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 prevention 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.

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

- Women: down 16%
- Black MSM: stabilizing
- Hispanic/Latino MSM:
  - all ages: up 14%
  - age 13–24: up 19%
  - age 25–34: up 21%

Percentage HIV Diagnoses in 2016

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

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

- Aged <13: 122 (0.3%)
- Aged 13-19: 1,675 (4%)
- Aged 20-29: 14,740 (37%)
- Aged 30-39: 9,943 (25%)
- Aged 40-49: 6,490 (16%)
- Aged 50-59: 4,882 (12%)
- Aged 60+: 1,930 (5%)

39,782 total new HIV diagnoses

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?
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**

- **Very Early Therapies (<48 hours)**
  - P1115 Version 1 and Version 2: early intensive ART
  - + T cell based vaccines and immunotherapeutics

- **Early Therapies (<12 weeks)**
  - IMPAACT 2008 (VRCO1 to promote viral clearance)
  - Long-term suppression + LRAs + bNAb
  - + T cell based vaccines and immunotherapeutics

- **Late Therapies (>12 weeks)**
  - Long-term suppression + bNAb
  - ART+LRAs+bNAb+/-T-cell based vaccines & immunotherapeutics

- **Behaviorally Infected Adolescents**
  - IMPAACT 2015 (CNS Reservoirs)

- **Perinatally Infected Youth**
  - CNS Reservoir Intervention studies
Study Highlight: IMPAAACT 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

**Mortality**

250,000
This includes 52,000 TB deaths among children who were HIV-positive

**Preventive TB treatment**

161,740
Only 13% of eligible children (1.3 million) received preventive TB treatment in 2016.

# Tuberculosis and HIV

## Key Challenges

| 37% of deaths among people with HIV due to TB | 54% of all people with HIV-associated TB did not reach care according to reported data | 18/30 countries with high burden of HIV-associated TB did not report IPT for PLHIV newly enrolled in HIV care |

## Achievements in 2016

| 6.2 million lives saved of people with HIV through scale-up of collaborative TB/HIV activities since 2005 | 82% known HIV status among notified TB cases in the Africa, up from 22% in 2006 | 85% ART coverage among notified TB cases living with HIV, up from 46% in 2006 | >1.3 million PLHIV started TB preventive Treatment up from 27,000 in 2006 |

Study Highlight: IMPAAACT 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

Anticipate Version 1.0 to sites by early 2019

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

<table>
<thead>
<tr>
<th>Year</th>
<th>People living with HIV</th>
<th>People receiving treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>28.9 million</td>
<td>770,000</td>
</tr>
<tr>
<td>2005</td>
<td>31.8 million</td>
<td>2.2 million</td>
</tr>
<tr>
<td>2010</td>
<td>33.3 million</td>
<td>7.5 million</td>
</tr>
<tr>
<td>2012</td>
<td>34.5 million</td>
<td>11 million</td>
</tr>
<tr>
<td>2013</td>
<td>35.2 million</td>
<td>13 million</td>
</tr>
<tr>
<td>2014</td>
<td>35.9 million</td>
<td>15 million</td>
</tr>
<tr>
<td>2015</td>
<td>36.7 million</td>
<td>17 million</td>
</tr>
<tr>
<td>2016</td>
<td>36.7 million</td>
<td>19.5 million</td>
</tr>
</tbody>
</table>

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**

- **New ARVs and Pediatric Formulations**
  - IMPAACT 2014 (Doravirine)
  - IMPAACT 2019 (Triumeq in Young Children)
  - P1026s/IMPAACT 2026 (ARVs and Contraceptives)
  - CS 5012 (Dolutegravir in Neonates)
  - IMPAACT 2007 (Maraviroc in HIV-exposed infants)
  - P1106 (ARVs and TB meds in Low Birth Weight infants)
  - P1097 and P1110 (Raltegravir)
  - IMPAACT 2010 (Dolutegravir-regimen vs Efavirenz-regimen)
  - P1101 (RAL in TB/HIV+ children)

- **Pregnancy**
  - P1093 (Dolutegravir dosing)
  - P1090 (Etravirine dosing)
  - IMPAACT 2014 (Doravirine)
  - IMPAACT 2017 (LA Cabotegravir + Rilpivirine)
  - IMPAACT 2019 (Triumeq in Young Children)
  - CS 5018 (LA CABO + RIL in non-adherent youth)
  - P1026s/IMPAACT 2026 (ARVs and Contraceptives)
  - IMPAACT 2010 (Dolutegravir-regimen vs Efavirenz-regimen)
  - Newer ARVs in Pregnancy

- **Neonates**
  - P1097 and P1110 (Raltegravir)
  - IMPAACT 2007 (Maraviroc in HIV-exposed infants)
  - CS 5012 (Dolutegravir in Neonates)

- **ARVs**
  - P1101 (RAL in TB/HIV+ children)
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)
Study Highlight: IMPAAACT 2021
RSV Candidate Vaccine Study

- Randomized phase Ib placebo-controlled study among healthy RSV-seronegative children 6-24 months of age
- Purpose: assess ΔNS2/Δ1313/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

- **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).

*Source: UNAIDS 2016: Global AIDS Update*
IMPAACT Prevention Roadmap

1. IMPAACT 2009 (oral PrEP in pregnancy)
   - VRC07 (LA-bnAb acceptability)

2. PEPFAR PROMISE Follow-On (PROMOTE)

3. Available vaccine candidates
   - P1112 (VRC01, LS VRC01, LS VRC07)

- Young Women at Risk
- HIV+ Pregnant Women
- HIV Exposed Infants
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 needed 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
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)

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

*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!
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

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
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

Tuberculosis Research Agenda
Study Highlight: IMPAAACT 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

Began enrolling on 6 March 2017: 93 of 156 youth have been enrolled at 13 U.S. sites
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

Treatment Research Agenda

![Graph showing monthly and cumulative accrual](image-url)
# 32 Active Studies
## June 2017 to May 2018

<table>
<thead>
<tr>
<th>Category</th>
<th>6 In Development</th>
<th>6 Pending and Open</th>
<th>14 Enrolling</th>
<th>4 In Follow-up</th>
<th>5 Closed to Follow-up*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention</td>
<td></td>
<td>2009</td>
<td>P1112</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>2015, 2008</td>
<td></td>
<td>P1115, P1107</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*closed to follow-up in the last year
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

IMPAACT Science Generation
June 2017 to May 2018
## Six Protocols Currently in Development

<table>
<thead>
<tr>
<th>Year</th>
<th>Protocol Title</th>
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<tbody>
<tr>
<td>2026</td>
<td>Pharmacokinetic Properties of Antiretroviral, Anti-Tuberculosis, Contraceptive and Related Drugs During Pregnancy and Postpartum</td>
</tr>
<tr>
<td>2021</td>
<td>Randomized Phase IB Study of the Safety and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated Respiratory Syncytial Virus (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</td>
</tr>
</tbody>
</table>
## Protocols Currently in Development (cont’d)

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

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
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!