



International Maternal Pediatric AIDS Clinical Trials (IMPAACT) Network

**State of the Network
2017 Annual Meeting**

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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

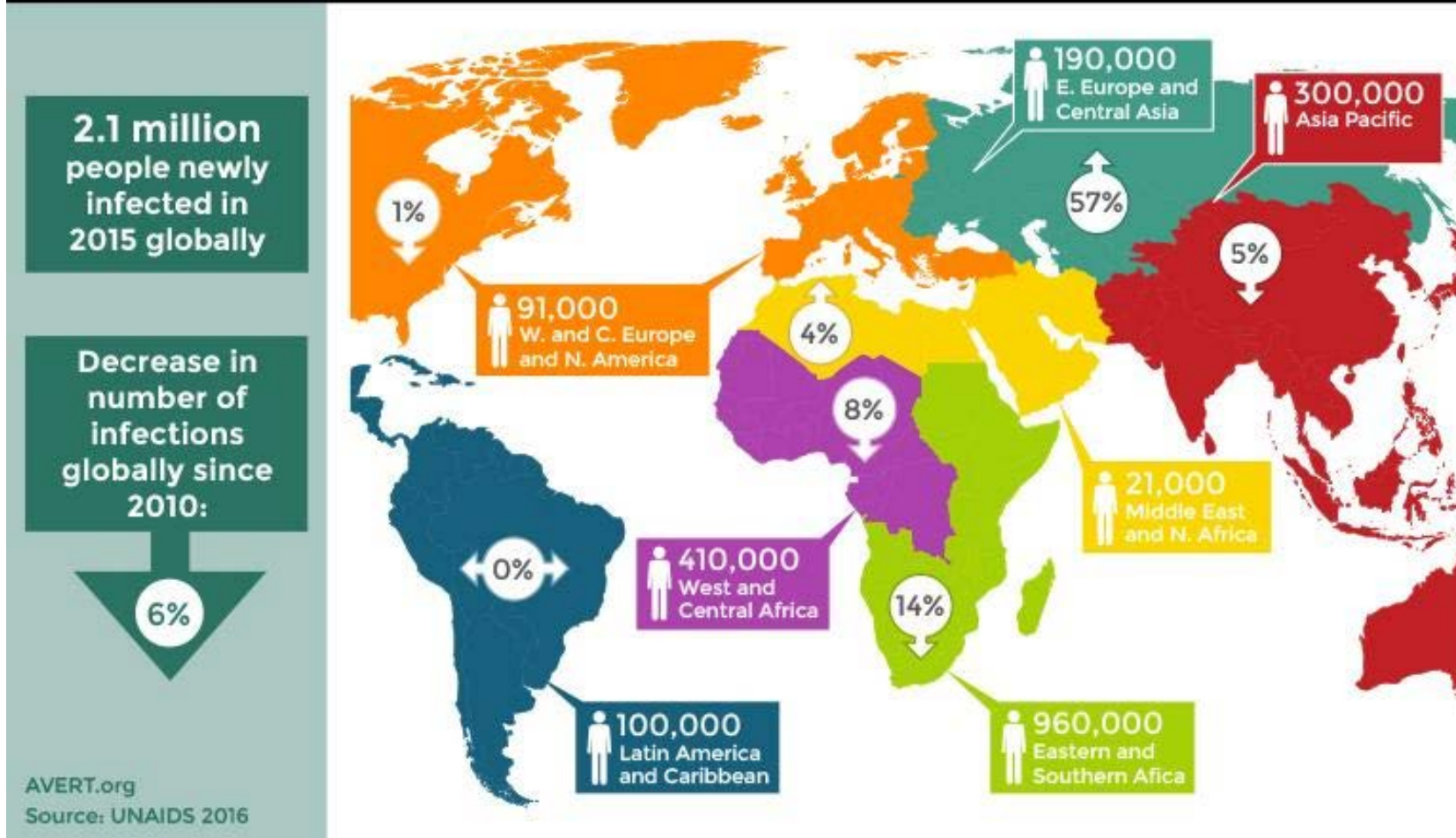
Real question: What is our scientific agenda for the next 10 years?



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 decline of 50% or more, while many have no measurable progress

Number of new HIV infections in 2015 and change since 2010



Source: Avert, <https://www.avert.org/global-hiv-and-aids-statistics>

In 2015, there were roughly 2.1 million new HIV infections, **150,000 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.

**1.8 MILLION
CHILDREN**

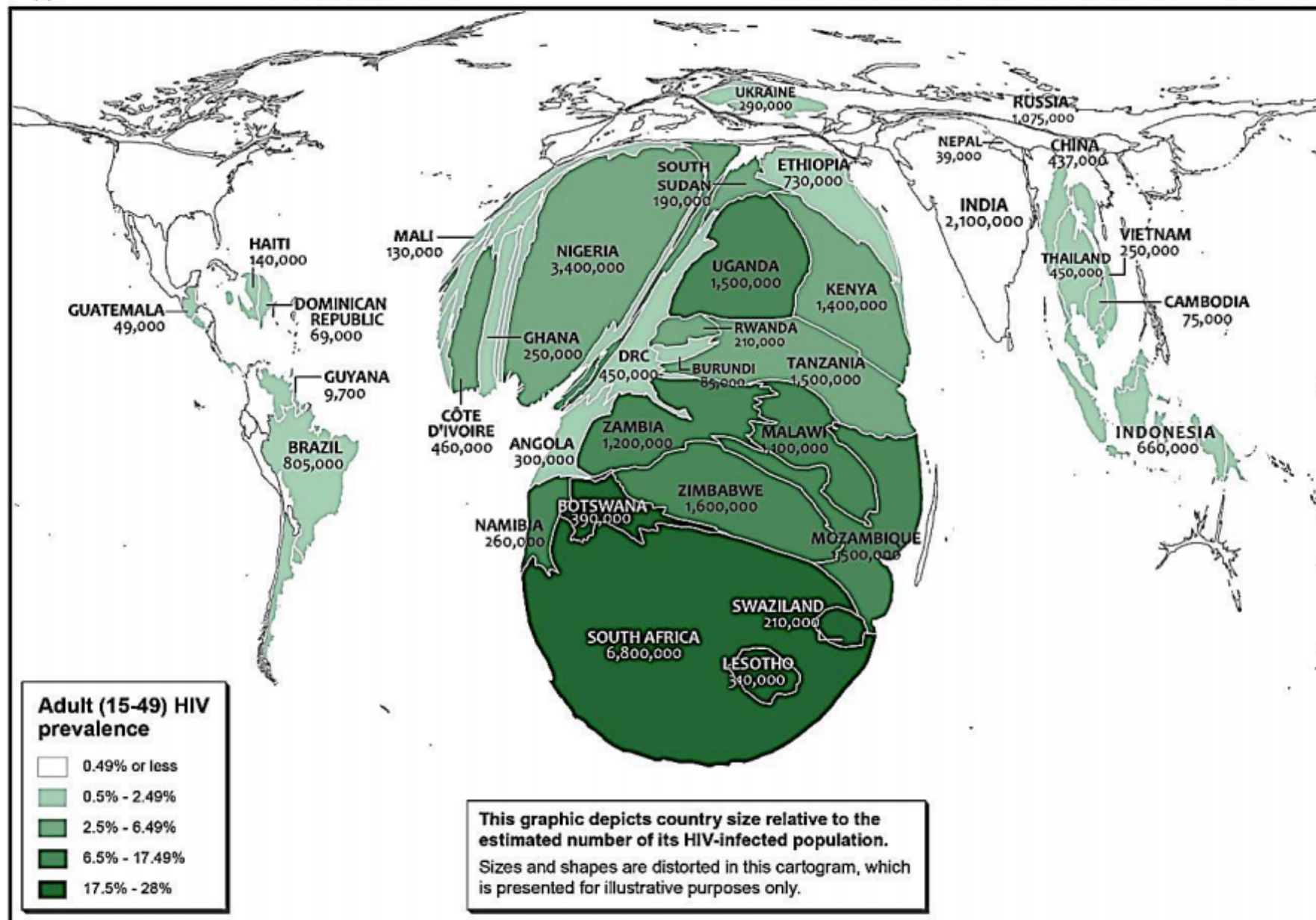
worldwide are living with HIV. Most of these children were infected by their HIV-positive mothers during pregnancy, childbirth or breastfeeding.



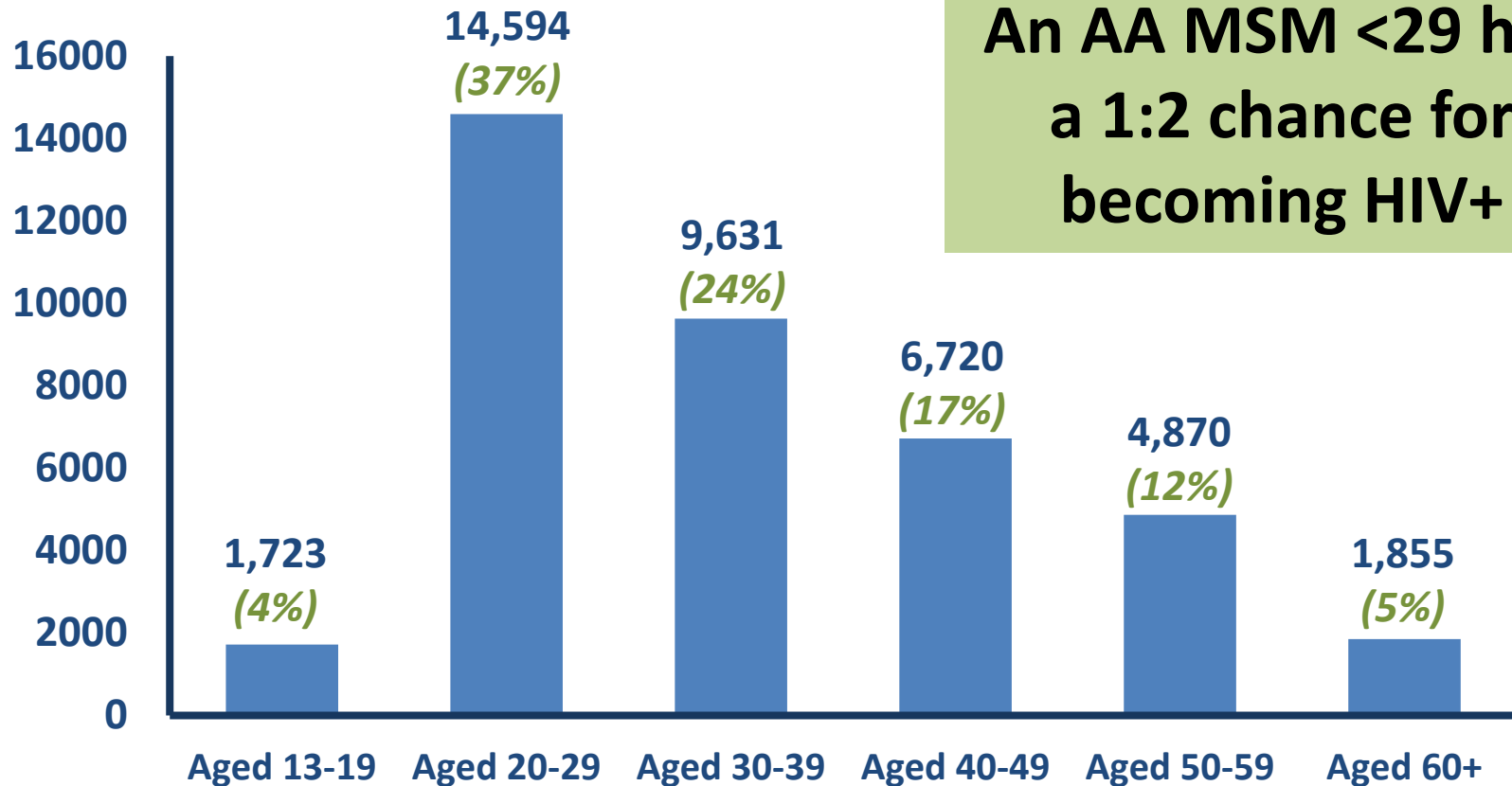
The vast majority of people living with HIV are in low- to middle-income countries, particularly in Sub-Saharan Africa.



HIV Prevalence and Estimated Number of Adults and Children Infected with HIV, 2014



New HIV Diagnoses in the US By Age, 2015



Source: CDC. Diagnoses of HIV infection in the United States and dependent areas, 2015. HIV Surveillance Report 2016;27.

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

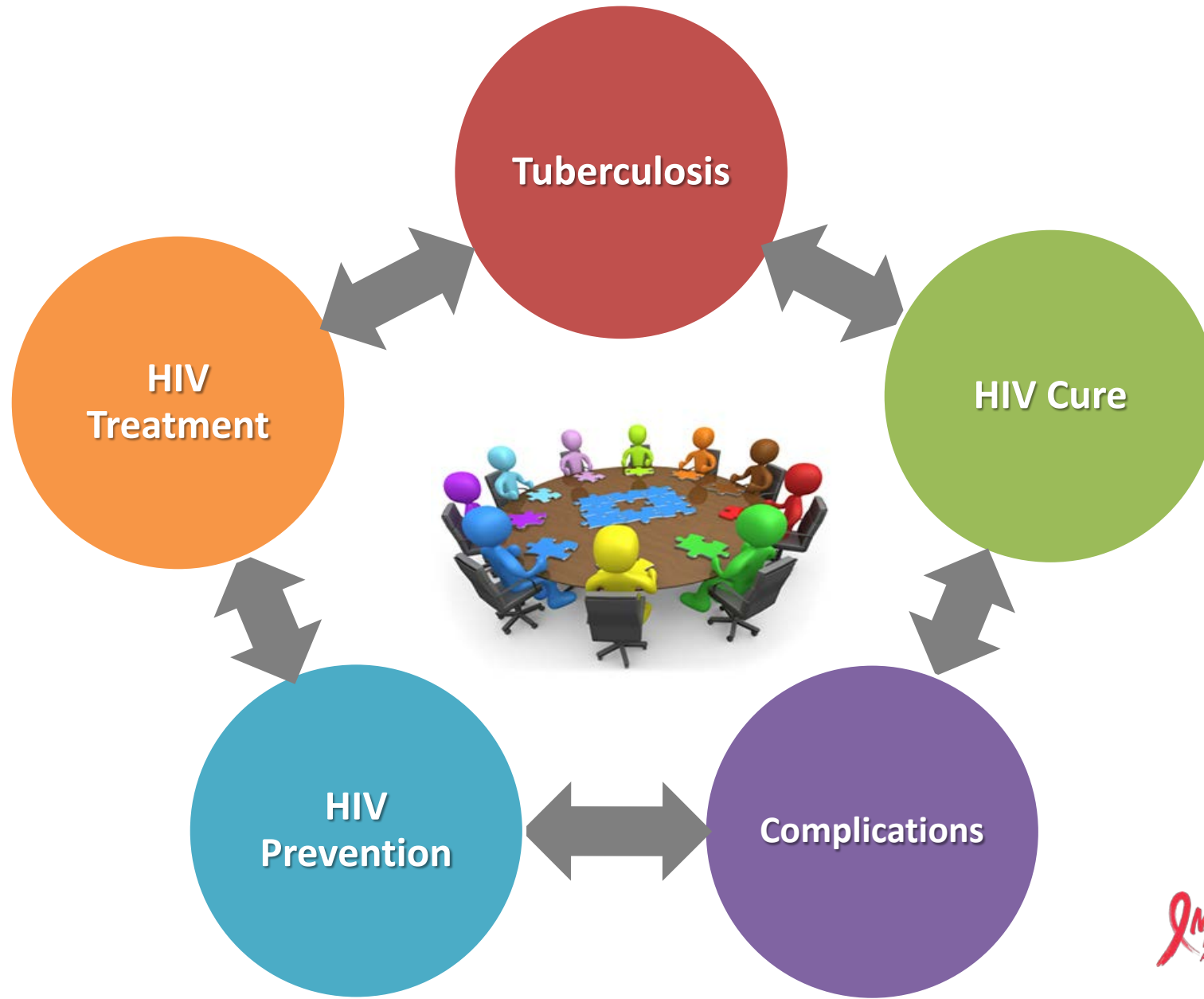


IMPAACT Agenda

Priorities	United States	International
Prevention of infection in youth	<ul style="list-style-type: none">• MSM	<ul style="list-style-type: none">• Young women
Complications	<ul style="list-style-type: none">• Minimizing complications while aging• Neurocognition in youth	<ul style="list-style-type: none">• Tuberculosis• Hepatitis• Neurocognition in infants and children
New ARVs and Fixed Dose Combinations	<ul style="list-style-type: none">• Adolescents• Pregnant women	<ul style="list-style-type: none">• All ages and populations

What are the scientific questions for the next 10 years?

How do we end HIV?





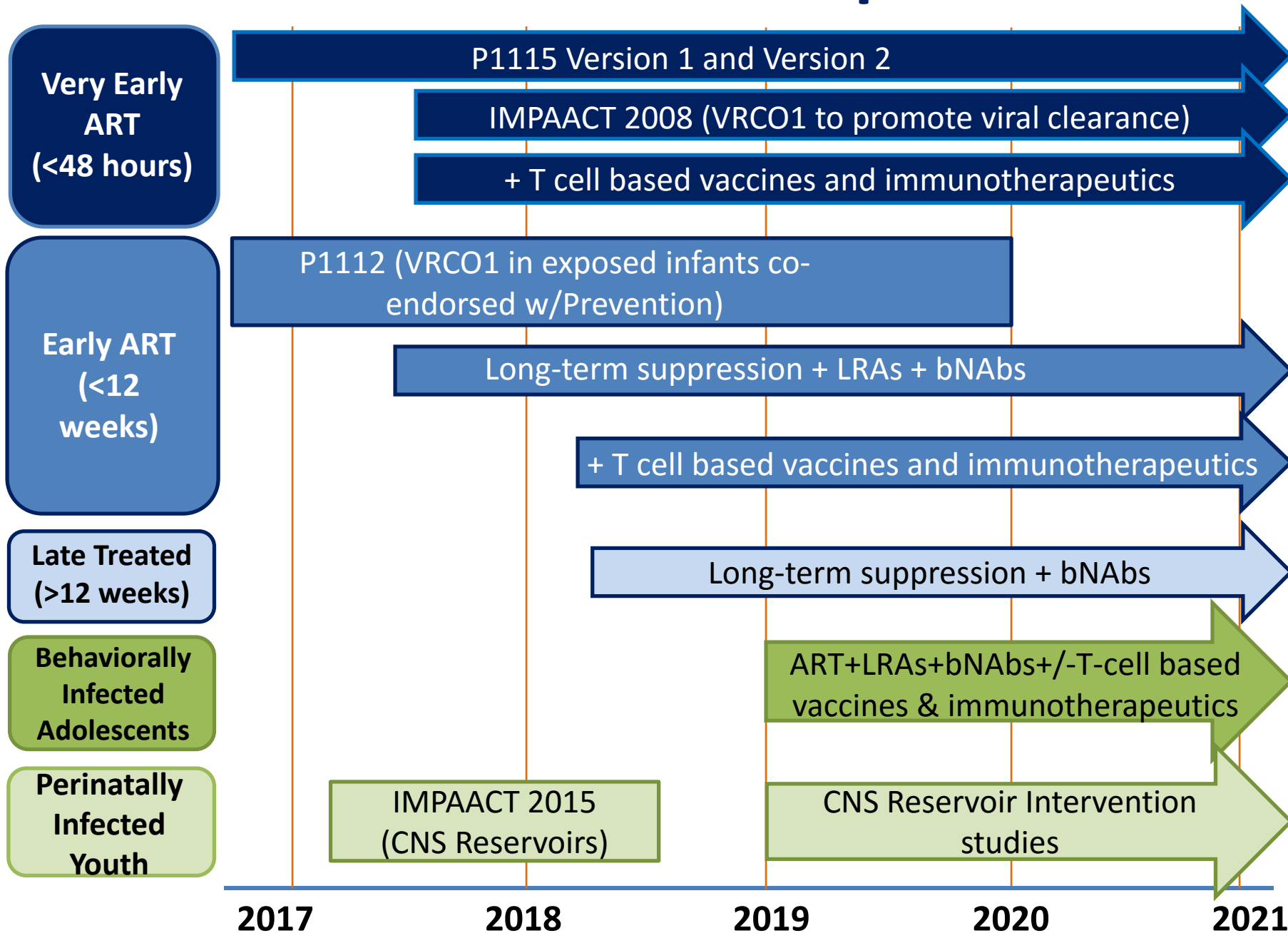
**What is driving
the Cure agenda?**

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



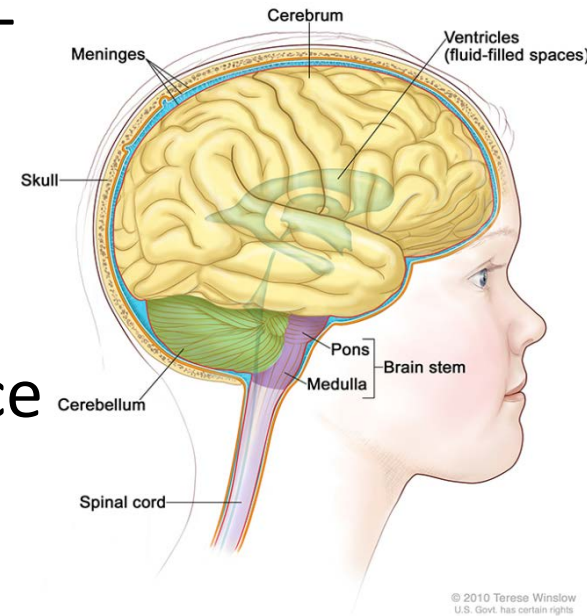
Cure Roadmap



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 Version 1.0
to sites by July 2017

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

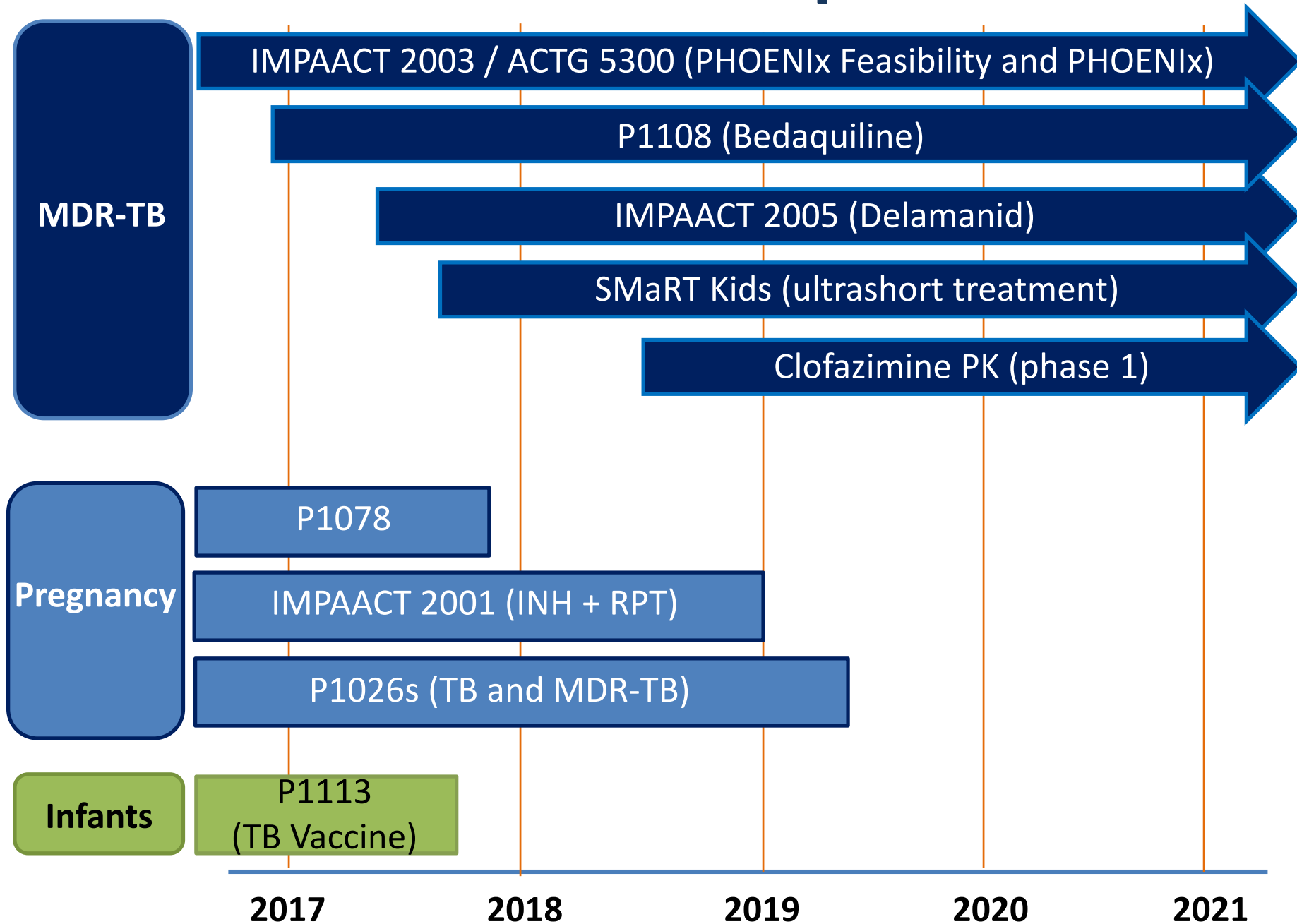
Estimated total cases in children	1,000,000 (10% global burden)
Childhood cases notified	360,000
TB deaths	136,000 (81,000 HIV-) 13.6% case fatality rate
Pediatric MDR-TB cases	32,000 (underestimate)
TB infections	10.4 million

BUT ONLY 87,000 children under five, 7% of those eligible: TB+ HIV+, were started on ARV therapy

Source: WHO 2016 Global TB report, www.who.int



TB Roadmap



Study Highlight: IMPAACT 2003b

PHOENIX, ACTG 5300b

- Collaboration with ACTG
- Phase III cluster-randomized superiority design study (n=~3400 contacts from ~1700 households)
- Primary objective: compare efficacy and safety of delamanid vs isoniazid for TB prevention



Anticipate Version 1.0
to sites by July 2017

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

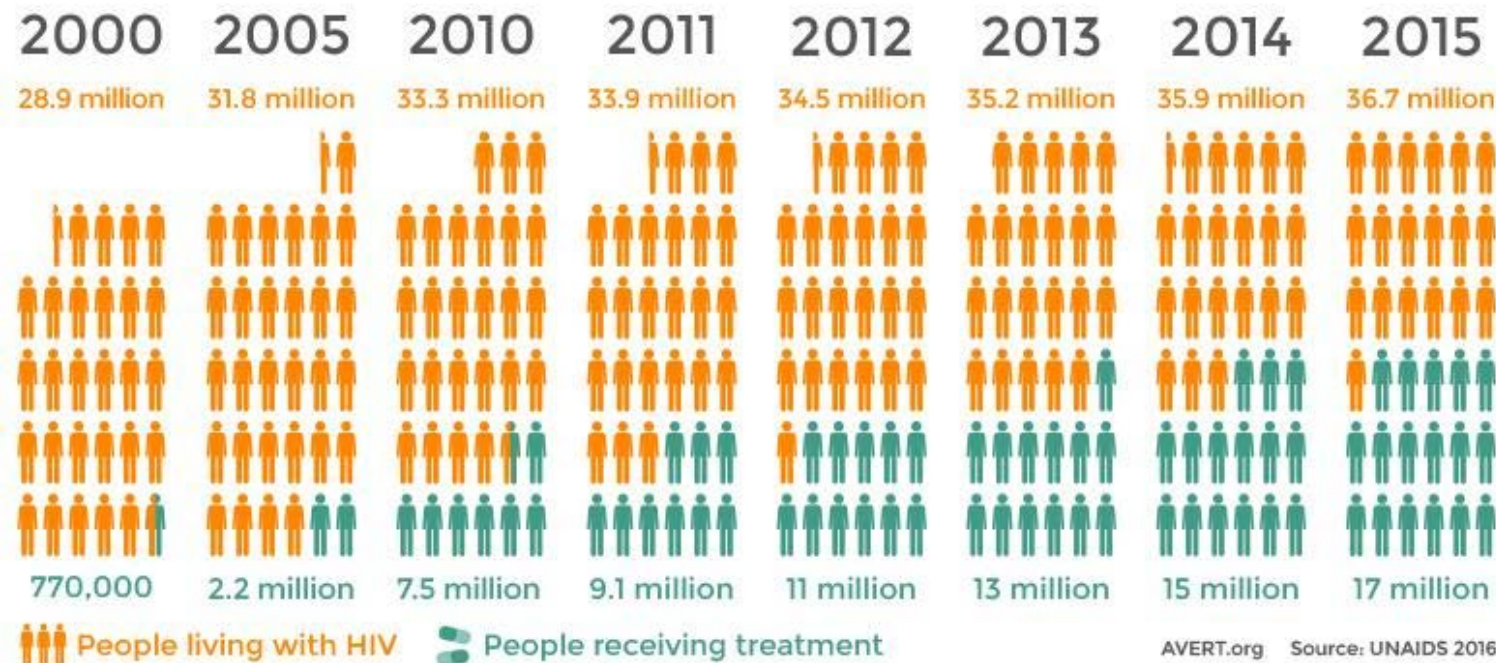




**What is driving
the Treatment agenda?**

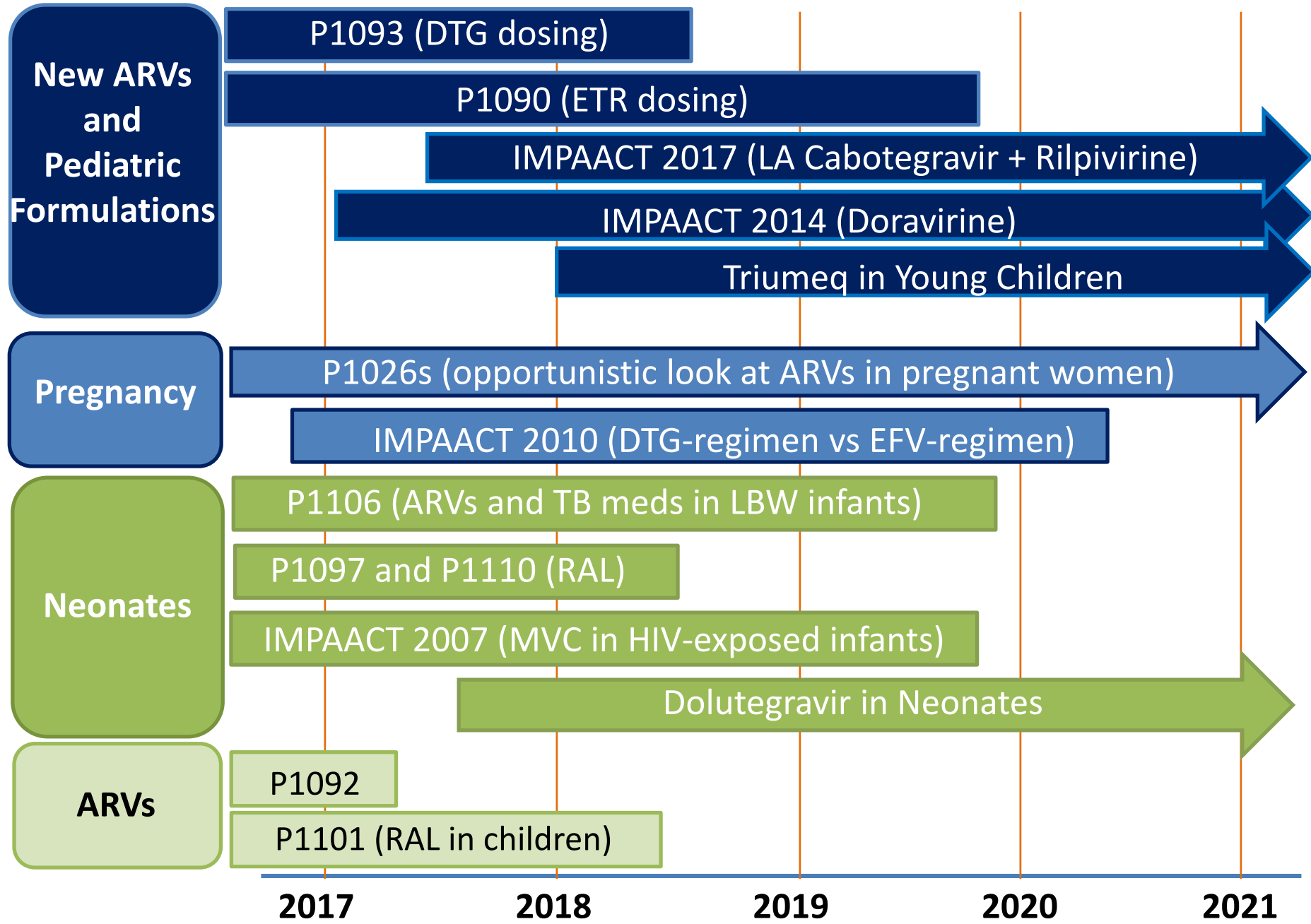
17 million people living with HIV were receiving antiretroviral treatment in 2016, up from 15.8 million in June 2015 and 7.5 million in 2010.

Number of people living with HIV and accessing treatment globally



46% of all adults and 49% of all children living with HIV are now accessing ART

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 Version 1.0 to sites by November 2017

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



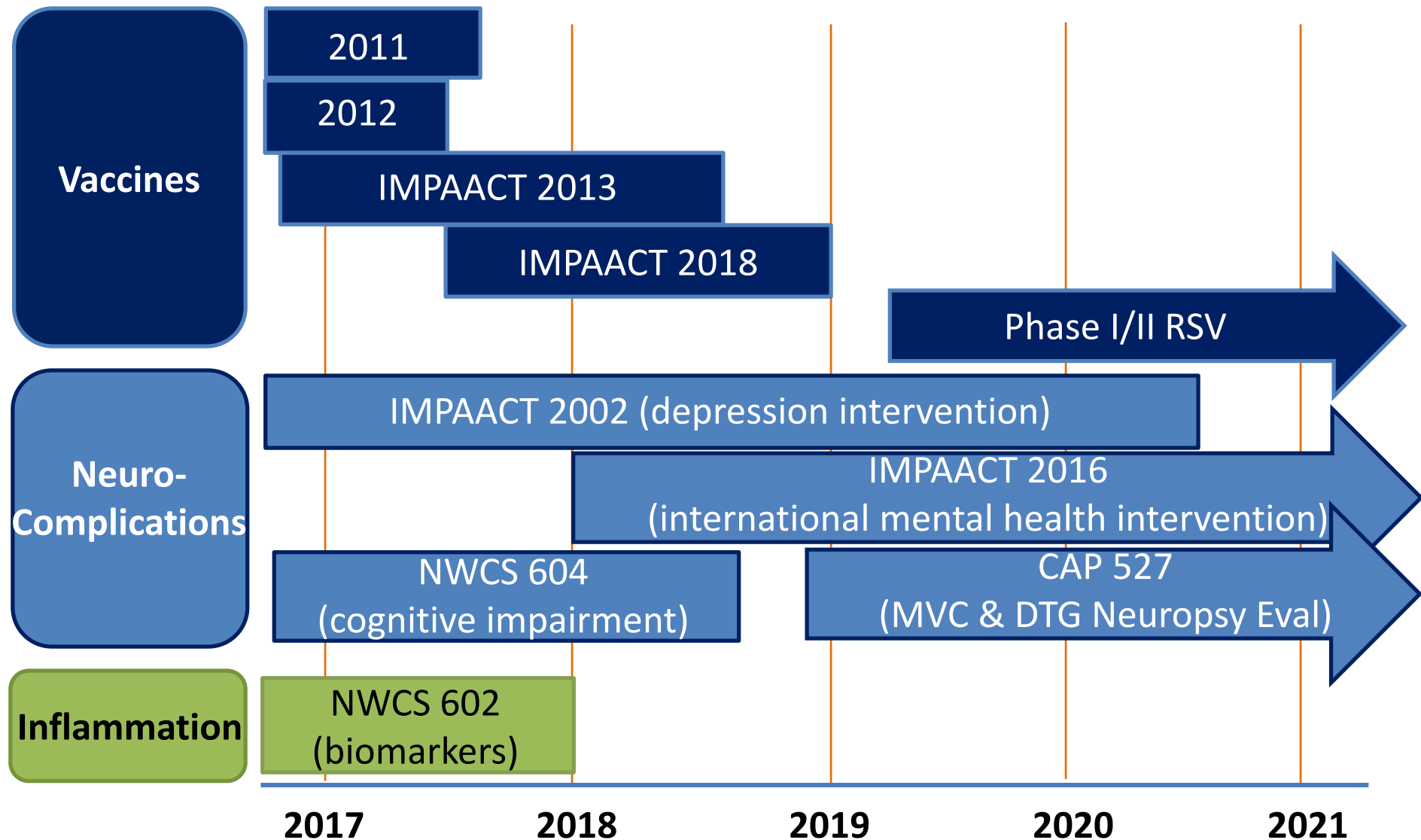
HIV/ARV Complications & Comorbidities

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)



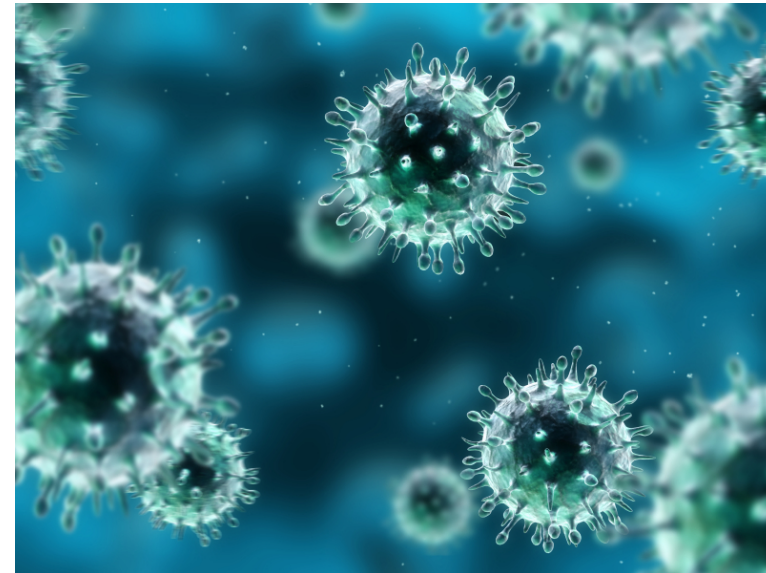
Complications & Comorbidities Roadmap



Study Highlight: IMPAACT 2018

RSV Candidate Vaccine Study

- Phase I placebo-controlled study among healthy RSV-seronegative children 6-24 months of age
- Purpose:
assess Δ NS2/ Δ 1313/I1314L
or RSV 276 vaccine



Anticipate Version 1.0 to
sites by July 2017

Focus for the Future: Complications & Comorbidities

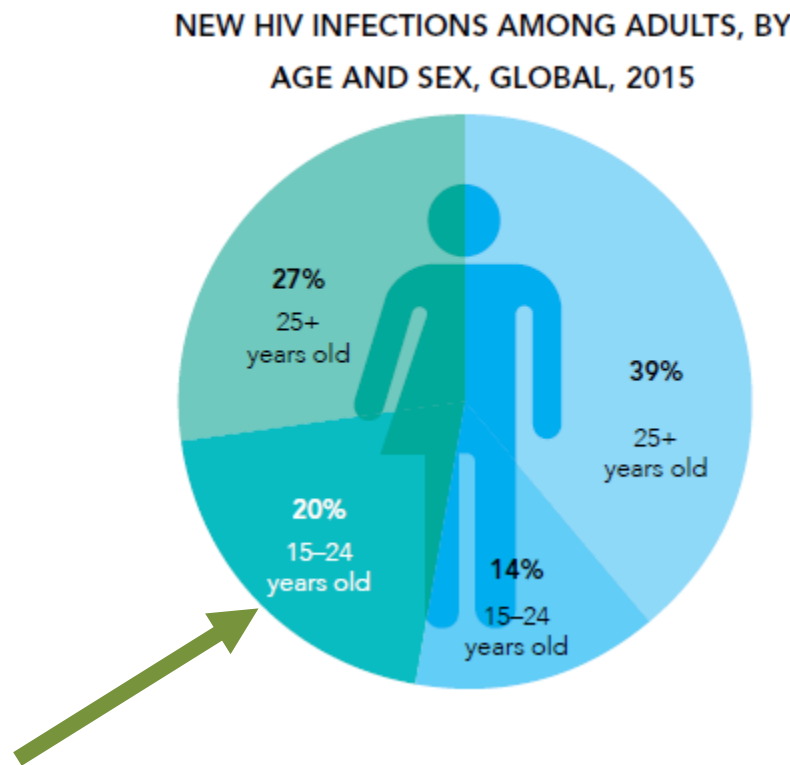
- **Revisit the hepatitis treatment and prevention questions**
 - New drugs
 - New data sets
- **Non-HIV, infectious diseases**
- **Treat and/or prevent neuropsychiatric issues (e.g., maraviroc)**
- **Current and emerging pathogens?**
 - RSV
 - Others



**What is driving
the Prevention agenda?**

Young Women at High Risk for HIV

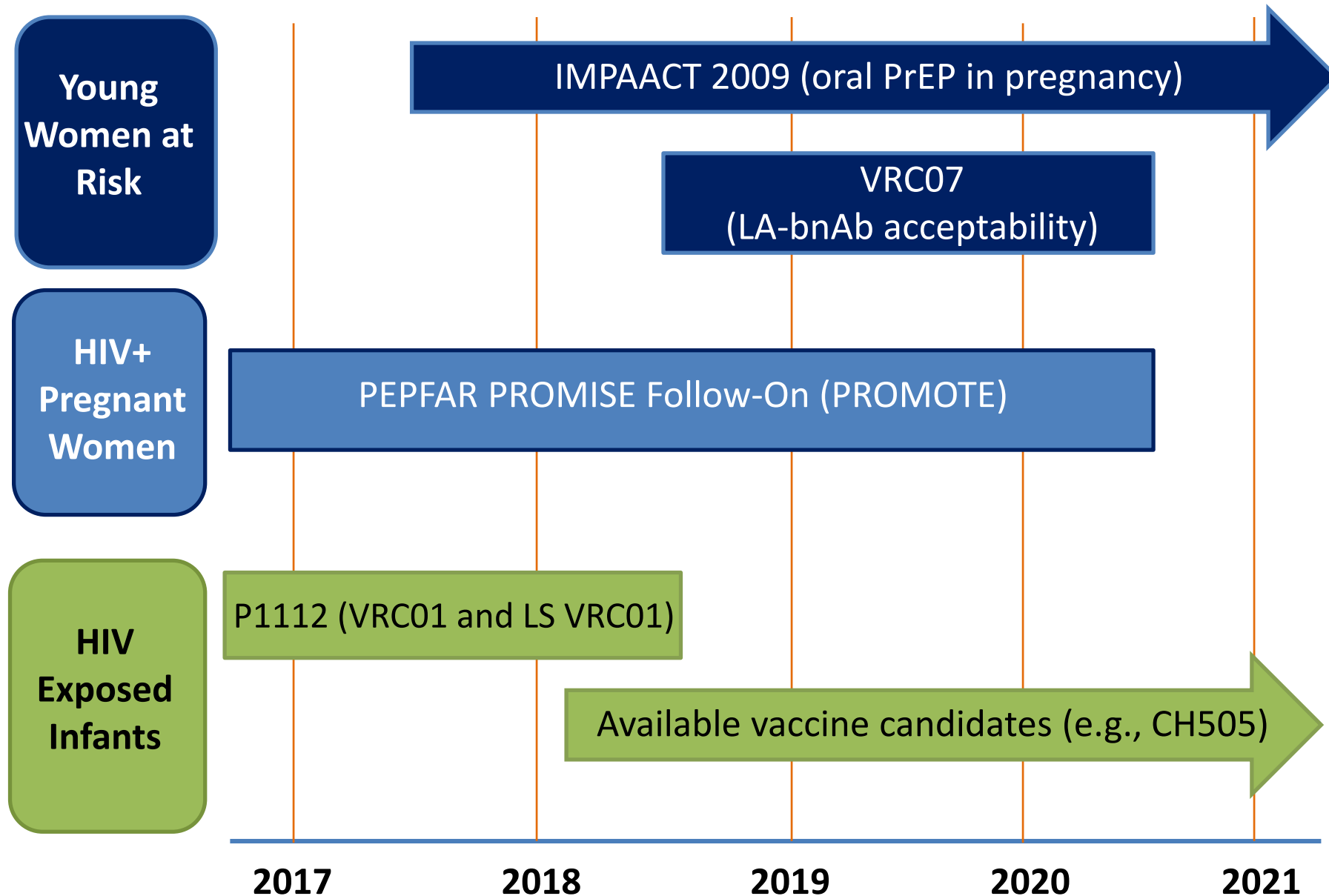
More Pronounced in Sub-Saharan Africa



- **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 (such as HPTN and MTN).

Source: UNAIDS 2016: Global AIDS Update

Prevention Roadmap

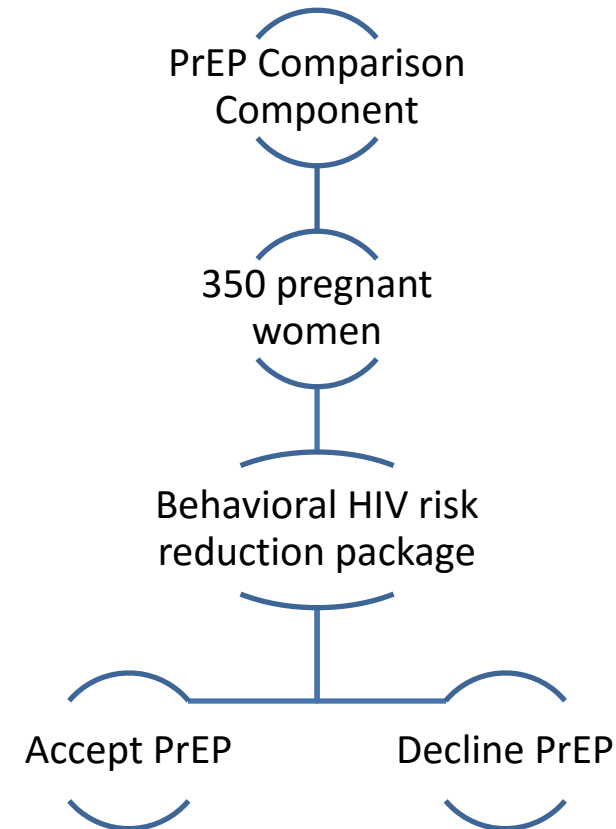


Study Highlight: IMPAACT 2009

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 Version 1.0
to sites by July 2017

Gaps in Prevention

■ Key Populations

- Adolescent/young MSM in the US 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
- US adolescent agenda?

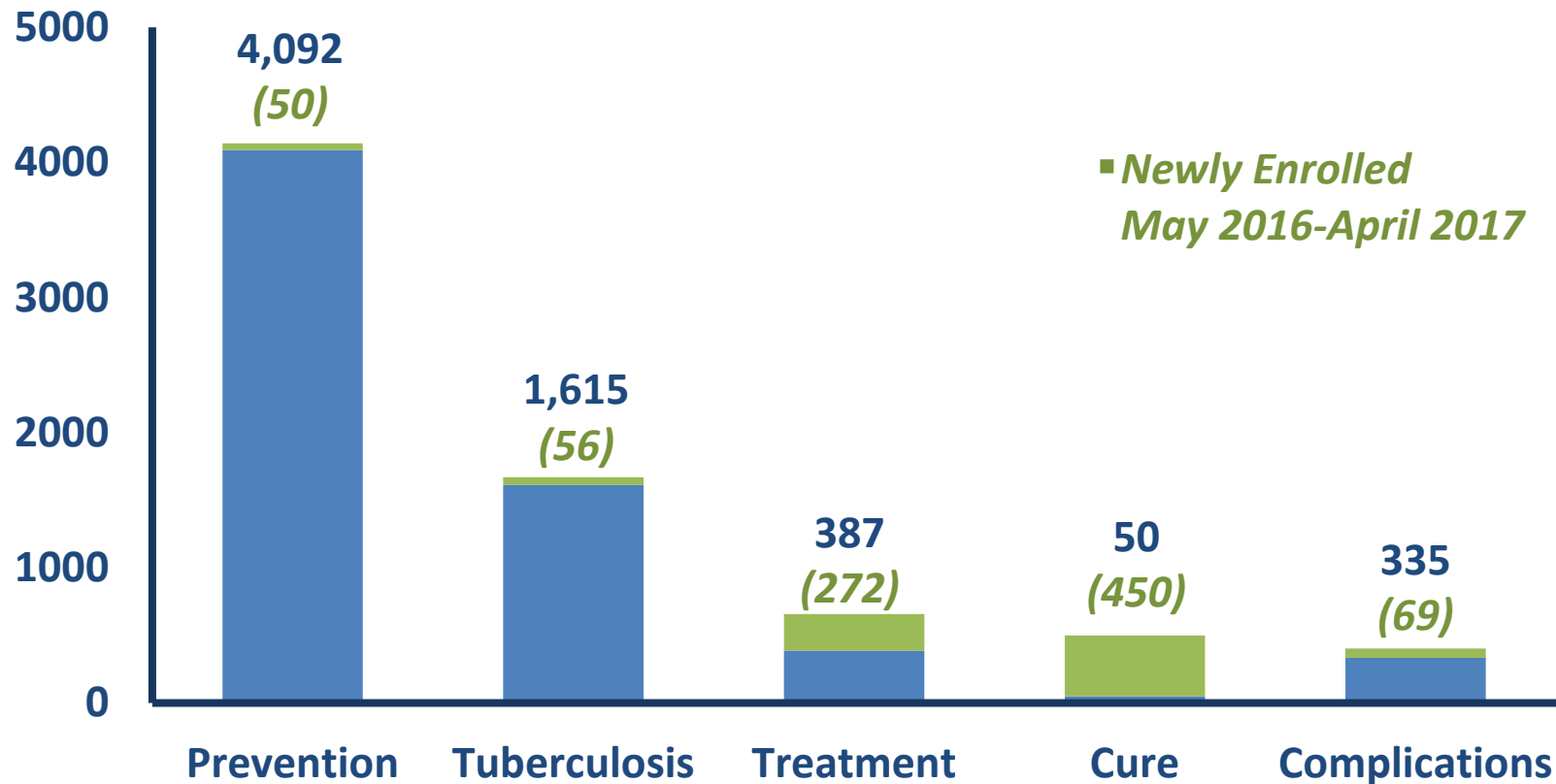




Activities in the Past Year

IMPAACT Participants on Study

May 2016 to April 2017

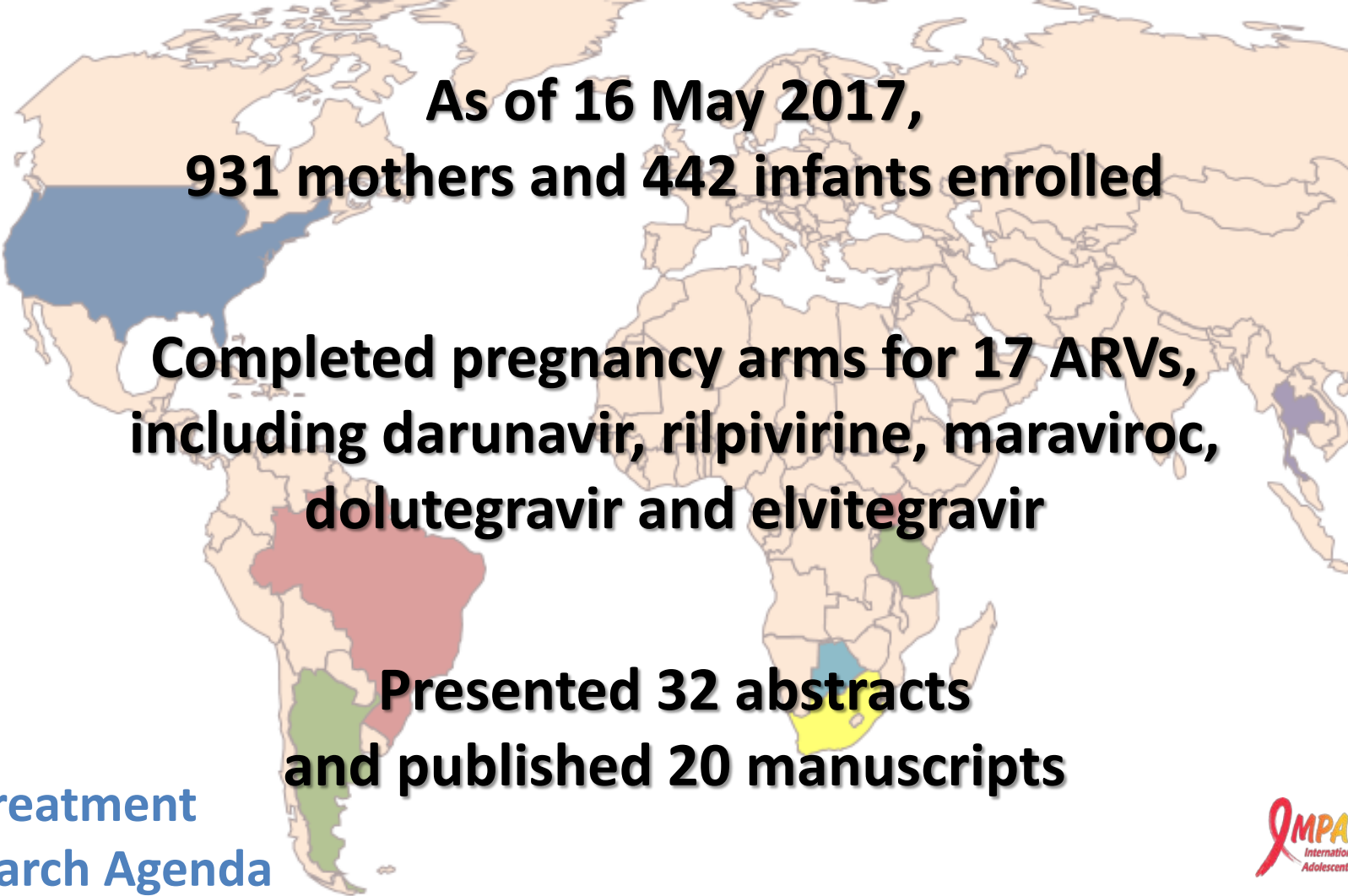


Total On Study = 7,376 participants

Newly Enrolled = 897 participants

Study Highlight: P1026s

PK Properties of ARVs during Pregnancy

A world map with several regions highlighted in different colors: North America (blue), South America (red), Africa (green), and Asia (yellow).

**As of 16 May 2017,
931 mothers and 442 infants enrolled**

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

**Presented 32 abstracts
and published 20 manuscripts**

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: 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 1-3
- Purpose for Dose Group 4: assess safety and PK profile of VRC01LA



**Prevention
Research Agenda**

**First Enrollment into
Dose Group 4 Anticipated
May 2017**

Study Highlight: IMPAACT 2001

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

- Four of six sites have been activated.
- Began enrolling as of 13 March 2017, with 7 mother-infant pairs enrolled to date in **Haiti** and **Thailand**!



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



Complications & Co-Morbidities
Research Agenda

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
- Purpose: compare virologic efficacy and safety of three ARV regimens



Treatment
Research
Agenda

Anticipate opening to
accrual by July 2017

32 Active Studies

May 2016 to April 2017

	5 Pending and Open	13 Enrolling	7 In Follow-up	7 Closed to Follow-up*
Treatment	2007, 2010	P1026s, P1090, P1093, P1097, P1101, P1106, P1110	P1092, P1102	P1060, P1066
Prevention		P1112		1077BF, 1077FF, 1077HS
Complications		2002, 2013	2011, 2012	P1076, P1104s
Tuberculosis	P1108, 2005	2001	P1078, P1113, 2003	
Cure	2008	P1107, P1115		

*closed to follow-up in the last year

IMPAACT Science Generation

June 2016 to May 2017

11 New Capsules for Review

- 3 Treatment
- 1 Prevention
- 3 Complications
- 1 Tuberculosis
- 1 Cure
- 1 Adherence

4 New Concept Sheets Reviewed

- 2 Treatment
- 1 Prevention
- 1 Complications

3 New Protocols Approved for Development

- 1 Treatment
- 2 Complications

Seven Protocols Currently in Development

2018	Randomized Phase I Study of the Infectivity, Safety and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated RSV Vaccines RSV Δ NS2/ Δ 1313/I1314L or RSV 276 or Placebo, Delivered as Nose Drops to RSV-Seronegative Infants 6 to 24 Months of Age
2017	Phase I/II Study of Safety & PK of Oral & <u>Long-acting Injectable Cabotegravir & Long-acting Rilpivirine</u> in Virologically Suppressed HIV-Infected Children and Adolescents
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

Protocols Currently in Development (cont'd)

2015	Evaluating the <u>HIV Reservoir in the CNS</u> in Perinatally-Infected Individuals on ART
2014	Phase I/II Trial of the Pharmacokinetics, Safety, and Efficacy of MK-1439 (<u>Doravirine</u> or DOR) and MK-1439A (FDC of DOR + lamivudine + TDF) in <u>HIV-infected Adolescents</u>
2009	PK, Feasibility, Acceptability, & Safety of <u>Oral PrEP</u> for Primary HIV Prevention <u>during Pregnancy</u> & Postpartum in Adolescents & Young Women

Community Engagement Achievements

- Comprehensive community reviews of 5 IMPAACT studies
- 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

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



Abstracts



16 abstracts at CROI 2017

- Neuropsychological outcomes in pediatric observational study
- Antenatal ART and adverse birth outcomes
- Sertraline PK in HIV-infected youth
- Safety and PK of VRC01 in HIV-exposed newborns

Additional abstracts accepted to
IAS 2017, ICAAC, ICAAP, ICASA, and ID week



Cross Network Study Initiatives



- MDR-TB Prevention (PHOENIX)



- TB and HIV Vaccine Studies (Aeras/P1113)



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



Pharma Collaborations: New Formulations/Products



Plans for the Upcoming Year...

**Publish
PROMISE**

**Complete
and publish
P1078 and
P1092**

**Begin (and
complete)
the RSV
studies**

**Start
enrolling
Version 3 of
P1101 &
P1112**

**Continue
ongoing
studies**

**Develop
IMPAACT
2016 &
2017**

**Finalize
Version 2 of
IMPAACT
2008**

**Finalize
IMPAACT
2009, 2014
& 2015**

**Continue
enrolling
IMPAACT
2001 & 2002**

**Begin
IMPAACT
2005 &
P1108**

**Enroll
IMPAACT
2007**

**Begin
IMPAACT
2010**



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



Let's continue to move the science forward!