Study Design Considerations for Efficacy Trials of Infant Postnatal Prophylaxis Against HIV

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IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

ANNUAL MEETING
2024

Disclosures and Disclaimer

- **Disclosures:**
  - Mark Giganti has received research support from ViiV Healthcare, paid to institution
  - Dwight Yin was previously an unpaid technical advisor to the HIV non-profits Maipelo Trust and Cover the Globe, ended in 2021

- **Disclaimer:** The views expressed in this talk are the speakers' own and do not represent the opinions of the National Institutes of Health, Department of Health and Human Services, or United States government

Key Messages

- **What is the main issue or key question our work addresses?**
  - It is hard to study new ways to prevent vertical transmission of HIV. To see if anything works, very large numbers of participants need to be enrolled. How can we design better studies to prevent vertical transmission of HIV?
- **What was the key finding or "take home message"?**
  - It may be possible to combine a randomized controlled trial (RCT) with real-world data. This alternative type of study is called a fusion design.
- **How is this important for the IMPAACT Network?**
  - The IMPAACT Network needs new ways to study prevention of HIV vertical transmission. A fusion design may be a better way to do vertical transmission studies.

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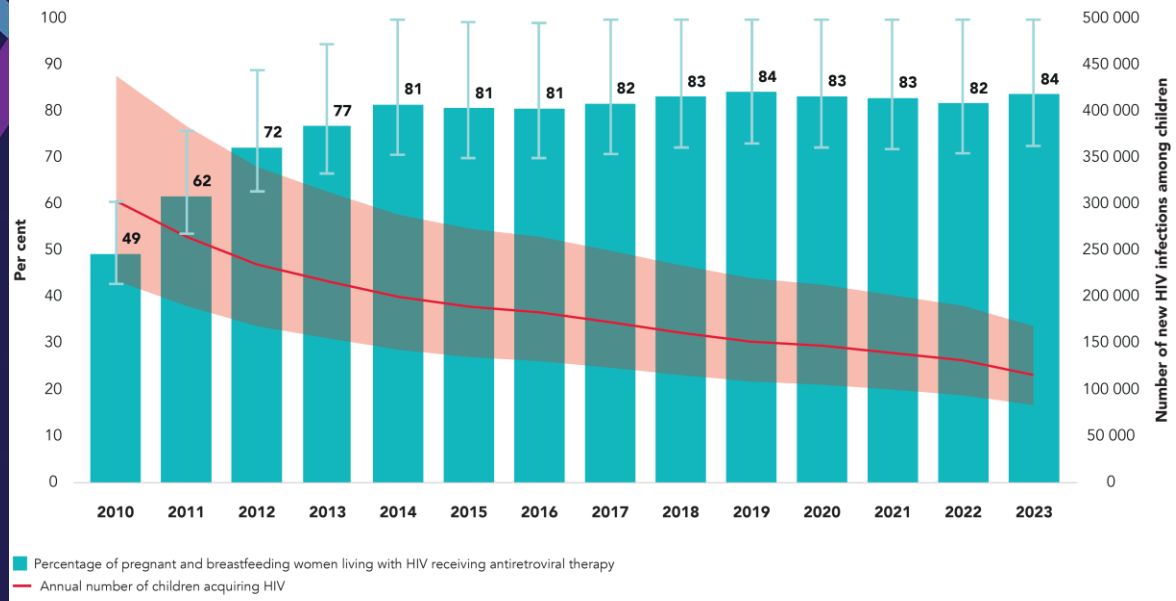
How Do We Address the Persistent Gaps in Treatment During Pregnancy/Breastfeeding and Prevention of Vertical Transmission?

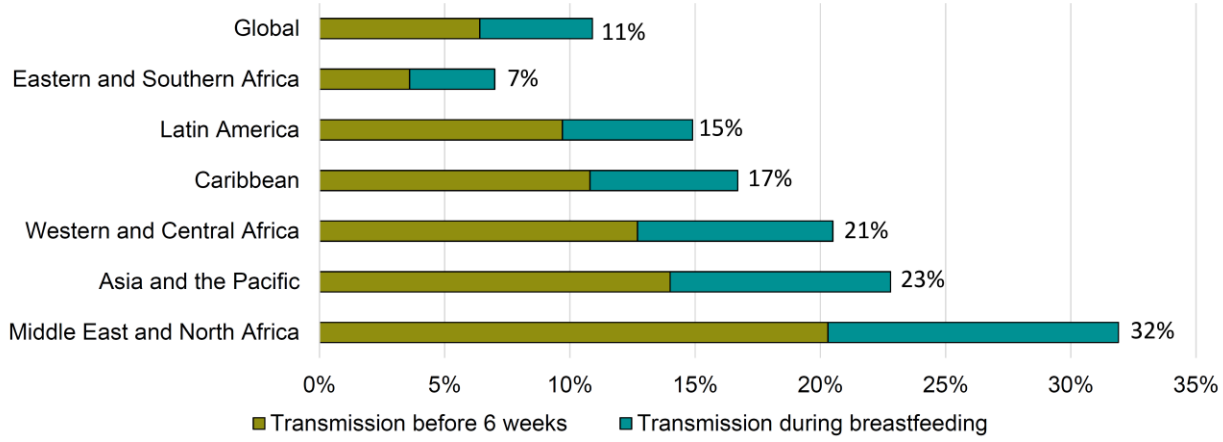
Ongoing Burden of HIV Vertical Transmission

Globally, 120,000 new pediatric HIV infections in 2023

Infants still acquire HIV despite high ART coverage during pregnancy/breastfeeding



~50% of vertical transmission occurs during breastfeeding



Source: UNAIDS epidemiological estimates, 2024 (https://aidsinfo.unaids.org/), UNAIDS epidemiological estimates, 2023 (https://aidsinfo.unaids.org/)

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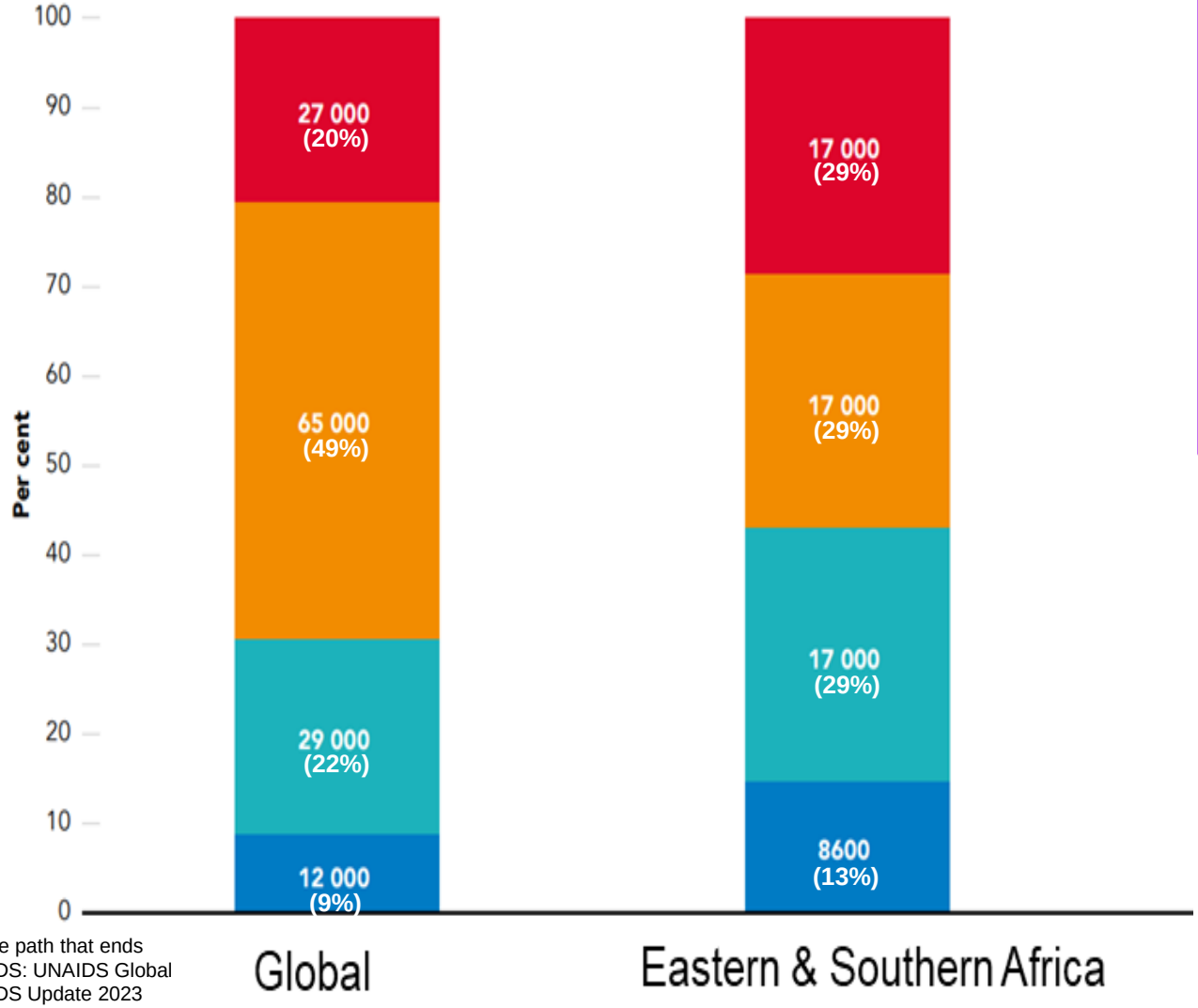
How Do We Address Persistent Gaps in Treatment During Pregnancy/Breastfeeding and Prevention of Vertical Transmission?

Infant HIV Acquisition in Pregnancy/Breastfeeding



The path that ends AIDS: UNAIDS Global AIDS Update 2023

Strategies

For mothers:

- Prevention
- Testing
- Linkage
- Treatment
- Retention

For infants:

- Postnatal prophylaxis immediate postpartum period
- Postnatal prophylaxis during breastfeeding

Mother acquired HIV during pregnancy or breastfeeding

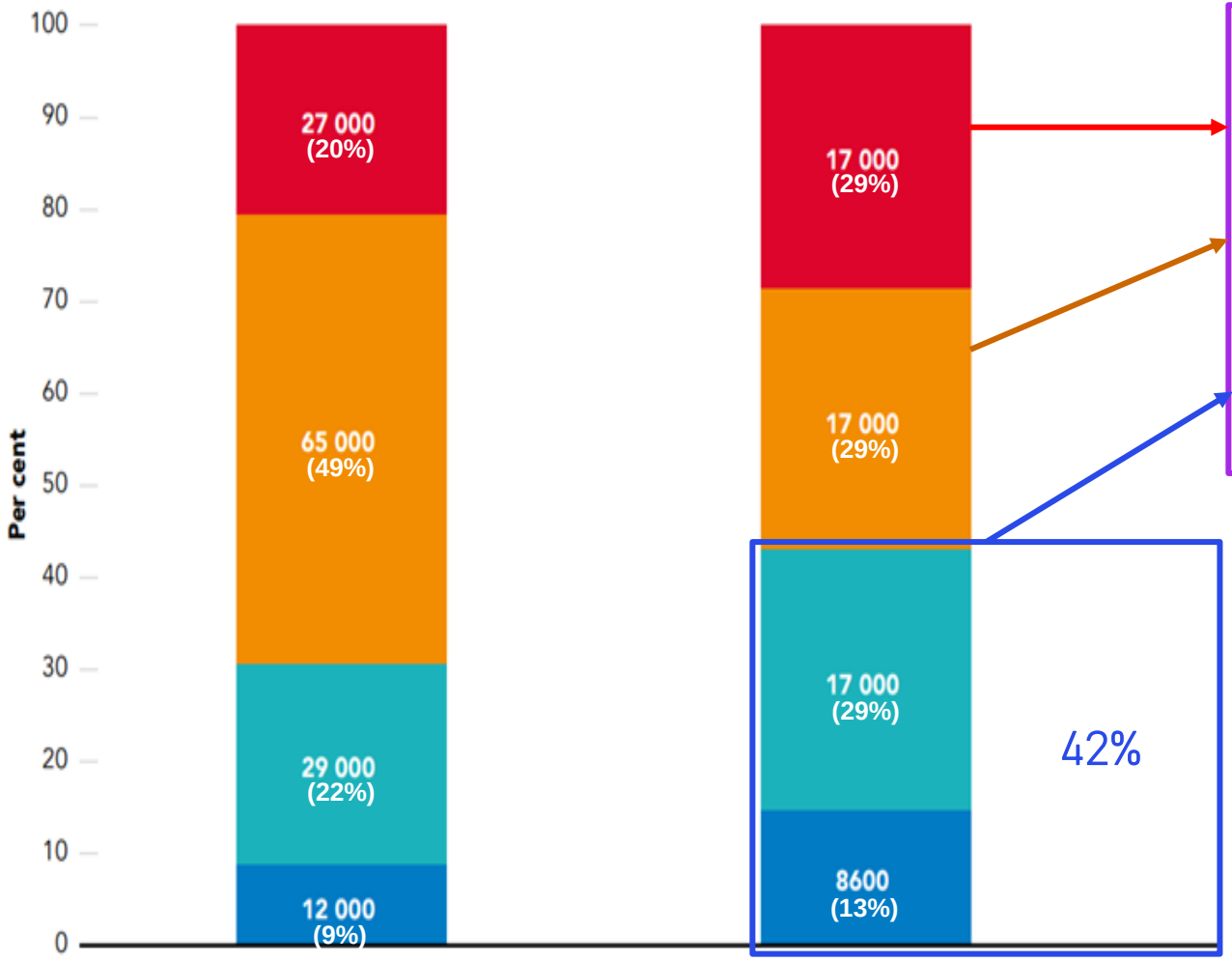
Mother did not receive antiretroviral therapy during pregnancy or breastfeeding

Mother did not continue antiretroviral treatment during pregnancy or breastfeeding

Mother was on antiretroviral treatment but did not achieve viral supression

How Do We Address Persistent Gaps in Treatment During Pregnancy/Breastfeeding and Prevention of Vertical Transmission?

Infant HIV Acquisition in Pregnancy/Breastfeeding



The path that ends AIDS: UNAIDS Global AIDS Update 2023

Strategies

For mothers:

- Prevention
- Testing
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- Retention

O-PrEP, HPTN 084, 102

Systems/ Implementation

IMPAACT 2026, 2040 Implementation

- Mother acquired HIV during pregnancy or breastfeeding
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How Do We Address Persistent Gaps in Treatment During Pregnancy/Breastfeeding and Prevention of Vertical Transmission?

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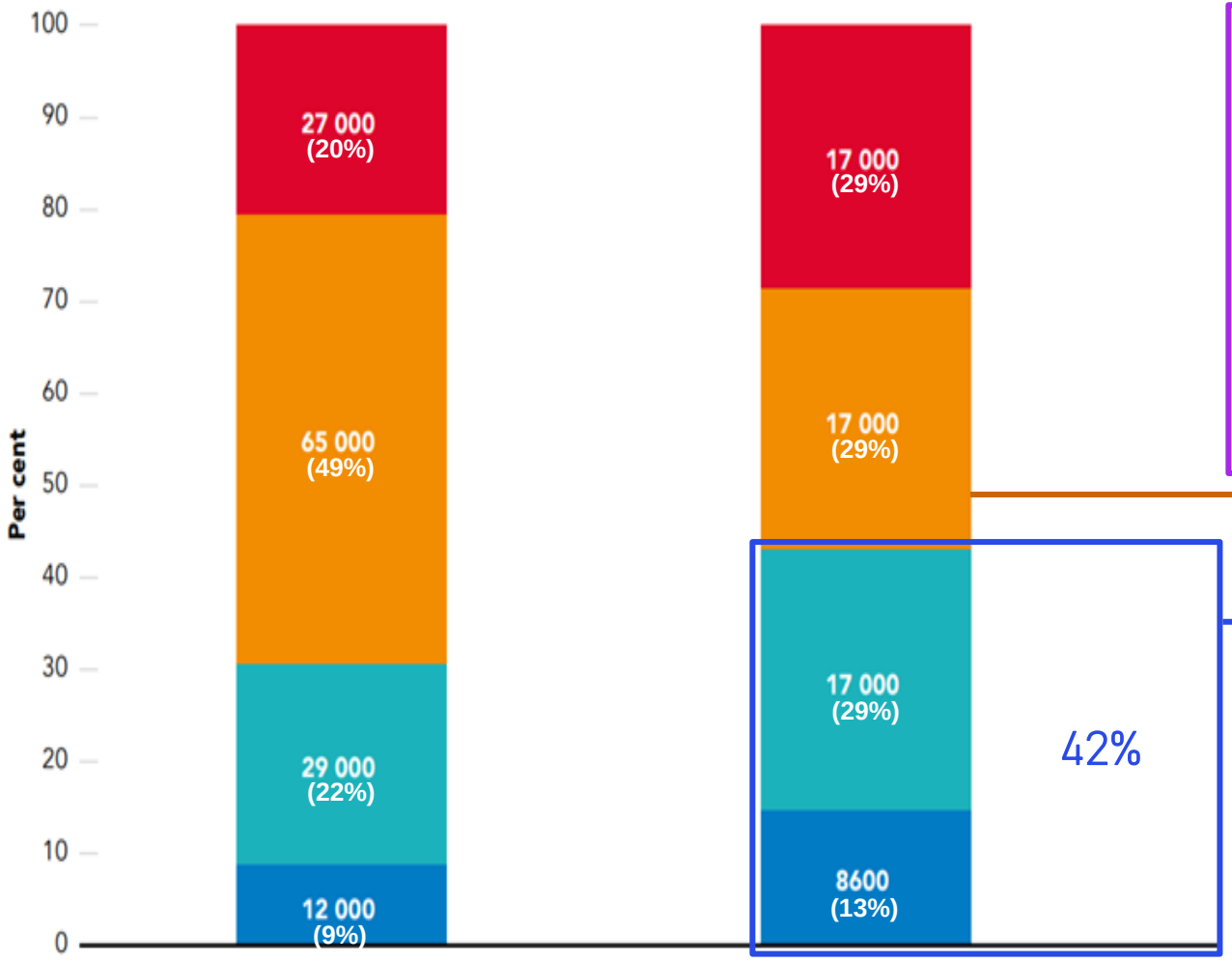

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Why Give Infants Postnatal HIV Prophylaxis?

Why Give Infants Postnatal HIV Prophylaxis (PNP)?

- Definitions
  - **Postpartum** ART = antiretroviral therapy after delivery, administered to **lactating persons**
  - **Postnatal** prophylaxis (PNP) = preventative agent(s) after birth, administered to **infant**

- Gaps in current prevention of vertical transmission cascade
  - In sub-Saharan Africa, pregnant persons frequently present late in pregnancy
  - Historically, 1 in 3 people on postpartum ART had postpartum viral rebound
    - 21% of postpartum persons with HIV on DTG had viral loads >1,000 c/mL at 24 wks postpartum
  - People frequently disengage from care in the postpartum period

- Opportunities for PNP administered to infants
  - PNP provides a “safety net”
  - PNP has been part of the prevention toolkit since PACTG 076
  - New avenues for integrating postnatal prophylaxis into existing pediatric healthcare infrastructure

UNAIDS epidemiological estimates, 2023 (https://aidsinfo.unaids.org/)
Penazzato et al. 2023. J Int AIDs Soc. 2023 Feb;26(2):e26032. doi: 10.1002/jia2.26032.

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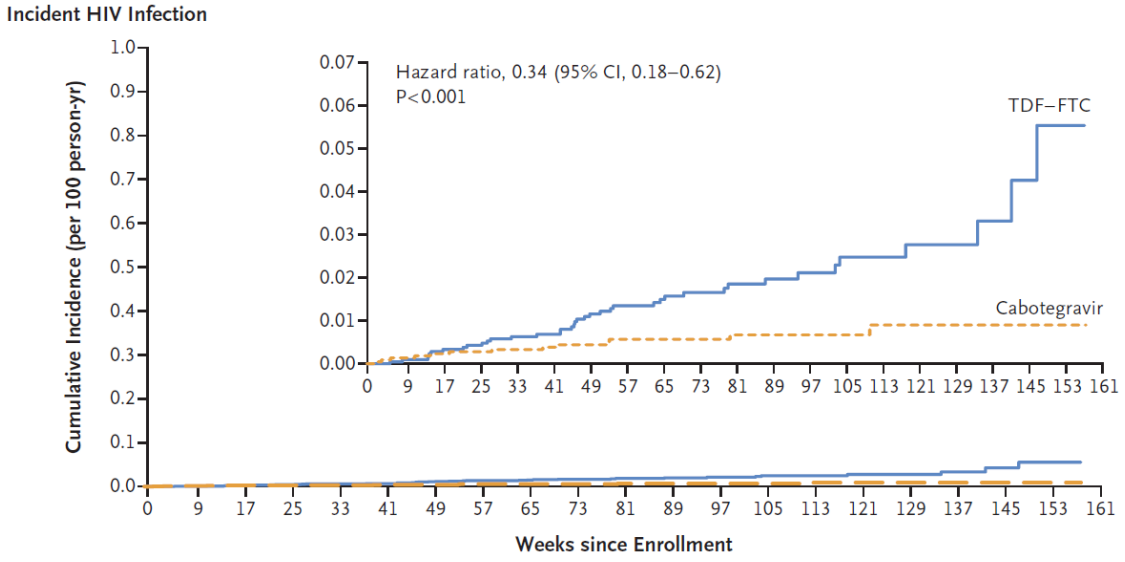
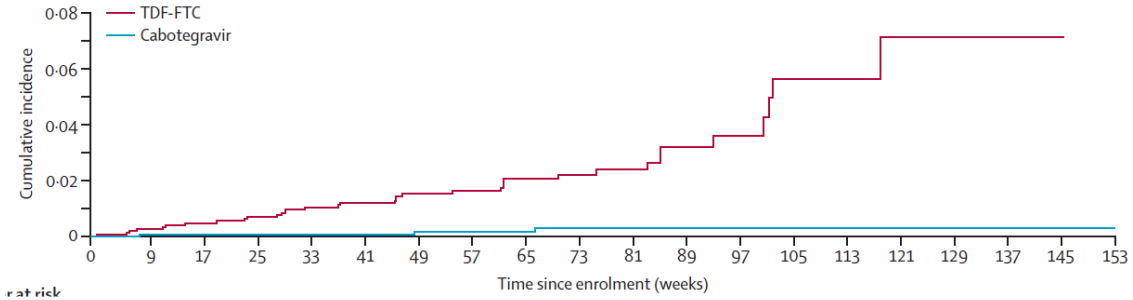
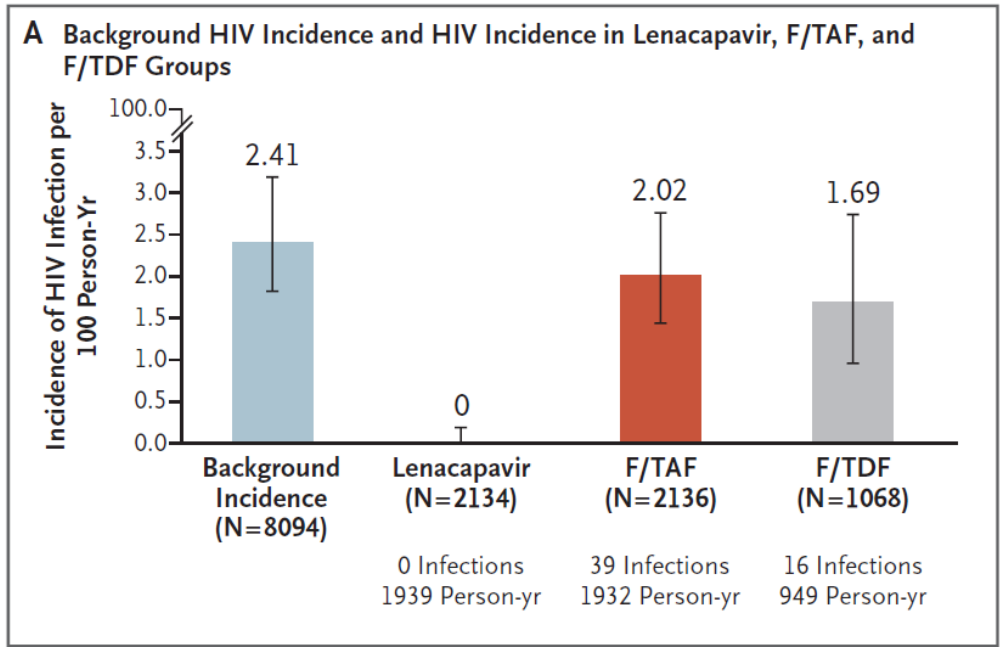
The Power of Long-Acting Agents for Prevention







Advantages

- No need for daily oral ARVs
- Lower barrier to adherence
- Overcomes administration problems
- No home storage
- Decreases stigma

Landovitz, R.J. et al. *N Eng J Med*. 2021 Aug 12;385(7):595-608
Delaney-Moretlwe, S. et al. *Lancet*. 2022 May 7;399(10337):1779-1789.
Bekker, L.-G. et al. *N Eng J Med*. 2024 Jul 24.

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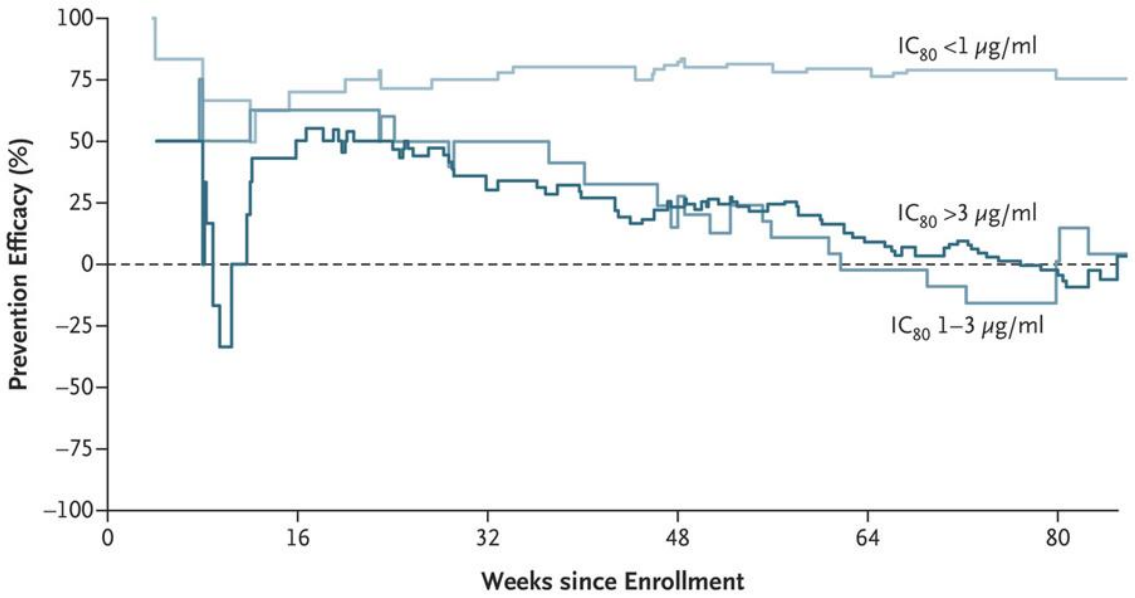
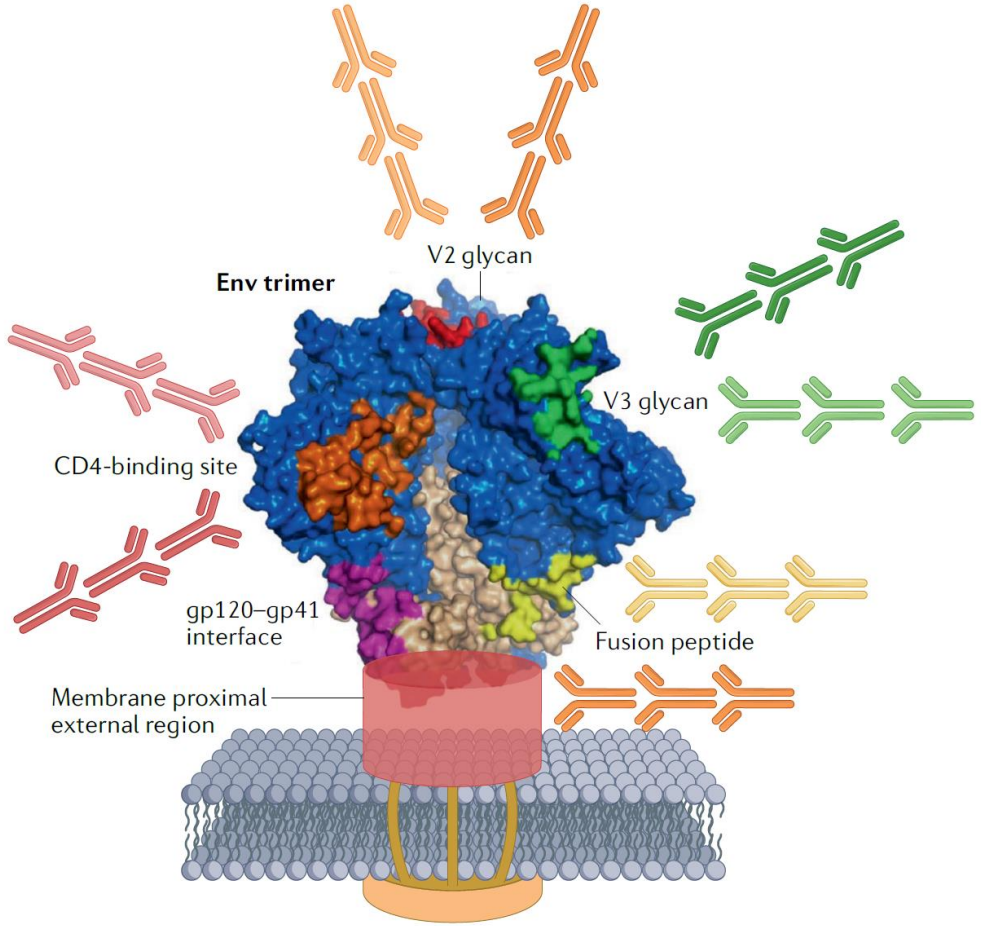
What Role Will bNAbs Have in Prevention of HIV Vertical Transmission?

Horizontal Transmission Prevention of Susceptible HIV-1 Infections





Corey, L., et al. *N Eng J Med*. 2021 Mar 18;384(11):1003-1014. doi: 10.1056/NEJMoa2031738.
Haynes, B.F. et al. *Nat Rev Immunol*. 2023 Mar;23(3):142-158.

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What are Important Study Design Considerations for Infant Postnatal Prophylaxis Efficacy Trials?

Designing HIV-1 Prevention Efficacy Studies in Pediatric Populations is Challenging

High efficacy of standard-of-care HIV prophylaxis

↓

Low underlying probability of HIV transmission

↓

Future studies require much larger sample sizes

Table 2. Infant HIV Infection through Week 1 (Periods 1 and 2 Combined) in All Mother–Infant Sets and According to Subgroup.*

Subgroup	ZDV Alone	ZDV-Based ART	TDF-Based ART	Difference, ZDV-Based ART and TDF-Based ART vs. ZDV Alone	P Value for Interaction
	no. of mother–infant sets/total no. (%)			*percentage points (repeated CI)*	
All mother–infant sets	25/1386 (1.8)	7/1385 (0.5)	2/325 (0.6)	−1.3 (−2.1 to −0.4)	
Maternal gestational age at trial entry†					0.68
<34 wk	16/1229 (1.3)	6/1230 (0.5)	1/274 (0.4)	−0.8 (−1.6 to −0.1)	
≥34 wk	9/157 (5.7)	1/154 (0.6)	1/51 (2.0)	−4.8 (−8.9 to −0.6)	
Maternal CD4 count at trial entry					0.70
350–499 cells/mm^3	16/577 (2.8)	4/592 (0.7)	1/136 (0.7)	−2.1 (−3.7 to −0.5)	
≥500 cells/mm^3	9/809 (1.1)	3/793 (0.4)	1/189 (0.5)	−0.7 (−1.6 to 0.2)	
Maternal viral load at trial entry					0.22
<1000 copies/ml	0/299	1/253 (0.4)	0/57	0.3 (−0.4 to 1.0)	
≥1000 copies/ml	25/1083 (2.3)	6/1129 (0.5)	2/268 (0.7)	−1.7 (−2.8 to −0.7)	
Missing data	4	3	0		

Fowler, M.G. et al. N Engl J Med. 2016 Nov 3;375(18):1726-1737

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What are Important Study Design Considerations for Future Efficacy Trials?

- Estimand framework can provide structure for outlining important study design considerations
  - What **treatment** is being evaluated?
  - What is the **target population**?
  - How is the **treatment effect** measured?
  - What is the desired **population-level summary measure**?

IMPAACT Template: Estimand Table

Clinical Question	
Attributes Describing the Estimand	
Treatment	
Population of Interest	
Variable	
Handling of Intercurrent Events	
Population Level Summary	

ICH E9 statistical principles for clinical trials - Scientific guideline | European Medicines Agency (EMA). 1998; published online Sept 1. https://www.ema.europa.eu/en/ich-e9-statistical-principles-clinical-trials-scientific-guideline

Research C for DE and. E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials. 2021; published online May 11. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9r1-statistical-principles-clinical-trials-addendum-estimands-and-sensitivity-analysis-clinical

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What Treatment Strategy Do We Want to Evaluate?

- What is the appropriate control?
  - Standard of care (SOC)
  - Potential SOC changes over time and assessing potential implications
  - Mechanisms of administration and blinding
- Should the candidate intervention be evaluated in tandem with SOC or not?
  - Incremental effectiveness versus stand-alone benefit
  - Ethical considerations

Defining the Trial Population in Efficacy Trials

- Two important questions to determine efficacy trial population:
  - Who is likely to receive the intervention in the future?
  - What are the practical limitations of implementing the study?

- Priority population:
  - All HIV-1 exposed infants at risk of HIV acquisition; or
  - Restricted population (e.g., participants with higher-risk profile)
    - May be more practical, given smaller sample size requirement
    - Intervention may be more effective within certain subgroups due to accessibility or acceptability considerations that lead to better uptake and/or adherence
    - Cannot generalize to broader population

How is the Treatment Effect Measured?

- HIV-1 acquisition
  - Rare event
  - Large sample size required
- HIV-1 acquisition and/or death
  - More cumulative events
  - Added noise if deaths not attributable to HIV-1 or study product
- Surrogate outcomes
  - Direct, infant-level biomarkers predictive of HIV acquisition
  - No such marker current exists

What is the Desired Population-Level Summary Measure?

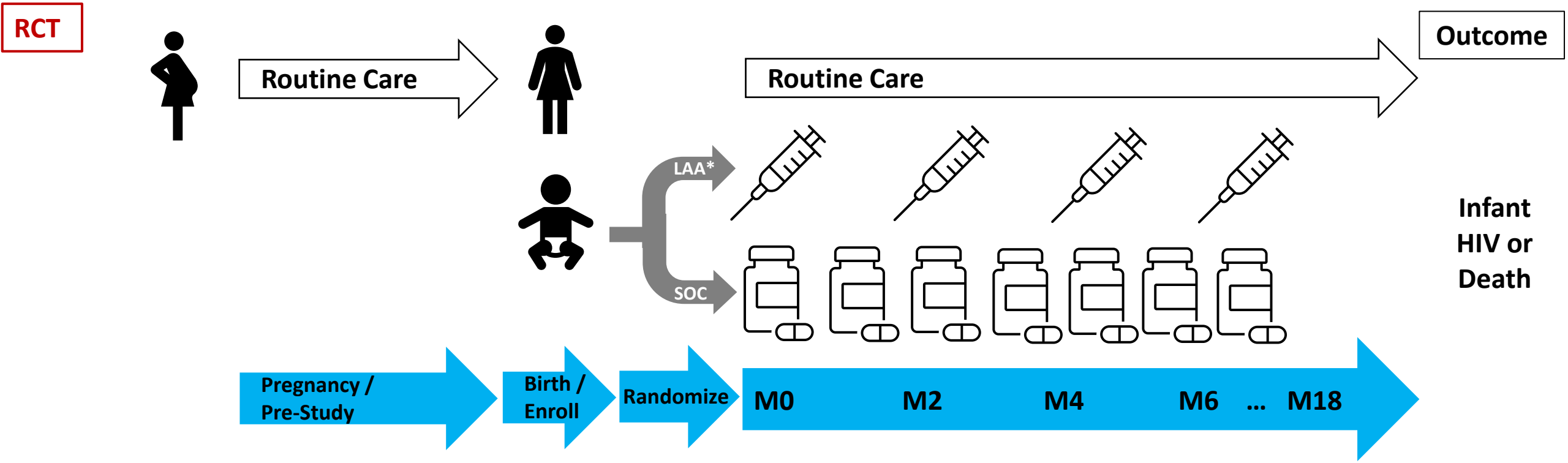
- Specific by-arm statistics, regression models, and statistical tests used to make comparisons will be dependent on how the outcome of interest is measured

- Examples:
  - Probability of event through a fixed time point for each arm and ratio of probabilities between arms
  - Instantaneous risk (i.e., hazard) of event between arms to account for timing of events

- Other considerations
  - Accounting for loss to follow-up
  - Accounting for death as competing risk
  - Quantify uncertainty to facilitate interpretations regarding statistical and clinical significance

Revisiting the Study Design Framework

Traditional RCT Study Design (Internal Control Group)



Would a traditional RCT be feasible and efficient?

*LAA = long-acting agent

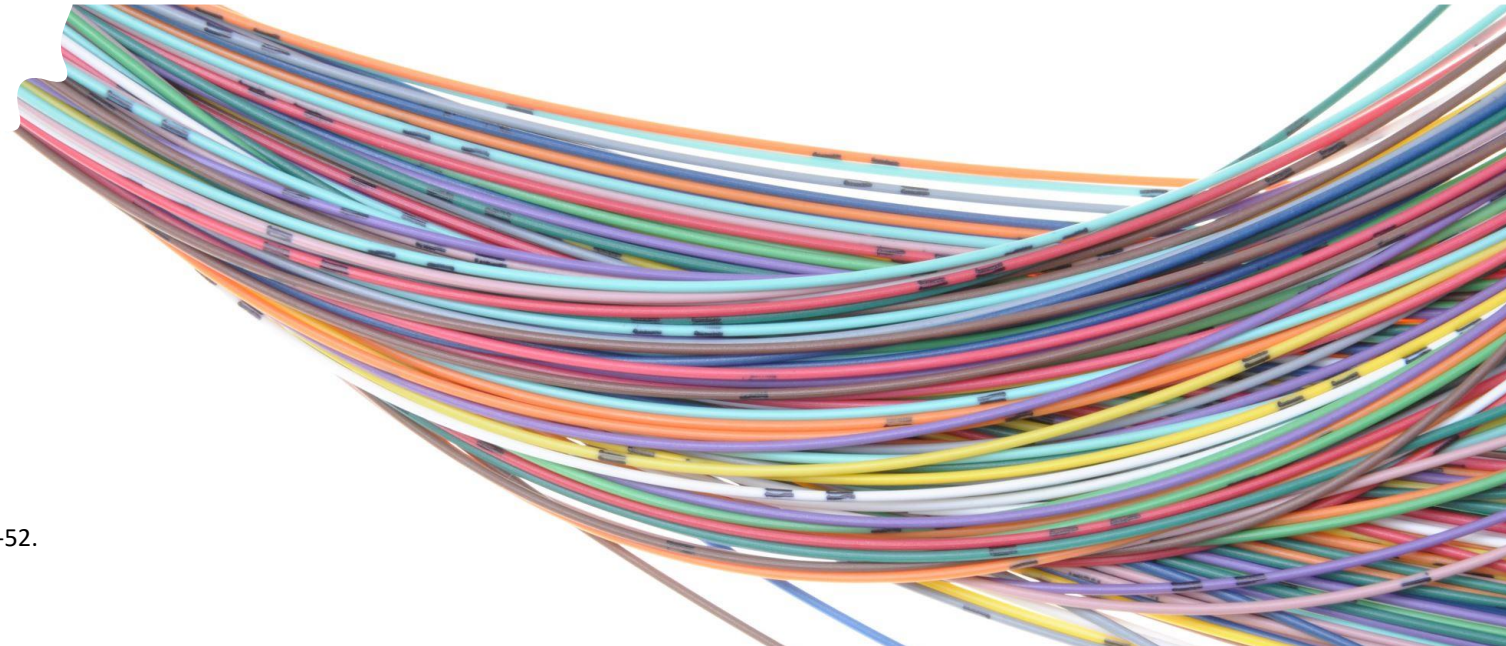
Alternative Trial Designs may Provide a Path Forward

- Regulatory guidance requires efficacy trials for infant postnatal prophylaxis:
  - **May not extrapolate** efficacy from adult horizontal transmission trials
- Traditional efficacy trials would require prohibitively large sample sizes and resources
- Alternative designs for HIV prevention have precedent in the lenacapavir PrEP registrational trial design
- Fusion designs allow bridging of randomized clinical trials with observational cohorts
  - Both internal (randomized) and external (observational) control groups

Breskin, A. *et al.* (2021) *Stat Med* 40, 3124-3137. 10.1002/sim.8963.
Cole, S.R. *et al.* (2023) *Am J Epidemiol.* 192, 467-474. 10.1093/aje/kwac067.y.
Dahabreh IJ *et al*. (2019) *Biometrics* 2019; 75(2): 685-94.
Lee, D. *et al.* (2023) *Biometrics* 2023;79(2):1213-1225.

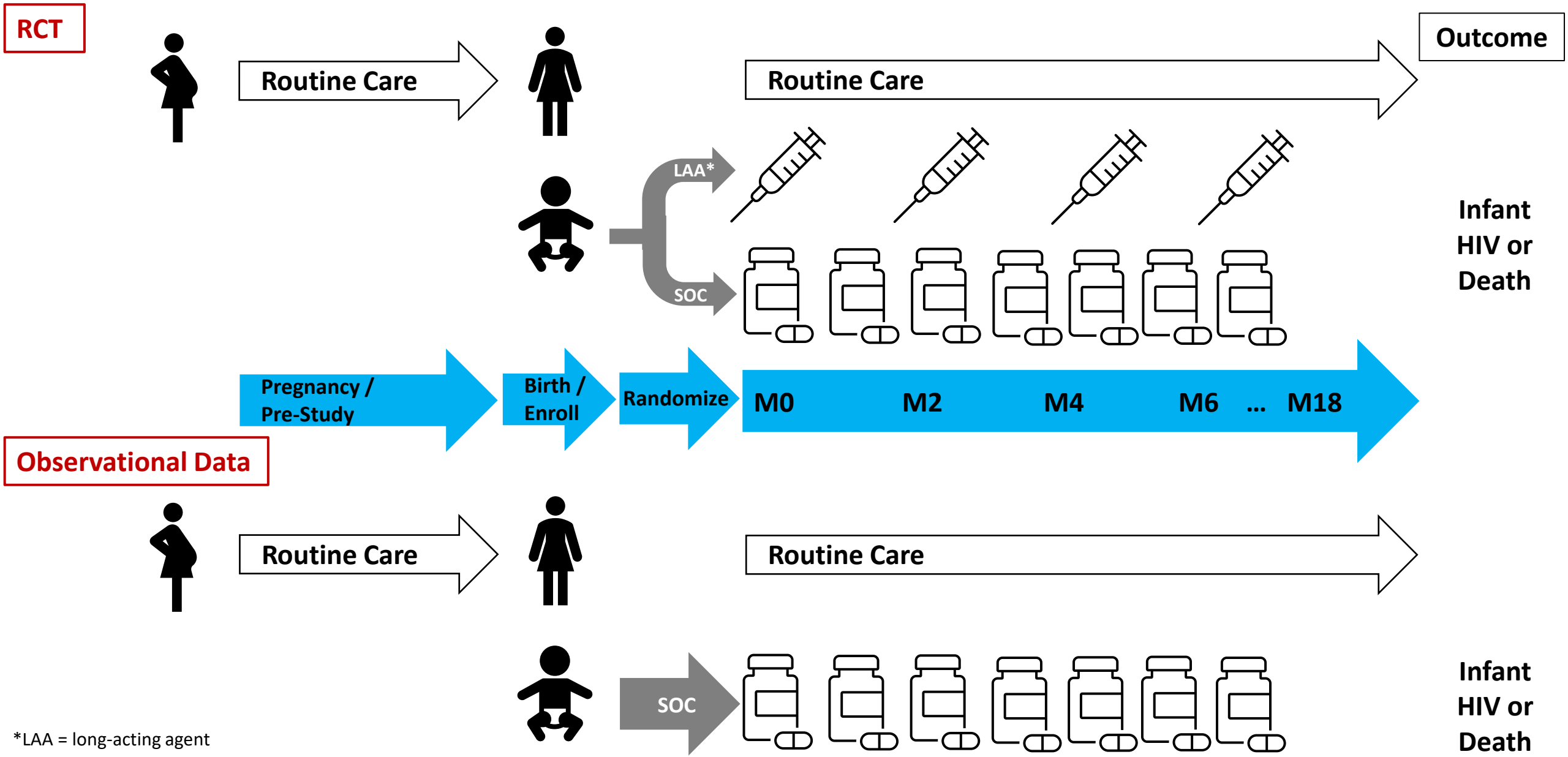
Intro to Fusion Designs

- “Data fusion” combines multiple heterogeneous datasets
- Fusion designs structured by a causal inference framework
- Common feature of fusion estimators is “transportability”
- Fusion estimator is a mathematical solution to the research question



Bareinboim E., Pearl J. (2016) Proc Natl Acad Sci U S A. 2016 Jul 5;113(27):7345-52.
Breskin, A. *et al.* (2021) *Stat Med* 40, 3124-3137. 10.1002/sim.8963.
Cole, S.R. *et al.* (2023) *Am J Epidemiol.* 192, 467-474. 10.1093/aje/kwac067.y.

Fusion Study Design (Internal & External Control Groups)



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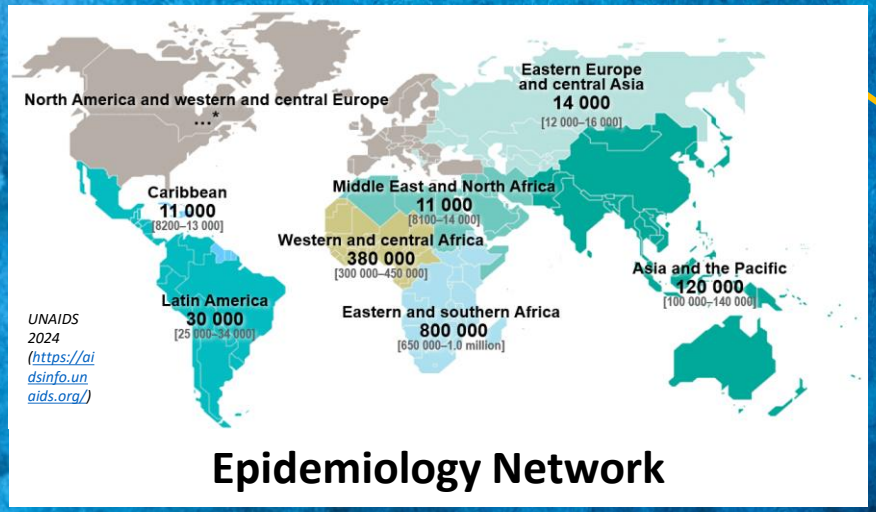

Epidemiology Network

Data Science & Harmonization

Clinical trial of HIV prevention Integrating Leveraged Data

Study Design & Analytical Methods

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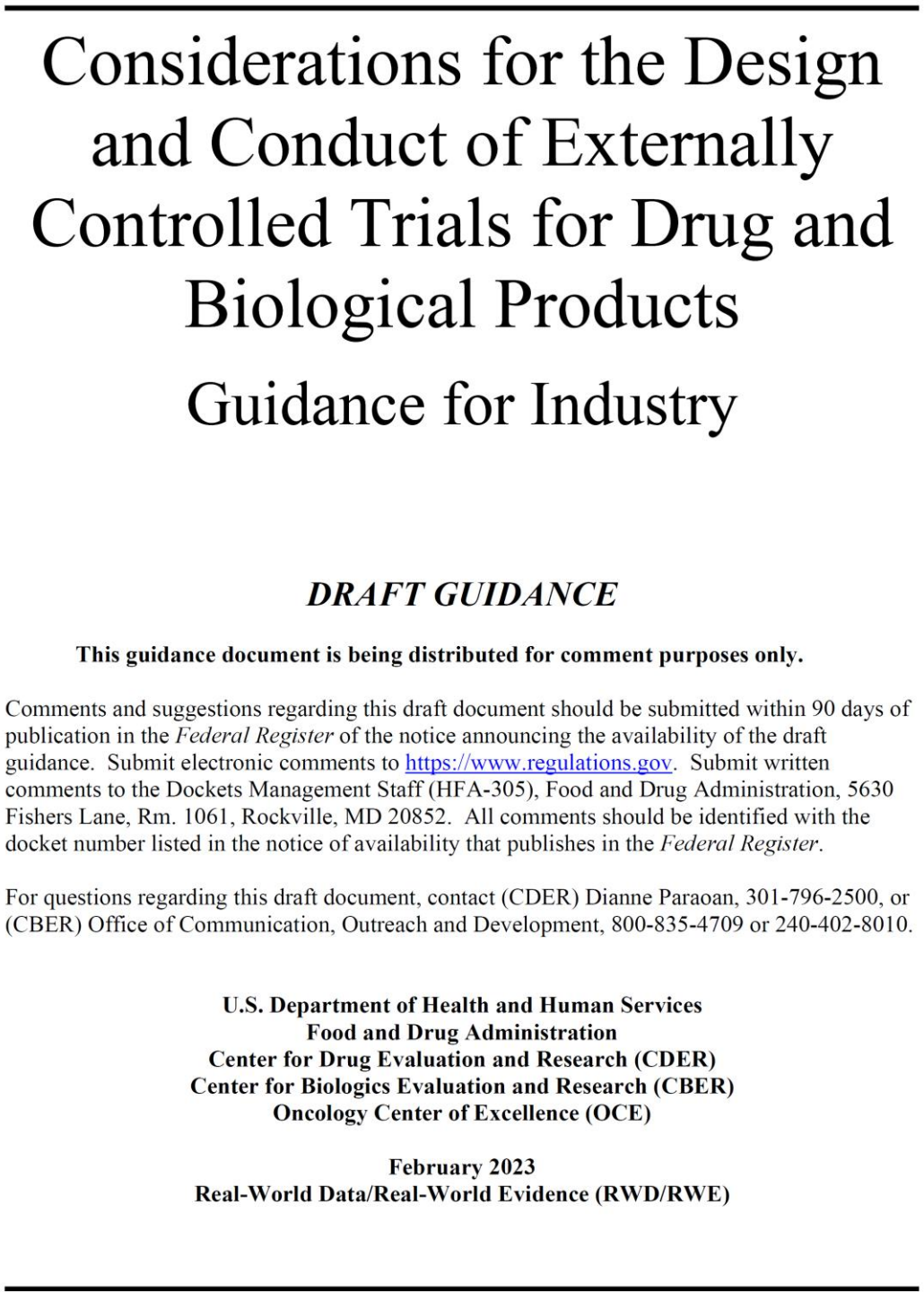

Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Dianne Paraoan, 301-796-2500, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

February 2023
Real-World Data/Real-World Evidence (RWD/RWE)

FRAMEWORK FOR FDA'S

REAL-WORLD EVIDENCE PROGRAM

- "Nevertheless, for decades the FDA has recognized the **potential value of other types of controls**, including historical controls as a type of **external control**. Clinical trials using these other types of controls can, when appropriate, serve as the **adequate well-controlled clinical investigations** generally required to provide **substantial evidence of effectiveness** under section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)."

- "Finally, this guidance also **does not discuss** considerations for using **external control data to supplement a control arm** in a traditional randomized controlled clinical trial."

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Pooling Data from Multiple Sources: a Statistical Overview

Generalizability and Transportability

- Generalizability
  - Generalize findings from study population to population of interest
  - Assume study population is randomly selected from population of interest
- Transportability
  - Extend findings from study population to population of interest
  - Assume study population overlaps with population of interest, but is not a random sample

Fusion Estimators

- **Goal:** Analytical strategy that allows for differences in underlying RCT and observational cohort populations, as long as there is overlap and the differences are identifiable

- **Solution:** Fusion Estimators
  - Inspired by transportability methods:

  - Re-weight each participant in observational cohort
    - Upweight participants who are underrepresented in observational cohort relative to RCT
    - Downweight participants who are overrepresented
  - Calculate population-level summary measures, accounting for these participant-specific weights

Cole SR, Stuart EA. Am J Epidemiol. 2010;172(1):107–115.
Westreich, D. et al. Am J Epidemiol. 2017 Oct 15;186(8):1010-1014.
Breskin, A. *et al. Stat Med* 2021 Jun 15;40(13):3124-3137.
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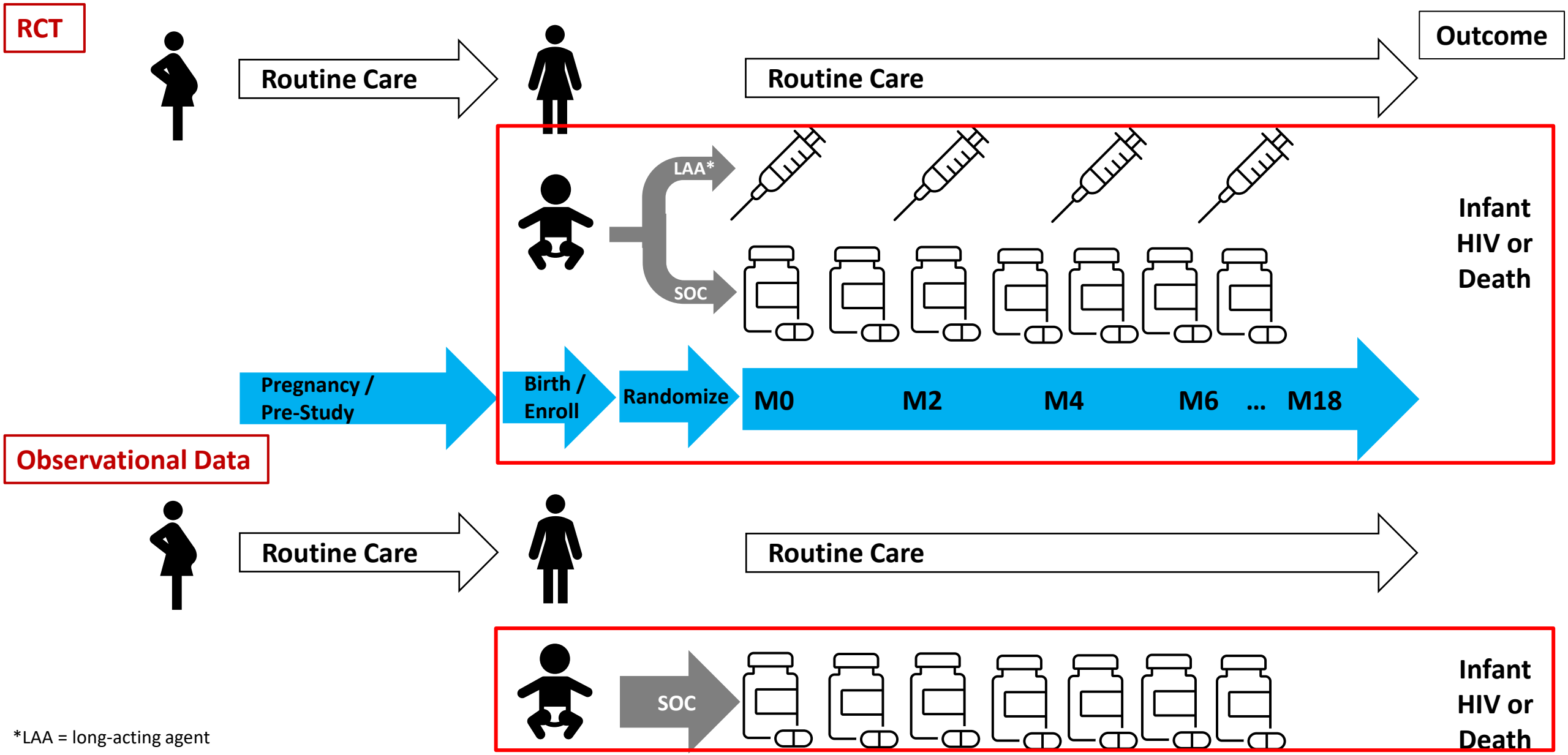
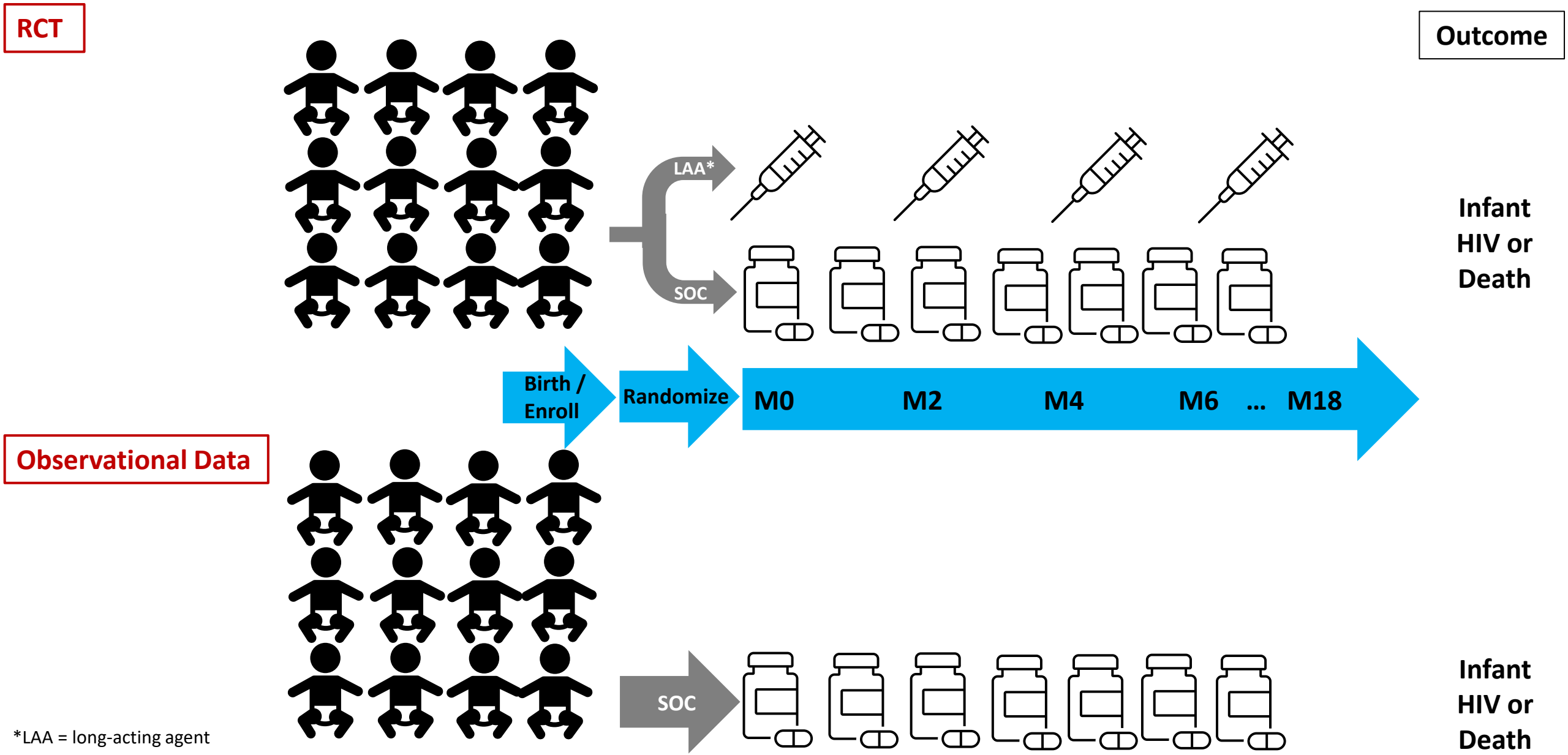


*LAA = long-acting agent

Infant Enrollment in RCT and Observational Cohorts



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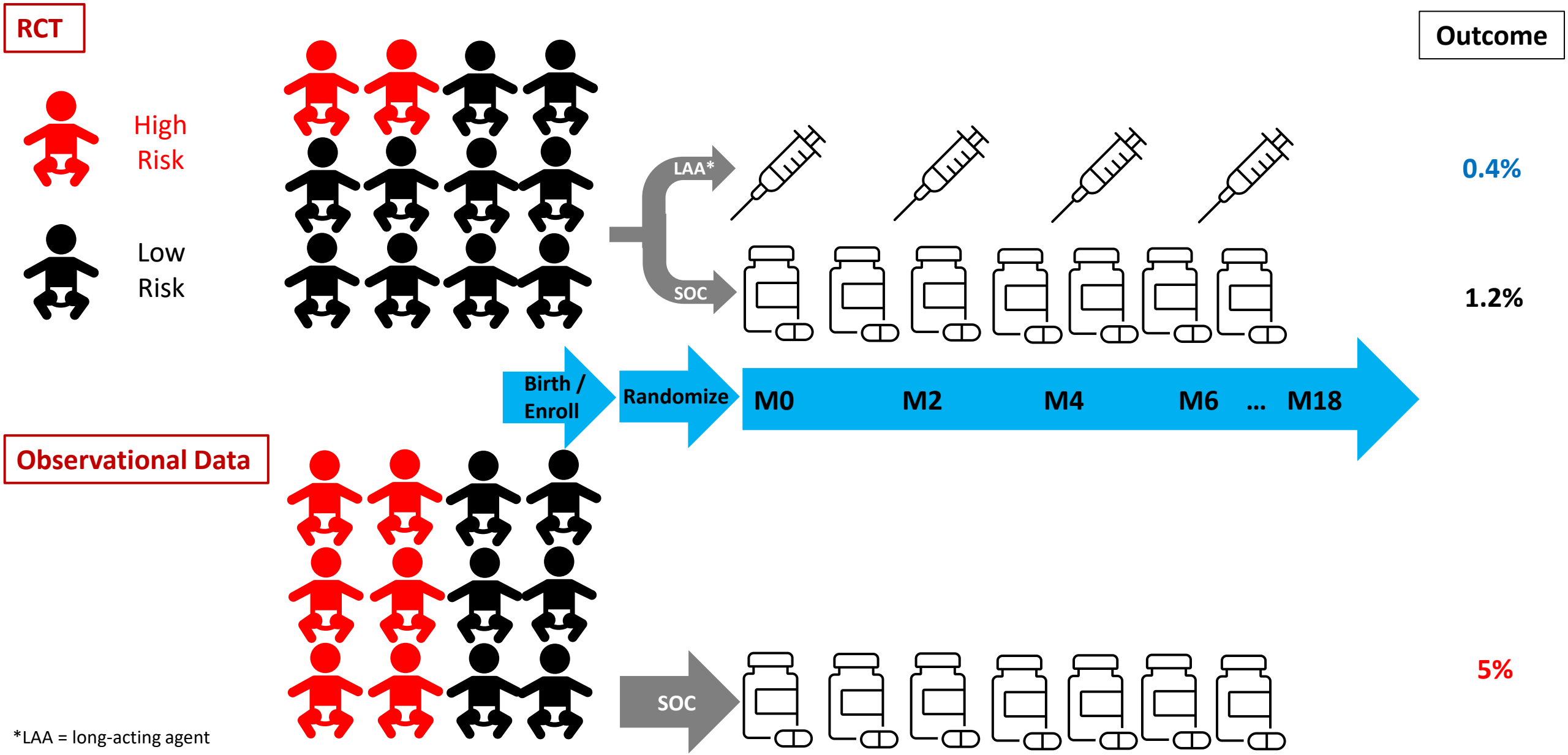
Imbalanced Baseline HIV Acquisition Risk



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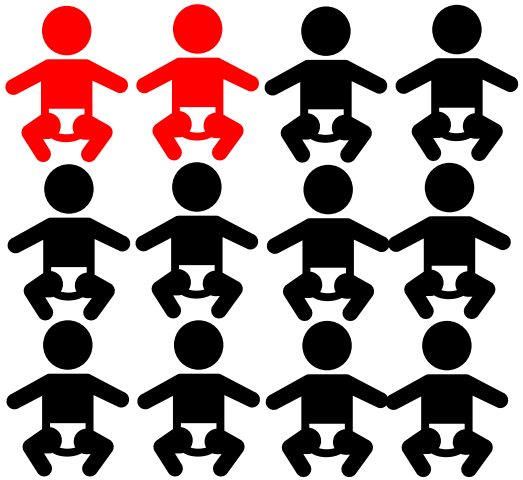
Balanced Baseline HIV Acquisition Risk with Standardization

RCT

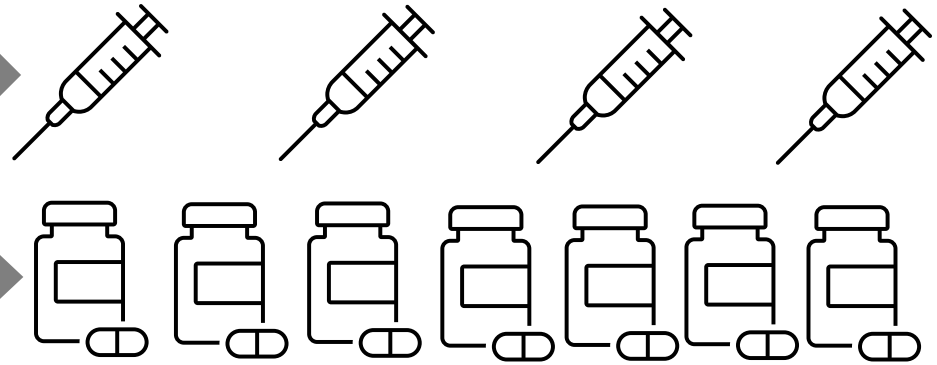
High Risk

Low Risk



LAA*

SOC



Outcome

0.4%

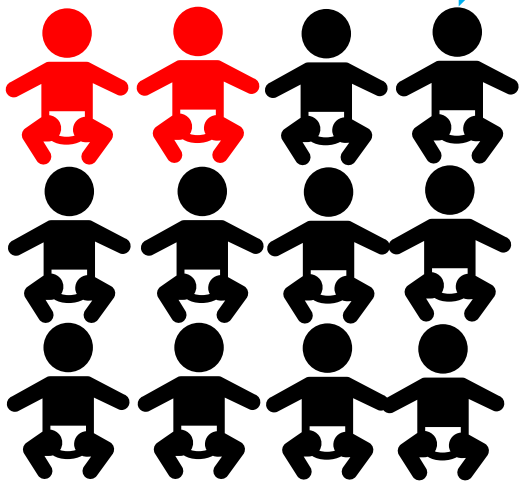
1.2%

Birth / Enroll

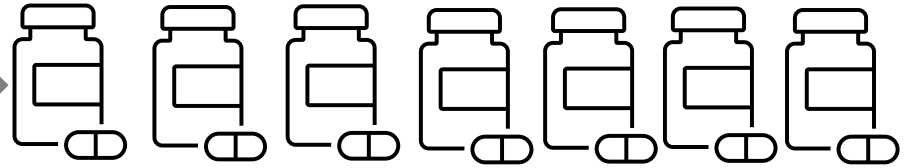
Randomize

M0 **M2** **M4** **M6** … **M18**

Observational Data



SOC

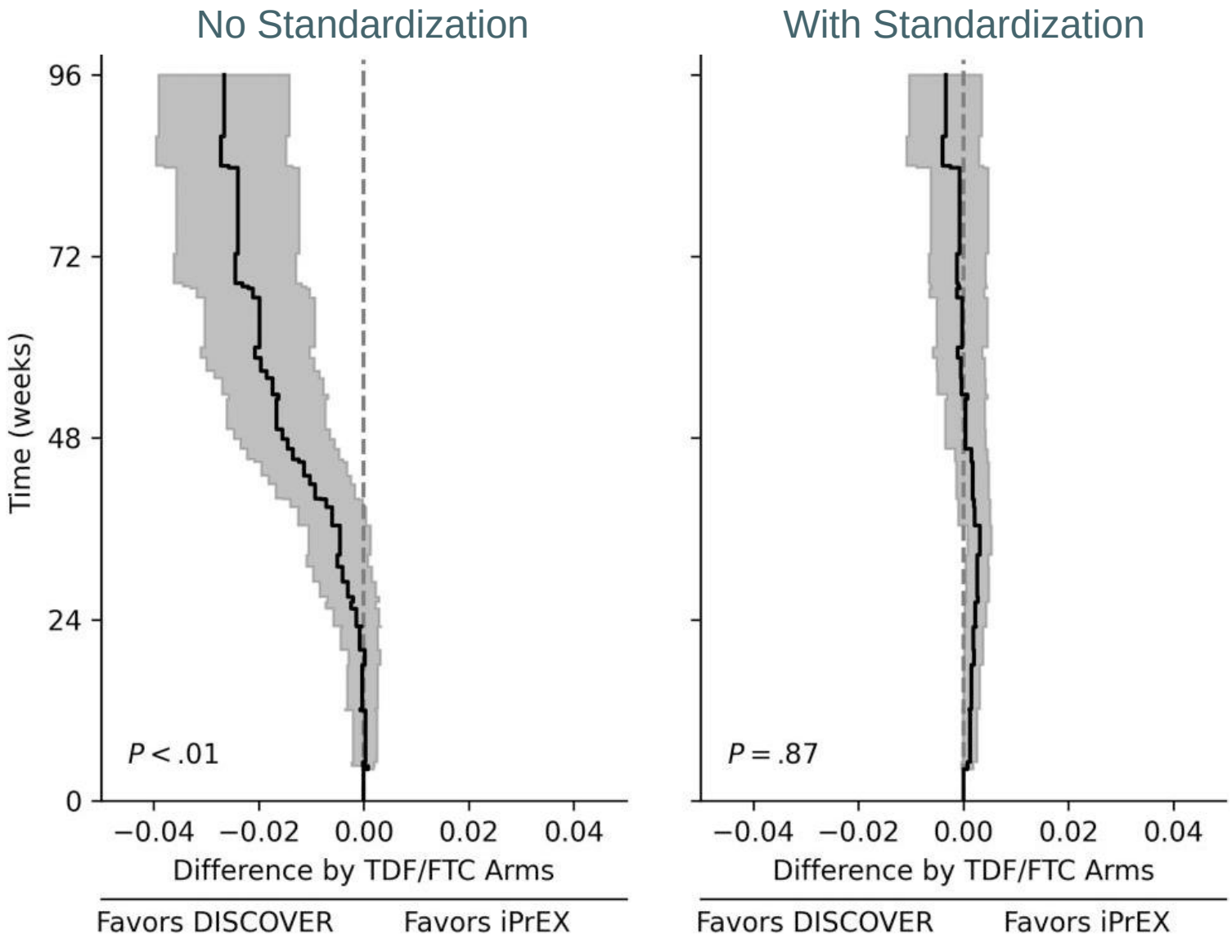


1.2%

*LAA = long-acting agent

Fusion Design Test-and-Pool Diagnostic

- Regulatory study should demonstrate that RCT and observational arms meet criteria for “pooling”
- Common approach is testing for “poolability” and combining if criteria met
- Fusion design diagnostic approach developed
- Limitation: Can only be done after a study starts

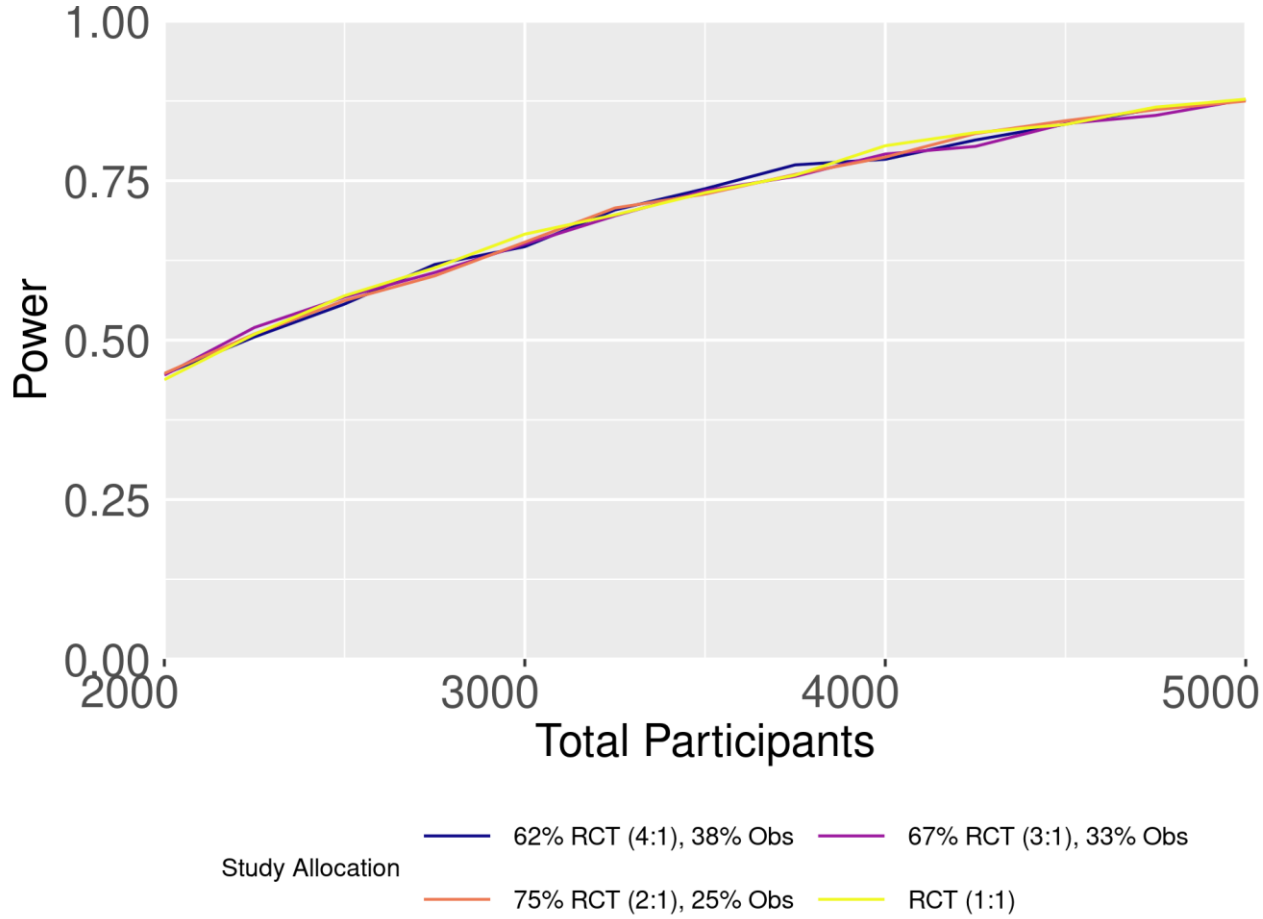


Zivich, P. et al. *J Infect Dis*. 2024 Apr 12;229(4):1123-1130.
Zivich, P. et al. *Am J Epidemiol.* 2024 Aug 31:kwae340.

Study Size and Final Thoughts

Fusion Studies Would Allow for Fewer RCT Participants

- Classic RCT (1:1)
  - Projected Sample Size*: ~4000 participants (2000 treatment, 2000 control)
- Fusion trial
  - RCT component (2:1)
    - n=3000 (2000 treatment, 1000 control)
    - 5% with higher risk for HIV acquisition
  - Observational Cohort component (0:1)
    - n=1000 (all control)
    - 20% with higher risk of HIV acquisition
  - Small loss of power (1-2%) if weights account for all confounders (e.g., risk status)



*Assuming study with 80% power and 5% type I error rate to detect 66% reduction in HIV acquisition or death (1.2% vs. 0.4%), with 10% loss to follow-up rate

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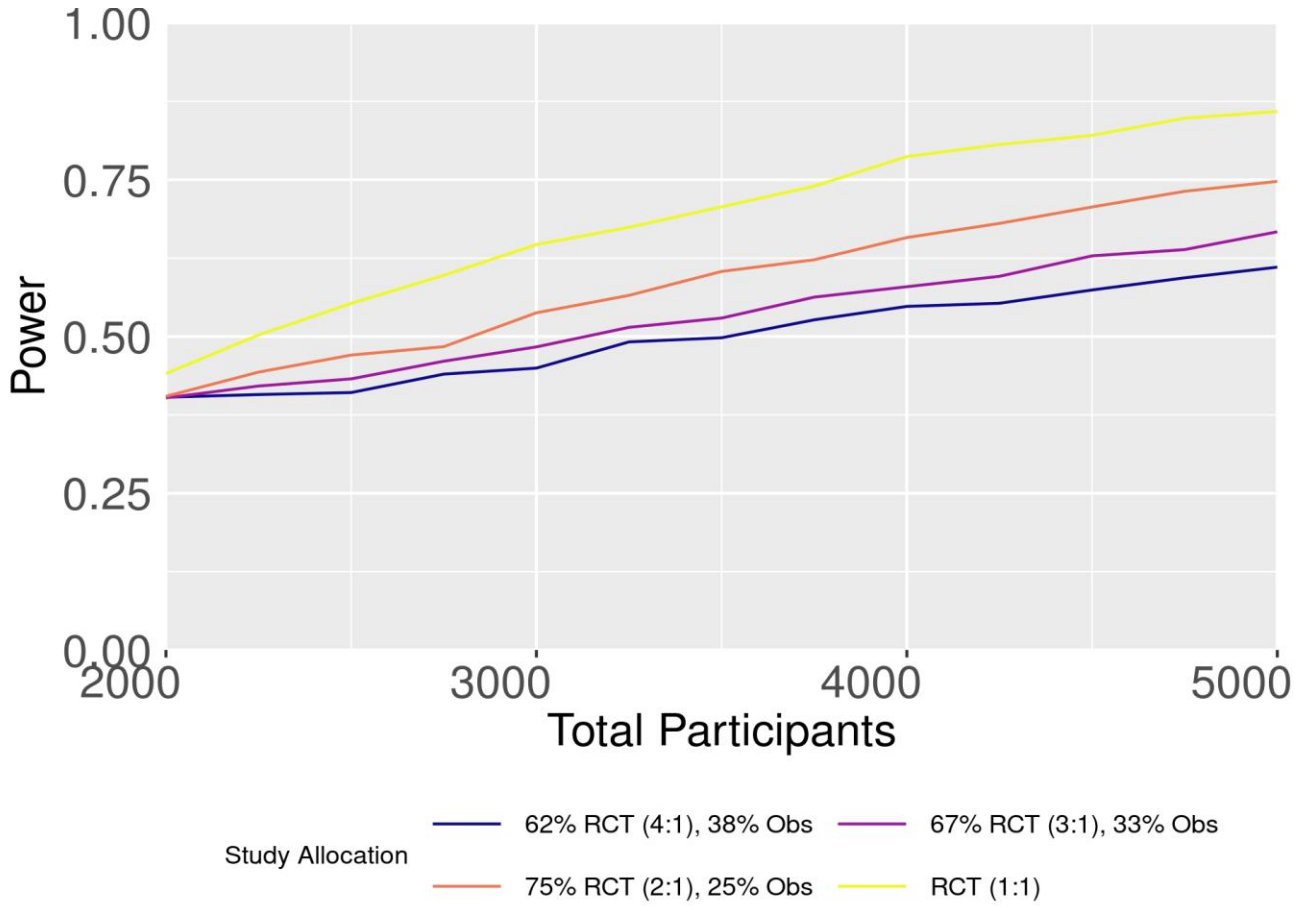
What if Discrepancies Between RCT and Observational Cohort are Unknown?

- Fusion estimator may provide biased results if discrepancies between data sources are due to unmeasured confounders

- Worst case scenario:
  - Analyze RCT data only
  - Less likely to observe treatment effect if truly present (i.e., power reduction)



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Limitations and Potential Mitigation Strategies

Limitations

- Divergence of SOC practices between RCT and observational sites
- Infeasibility of enrollment
- Unmeasured variables affecting enrollment and outcome
- Differential post-enrollment interventions affecting outcome
- Missing data
- Loss to follow-up
- Lack of poolability

Mitigation Strategies

- Collaborative planning on protocol and data collection between IMPAACT and epidemiology network
- Site selection to optimize overlap, esp. by country or guideline areas
- Pilot study using retrospective data
- Prospective observational cohort
- Prospectively plan retention measures in both RCT and observational cohorts, e.g. compensation for visit attendance
- Pooling diagnostic
- Adaptive pooling strategy

Next Steps

- Applying data fusion methods to combine data from multiple IMPAACT trials to estimate postnatal prophylaxis efficacy
- Pilot study using retrospective clinical trial data from IMPAACT and observational data from an external epidemiology network
- NIH workshop on innovative study design and analysis approaches for prevention of HIV-1 vertical transmission
- Form an inter-network methods working group
- Engage Community and Ethics
- Engage external stakeholders (epidemiology network, FDA, EMA, guideline leaders, pharmaceutical partners)

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Summary and Conclusions

- Infant postnatal prophylaxis offers an opportunity to prevent HIV-1 acquisition and a key safety net until universal maternal ART is achieved
- Efficacy studies are necessary to develop long-acting agents for use in postnatal prophylaxis
- Traditional RCTs may not be feasible
- Fusion designs may provide an innovative study design combining RCT and observational components
- Fusion designs present a separate set of challenges that might be mitigated with good planning

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THANKS!

Any questions?

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Fusion Estimators

Inverse Odds of Sampling Weights (IOSW)

Formula for calculating weights for each participant (i) who enrolled in the RCT or the observational cohort

$$Weight_i = \begin{cases} \dfrac{\Pr(RCT_i \mid X_i)}{\Pr(Obs_i \mid X_i)} \; X \; \dfrac{\Pr(Obs_i)}{\Pr(RCT_i)}, & Obs_i = Yes \\ 1, & RCT_i = Yes \end{cases}$$

Cole SR, Stuart EA. Am J Epidemiol. 2010;172(1):107–115.
Bareinboim E, Pearl J. J Causal Inference. 2013;1(1):107–134.
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Cole, S.R. *et al.* (2023) *Am J Epidemiol.* 2023 Feb 24;192(3):467-474.

FRAMEWORK FOR FDA'S

REAL-WORLD EVIDENCE PROGRAM

Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Tala Fakhouri, 301-837-7407, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

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Real World Data/Real World Evidence (RWD/RWE)

Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

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Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

Data Standards for Drug and Biological Product Submissions Containing Real-World Data

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