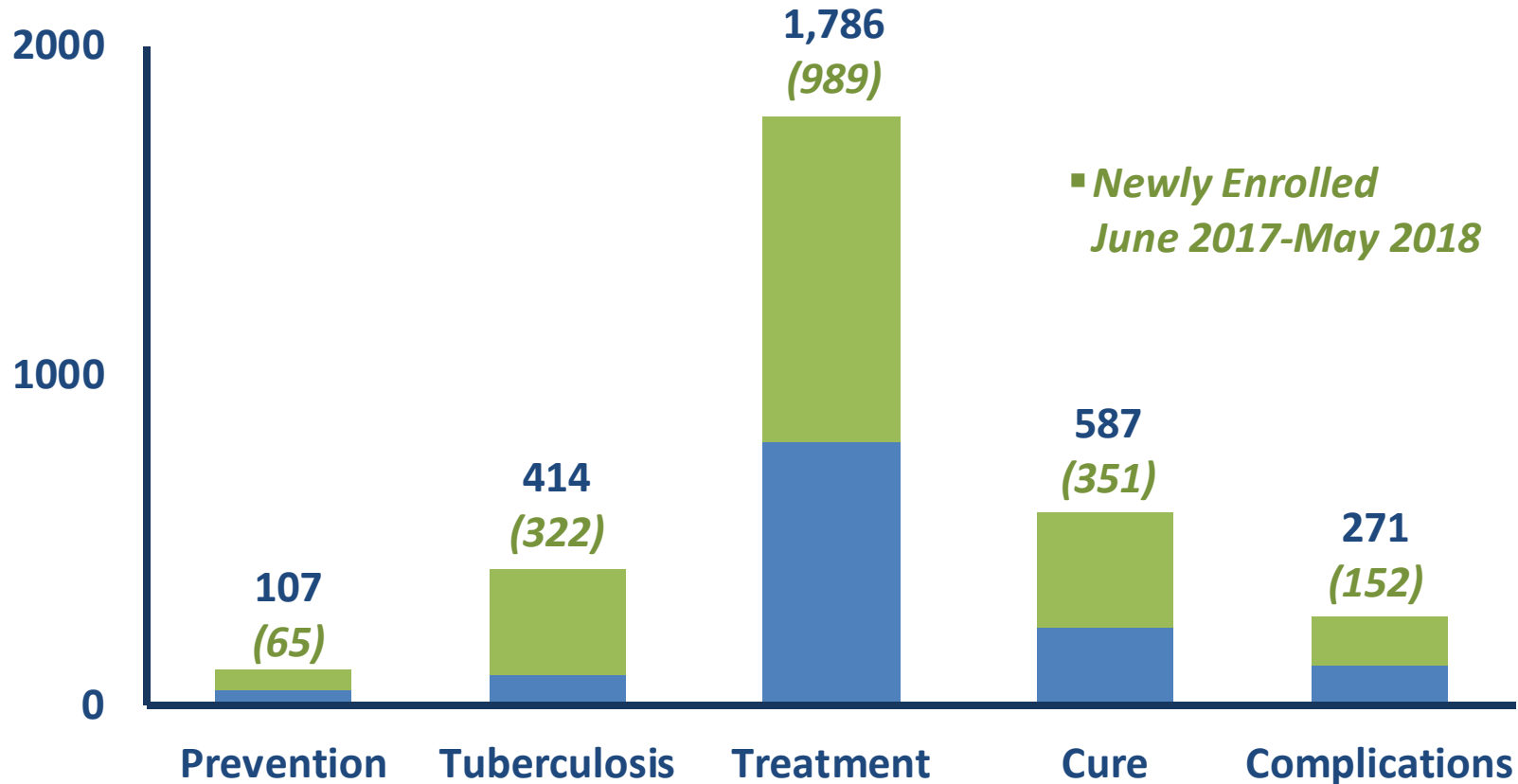




Activities in the Past Year

IMPAACT Participants on Study

June 2017 to May 2018



Total On Study = 1,879 participants
Newly Enrolled = 1,286 participants

Study Highlight: P1026s

PK Properties of ARVs during Pregnancy

**As of 5 June 2018,
985 mothers and 492 infants enrolled**

**Completed pregnancy arms for 17 ARVs,
including darunavir, rilpivirine, maraviroc,
dolutegravir and elvitegravir**

**Presented 34 abstracts
and published 23 manuscripts**

Treatment
Research Agenda

Study Highlight: P1026s

Contributions to Perinatal HHS Guidelines

- 27 ARV drugs in the current published HHS perinatal guidelines – PK data from P1026s cited for 17 (63%)
- 76 PK in pregnancy studies cited in perinatal guidelines for all ARVs – P1026s responsible for 24 (32%)
- P1026s data are the only cited source of PK data from studies in pregnant women for 4 of 27 drugs (15%; DTG, EFV, MVC, RPV)

Class	P1026s Citations/Total # of PK studies in Pregnancy* Citations	Percent of Data from P1026s
NRTI	3/19	16%
NNRTI	4/9	44%
PI	12/40	30%
INSTI	2/4	50%
Entry/Fusion	1/1	100%
PK Enhancers	2/3	67%

*Excludes case reports

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
- Ten participants enrolled in Cohort 1 (age ≥ 6 to 18 years)
- Study target accrual = 72 participants, expected to be completed in September 2019



First participant enrolled
in September 2017!

Tuberculosis
Research Agenda



Study Highlight: P1112

Safety and PK Parameters of Subcutaneous VRC01 and VRC01LS, Potent Anti-HIV Neutralizing Monoclonal Antibodies

- Phase I study among HIV-exposed infants
- Successfully completed enrollment of Dose Groups 1-4
- Purpose for Dose Group 5: include evaluation of a new bNAb called VRC07-523LS



Prevention
Research Agenda

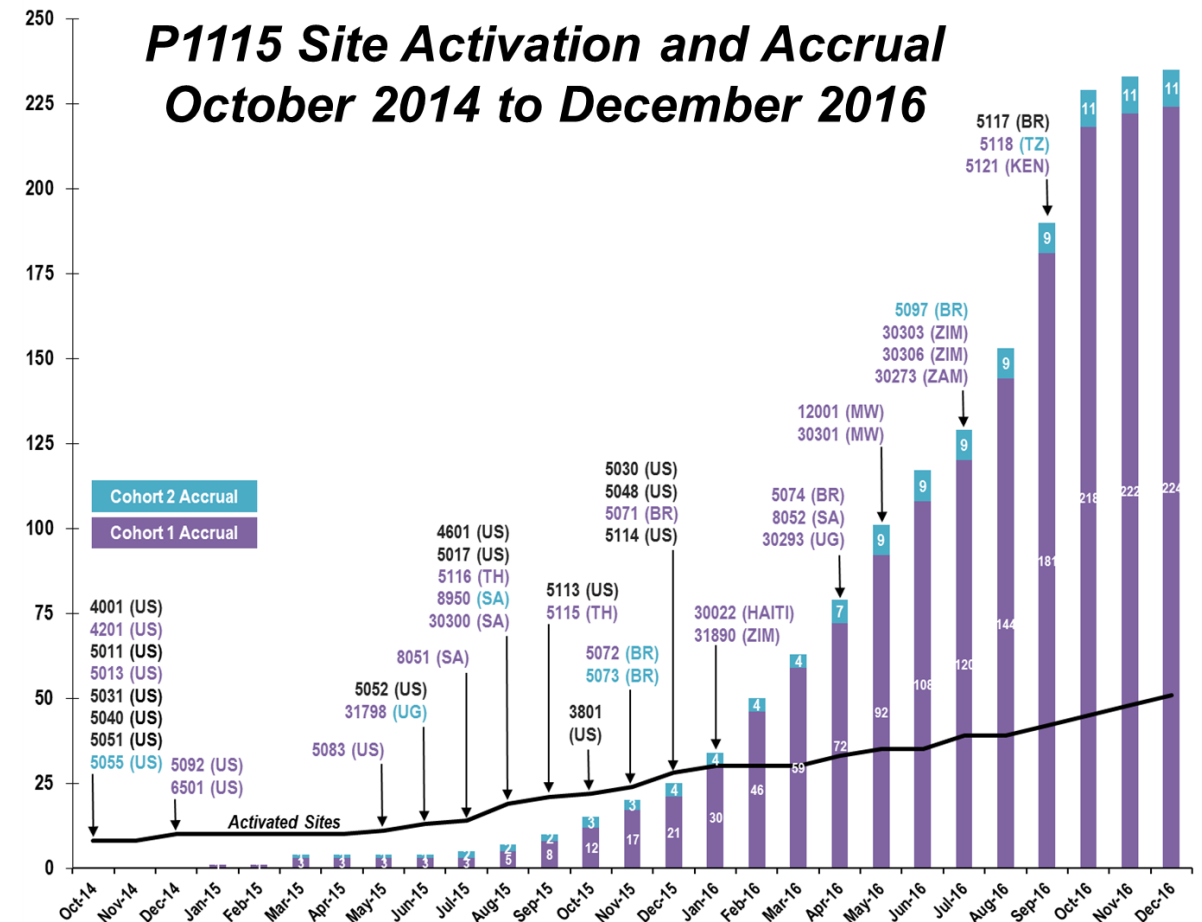
First enrollment into
Dose Group 5 anticipated
by end of 2018

Study Highlight: P1115

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

- Accrual of 460 mother-infant pairs completed in 2017
- Safety and PK data presented (publications in development)
- Expert panel convened in Sept 2017 was supportive of study as designed
- Version 2.0 expected to open soon to evaluate RAL- and VRC01-containing regimens

Cure Research Agenda



Study Highlight: IMPAACT 2001

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

- 49 of 50 mother-infant pairs were enrolled through 29 May 2018, with the **last pair enrolled in early June!**
- Anticipate results by the end of 2019



Study Highlight: IMPAACT 2002

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

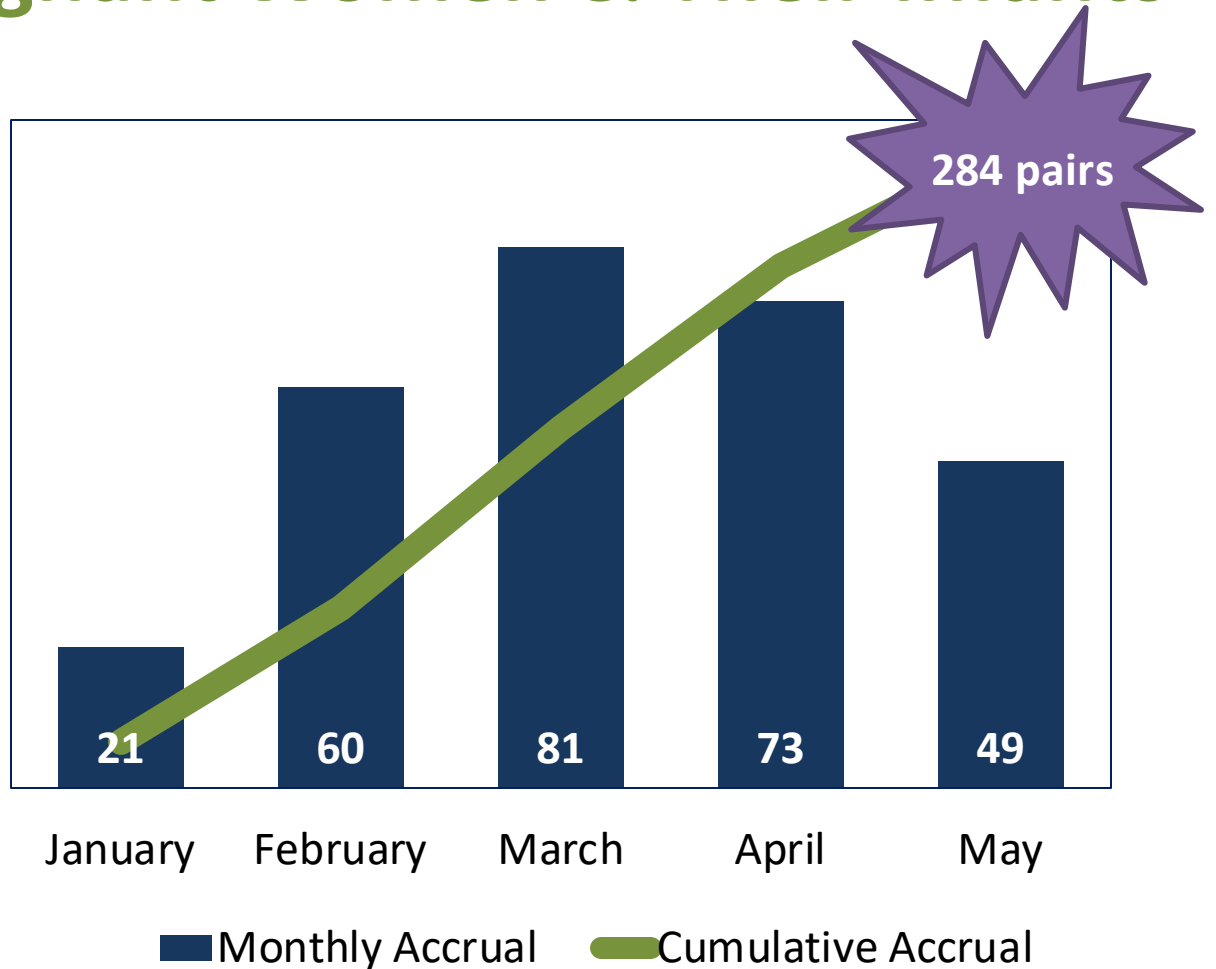
- Sites randomized to COMB-R or Enhanced Standard of Care arms to determine if the intervention for depression demonstrates improved outcomes for HIV-infected youth
- 56% of accrual target met and expect to complete accrual in March 2019



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
- 19 activated and 16 enrolling sites in Botswana, Brazil, South Africa, Tanzania, Thailand, Uganda, the United States, and Zimbabwe
- Accrual paused to incorporate recent DTG findings



32 Active Studies

June 2017 to May 2018

	6 In Development	6 Pending and Open	14 Enrolling	4 In Follow-up	5 Closed to Follow-up*
Treatment	2026, 2019	2017, 2014	2010, 2007, P1110, P1106, P1101, P1093, P1026s	P1102, P1097, P1090	P1092
Prevention		2009	P1112		
Complications	2021, 2016		2018, 2002	2013	2011
Tuberculosis	2020, 2003b	2005	2001, P1108		2003, P1113, P1078
Cure		2015, 2008	P1115, P1107		

*closed to follow-up in the last year

IMPAACT Science Generation

June 2017 to May 2018

7 New Capsules for Review

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

4 New Concept Sheets for Review

- 2 Treatment
- 1 Tuberculosis
- 1 Cure

4 New Protocols Approved for Development

- 2 Treatment
- 1 Tuberculosis
- 1 Complications

Six Protocols Currently in Development

2026	Pharmacokinetic Properties of Antiretroviral, Anti-Tuberculosis, Contraceptive and Related Drugs During Pregnancy and Postpartum
2021	<u>Randomized Phase IB Study</u> of the Safety and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated <u>Respiratory Syncytial Virus</u> (RSV) Vaccines RSV delta NS2/delta 1313/I1314L or RSV 276 or Placebo, Delivered as Nose Drops to RSV-Seronegative Infants 6 to 24 Months of Age

Protocols Currently in Development (cont'd)

2020	<u>Shortened Oral Treatment for Multidrug-Resistant Tuberculosis in Children</u> (SMaRT Kids): A Phase III Randomized Multi-center Trial
2019	Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of <u>Dolutegravir/Lamivudine/Abacavir</u> (Triumeq®) in HIV-1-Infected Children Less than 12 Years of Age
2016	Evaluating a Group-Based <u>Intervention</u> to <u>Improve Mental Health and ART Adherence</u> in HIV-Infected Adolescents in Low Resource Settings

Community Engagement Achievements

- Comprehensive community reviews of 4 IMPAACT protocols
- Collection of community research priorities aimed at:
 - Identifying community needs/concerns
 - Aligning community priorities with IMPAACT research objectives



Community Engagement Achievements

- Ongoing development of strategies for engaging youth and young adults into site CABs
 - Aids in identifying young people's needs/interests
 - Builds partnerships and promotes youth advocacy
 - Offers youth capacity building and leadership experience

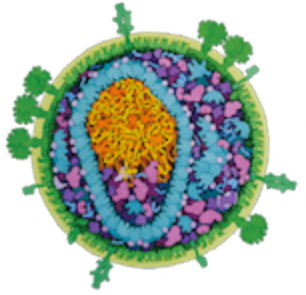


Publications

- **62** publications submitted for IMPAACT review in past 12 months
- **33** manuscripts published in NEJM, JAIDS, Journal of Clinical Pharmacology, PIDJ, CID, TB and Lung Disease, PLoS One, among others



Abstracts



CROI
Conference on Retroviruses
and Opportunistic Infections

14 abstracts at CROI 2018

- 4 abstracts from PROMISE 1077BF, FF, and HS related to maternal and child health
- Primary results from IMPAACT P1078/TB APPRISE
- Neurocognition in HIV-infected and HIV-affected children
- PK of raltegravir among HIV/TB co-infected children and of lopinavir/ritonavir among HIV-infected low birth weight infants

Additional abstracts accepted to upcoming meetings at
AIDS 2018 and the HIV Pediatrics Workshop
and in the past year at ICAAC, ICAAP, ICASA, and ID week



AIDS 2018



IAS2017



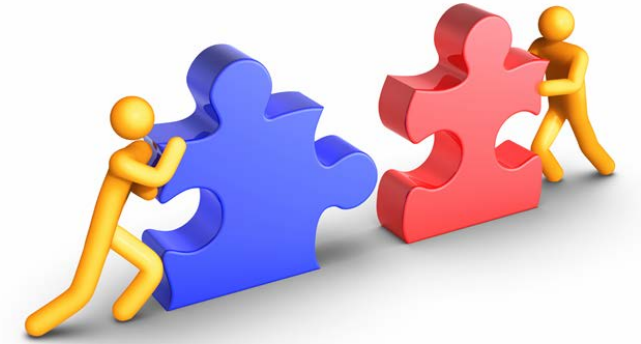
October 4-8 • San Diego, CA • www.idweek.org

IDWeek 2017™



**19TH
ICASA**
INTERNATIONAL CONFERENCE
ON AIDS AND STIs IN AFRICA
COTE D'IVOIRE - 2017

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



Plans for the Upcoming Year...

**Publish
P1092,
P1078 &
PROMISE**

**Complete
2018, 2013,
P1102 &
P1097**

**Begin
IMPAACT
2014, 2009,
2008 &
2005**

**Complete
enrolling
IMPAACT
2018**

**Continue
ongoing
studies**

**Finalize
IMPAACT
2026, 2021,
2020, 2019,
& 2016**

**Finalize
Version 2 &
begin
MOCHA**

**Publish
IMPAACT
2012 &
2011**

**Complete
enrolling
IMPAACT
2002, 2001,
& P1101**

**Begin &
complete
enrolling
IMPAACT
2015**

**Continue
P1108, P1106,
P1112, &
IMPAACT
2007**

**Resume
enrolling
VESTED**



Thanks for working together on IMPAACT on these days!



**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!