Statistical Issues in IMPAACT Studies

David Shapiro, Ph.D.
IMPAACT Statistical and Data Management Center

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HARVARD T.H. CHAN
SCHOOL OF PUBLIC HEALTH

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Outline

- Design issues in cluster randomized trials
- Analysis issue: Immortal time bias

IMPAACT Cluster Randomized Trials

- IMPAACT 2002: Combined Cognitive Behavioral Therapy and a Medication Management Algorithm for Treatment of Depression
  - Sites will be randomized to provide the CBT/MM intervention or enhanced standard of care

- PHOENIx: Trial of MDR-TB Prevention in Households
  - Households will be randomized to Delamanid or INH

Why Cluster Randomization?

- Reduce risk of "spill-over" of the study intervention:
  - IMPAACT 2002: Difficult for clinicians to provide CBT/MM to some patients and enhanced standard of care to others in same clinic
    - loss in fidelity of intervention and control
    - cross-talk between patients in the two arms
  - PHOENIx: Problematic to provide delamanid to one contact and INH to another contact in the same household.

Cluster Randomized Trial Design Issues

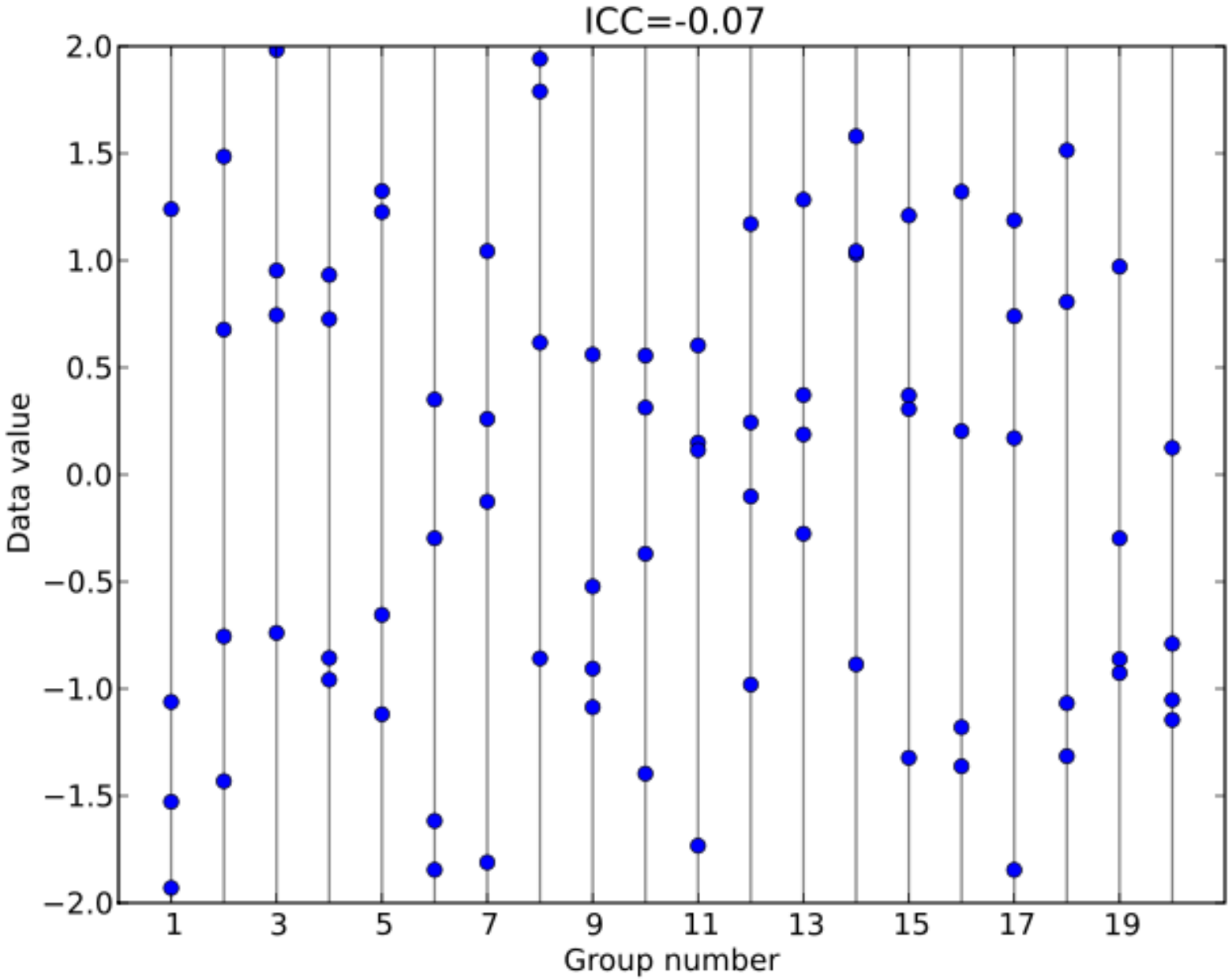
- Sample size requirements
- Balancing participant and site characteristics
- Avoiding selection bias

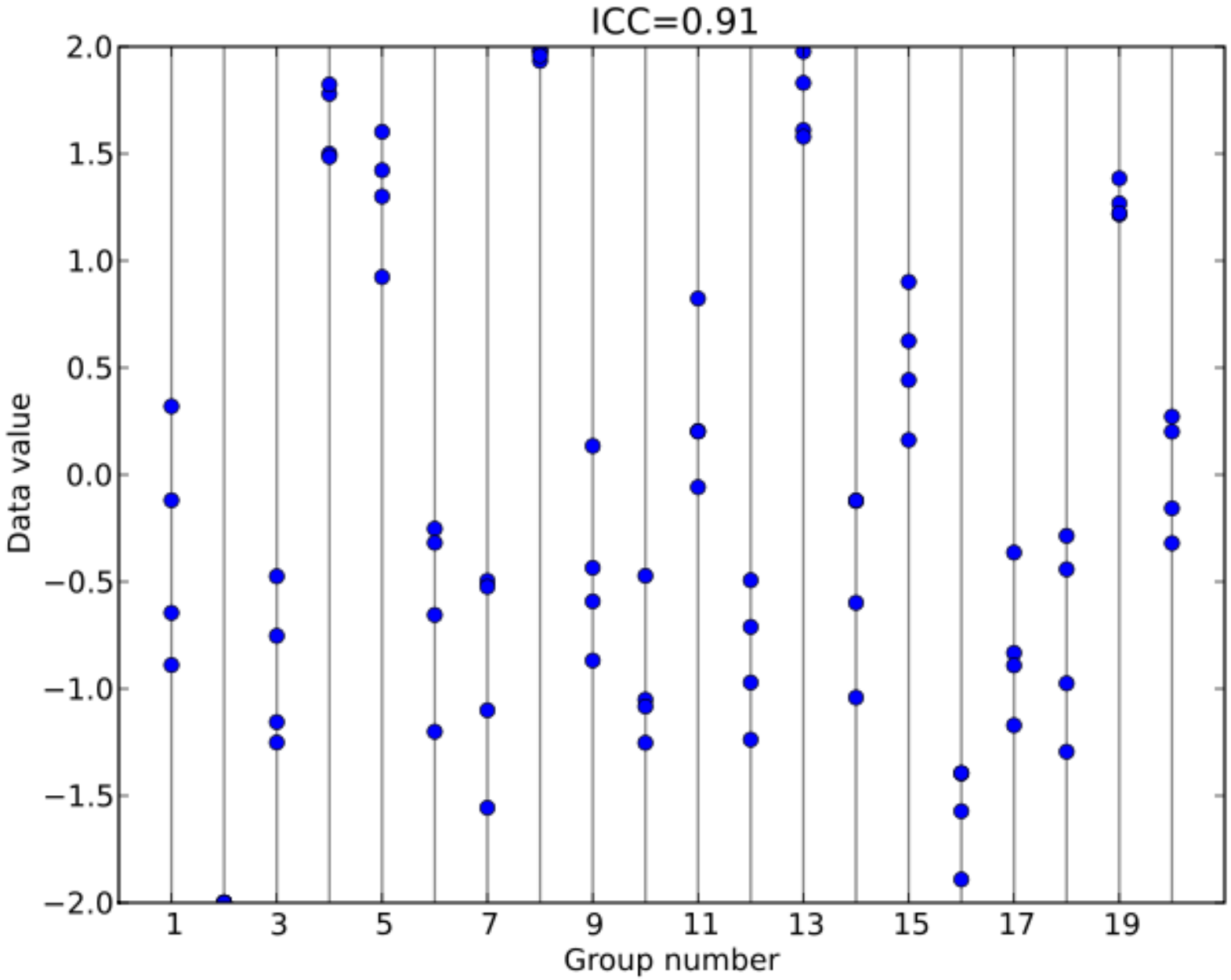
Sample Size Requirements

- Need larger sample size than individual-randomized trial
- Observations within clusters (sites or households) are potentially correlated
- Correlation reduces the amount of information provided by each individual participant
- Measure: Intracluster correlation coefficient (ICC)

  ICC = (between cluster variation) / (total variation)

- ICC = 0: no correlation; ICC = 1: perfect correlation





Source: Created by Skbkekas - Own work This graphic was created with matplotlib., CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=6982852

Sample Size Calculations

- Calculate sample size for individual-randomized trial and multiply by a factor called the "design effect"
- DE depends on ICC and average cluster size (m)

"Design Effect" = DE = 1+(m-1)ICC

- Better to have more clusters with fewer participants per cluster

$$\mathbf{SampleSize_{CRT} = SampleSize_{RT} * DE}$$

CRT= Cluster randomized trial; RT = Individual-randomized trial

Target Sample Sizes

- IMPAACT 2002: 156 participants from 14 sites, assuming an average of 11 per site
  - Design effect: 2.35 (ICC 0.15)
- PHOENIx: 3452 high risk household contacts from 1726 households, assuming an average of 2 contacts per household
  - Design effect: 1.2 (ICC 0.15)

Cluster Randomized Trial Design Issues

- Sample size requirements
- Balancing participant and site characteristics
- Avoiding selection bias

Imbalance Complicates Interpretation

- Example: Prior cluster randomized trial in HIV+ youth: Adolescent Trials Network (ATN) 080*:
  - 4 sites randomized to either 24 weeks of combination treatment (COMB) or treatment as usual (TAU)
  - 44 participants with moderate to severe depression
    - 69% male (COMB 95%, TAU 40%)

*Brown L et al. J Acquir Immune Defic Syndr, 2016 Jan;71(1):38-46.

IMPAACT 2002 Randomization

- Designed to balance key characteristics of site populations

1. Pre-study survey: 4 sites: primarily behaviorally HIV-infected; 4 sites: large numbers; 6 sites approximately balanced (gender and age well-balanced within above groupings)

2. Before randomization: Sites will identify potentially eligible participants and will submit summary information on sex, age, mode of HIV acquisition, viral load suppression, depression severity status

IMPAACT 2002 Randomization

3. Restricted Randomization*: Computer program will generate all possible site allocations that meet balance criteria, and then will select one randomly

**Hayes RJ, Moulton LH. Cluster Randomised Trials: Taylor & Francis; 2009.*

Cluster Randomized Trial Design Issues

- Sample size requirements
- Balancing participant and site characteristics
- Avoiding selection bias

Selection Bias

- Arises if not all potentially eligible patients are approached or participate
- Big concern in cluster-randomized trials where individuals are enrolled after randomization

Selection Bias

- Example*: 26 primary care practices randomized to active management (AM) vs. traditional management (TM) of back pain

- AM practices identified and recruited more than twice as many participants as TM practices, and characteristics of AM vs. TM participants differed

*Farrin A. et al. Clinical Trials 2005; 2: 119-124

IMPAACT 2002 Accrual Procedures

1. Site creates list of all potentially eligible youth and obtains screening numbers

2. SDMC will randomly order all of the screening numbers within each site into blocks.

3. Site may start screening and enrolling anyone from their first block of screening numbers. After all patients from the block are enrolled or have been approached but will not enroll into the study (for any reason), site may approach patients from next block.

IMPAACT 2002 Accrual Procedures

4. Screening Failure Result Form will collect reasons for not enrolling and key characteristics.
   - This will permit comparisons of those enrolled versus those not enrolled, to assess potential selection bias.

Analysis Issue: Immortal Time Bias (a.k.a. Survivor Bias)

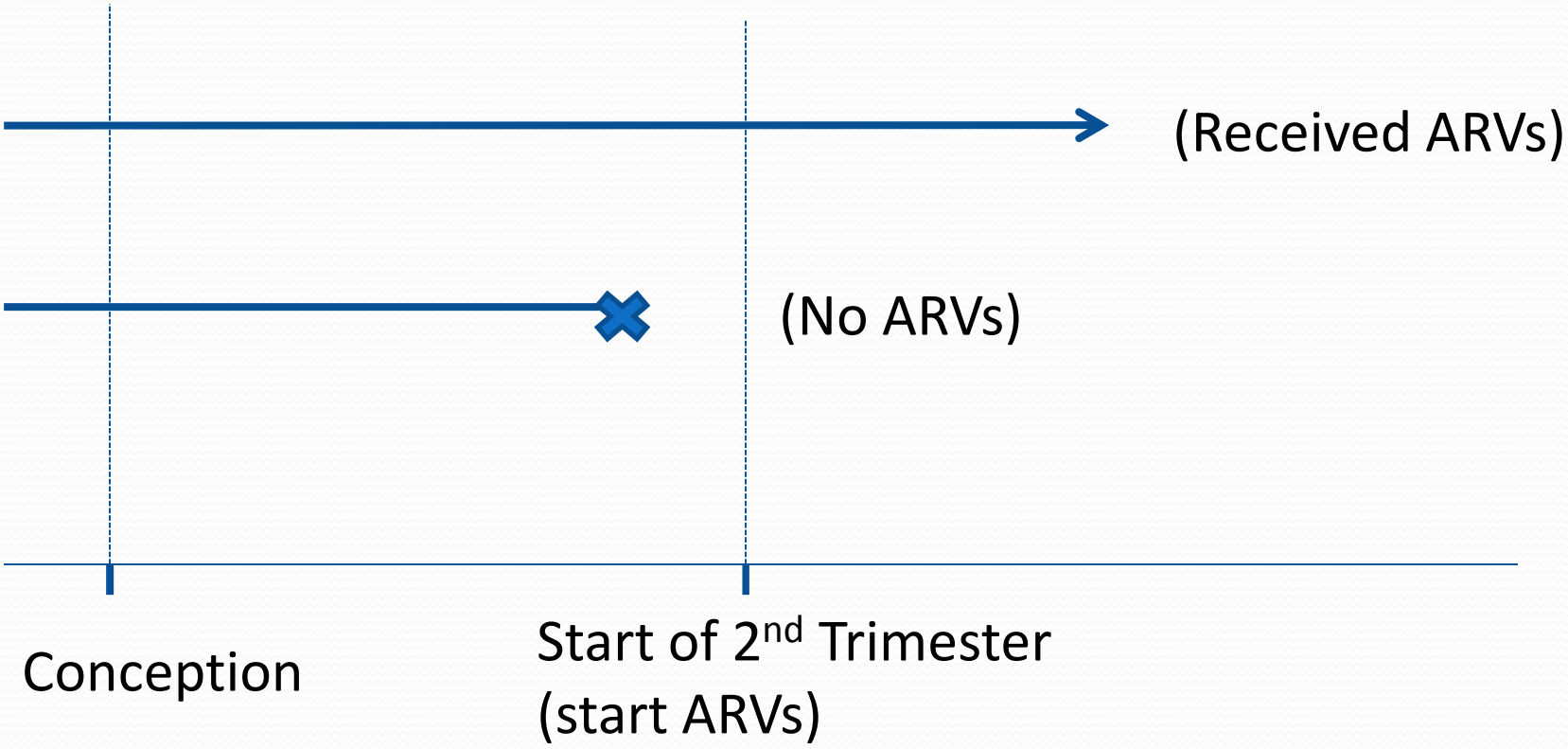
- Setting: PROMISE 1077HS women randomized to stop or continue triple antiretrovirals (ARV) after delivery, and then subsequently become pregnant

- Goal: Compare pregnancy outcomes according to ARV regimen received during the subsequent pregnancy

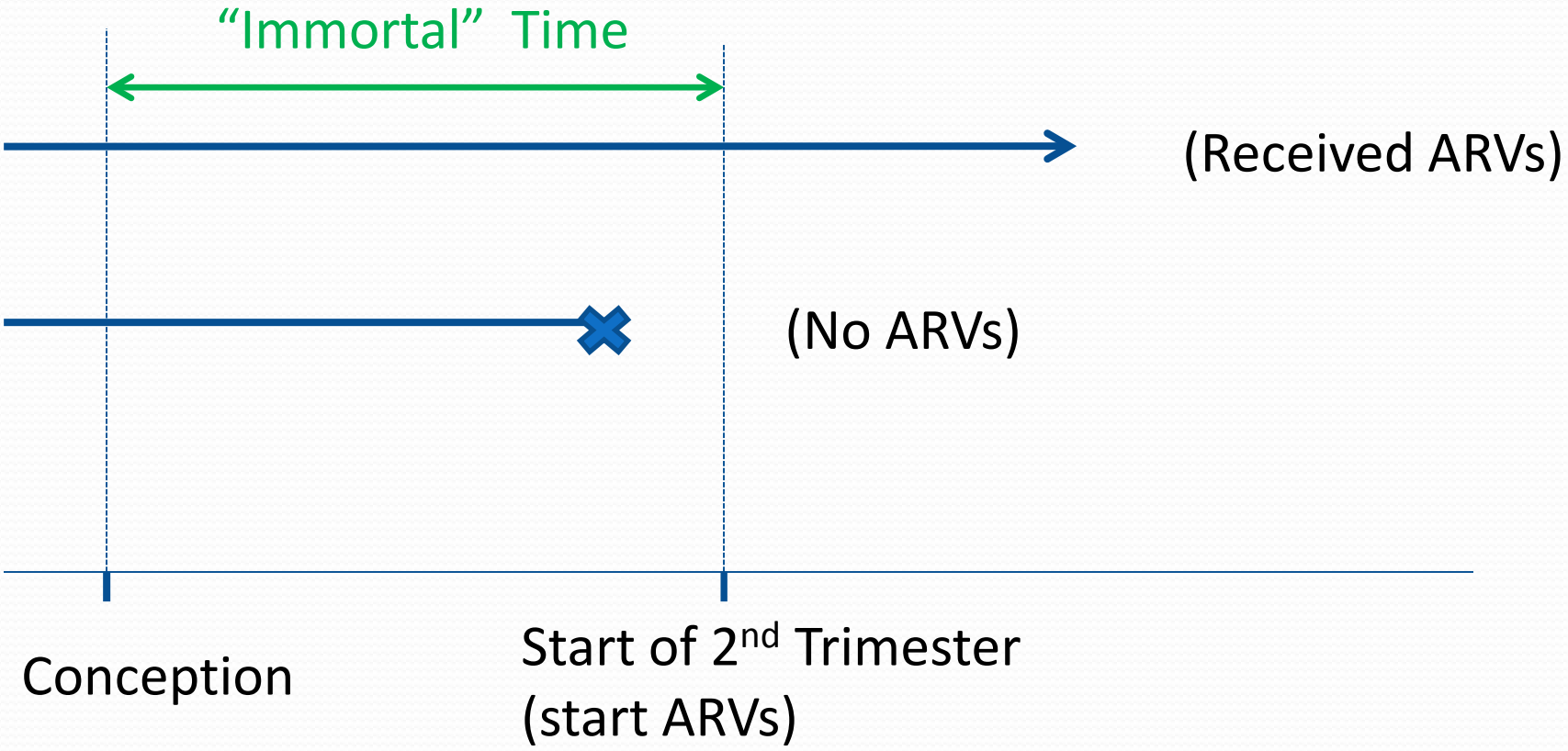
Immortal Time Bias

- Women off ARVs may not restart ARVs until 2nd trimester
- Women who had an adverse pregnancy outcome before restarting ARV are included in the "no ARV" group
- Women who received ARVs necessarily did not have an adverse pregnancy outcome before starting ARVs
  - The time period before starting ARVs is "immortal time" (event could not have occurred).
- Comparing outcomes with ARVs vs. no ARVs can produce a strong "significant" benefit of ARV, which is spurious

Immortal Time Bias



Immortal Time Bias



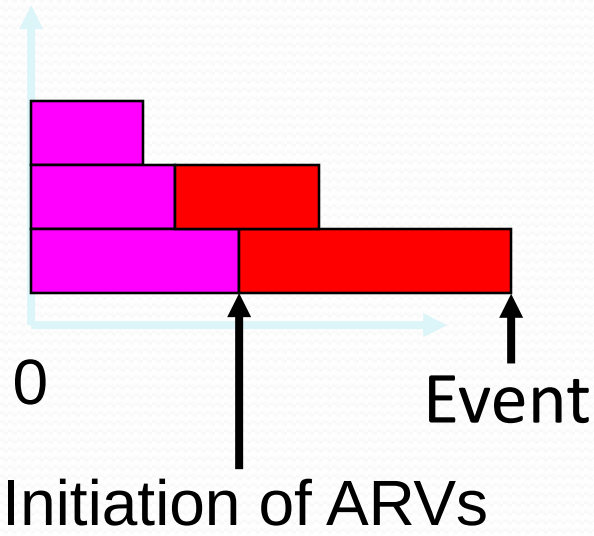
Immortal Time Bias

- Many examples of this bias have been identified in diverse observational study settings where there is a waiting time until drug exposure begins.
- Patients who survive longer are followed longer, which systematically increases the likelihood of using the drug.
- The solution is to analyze the drug exposure variable as a time-varying covariate in a time-to-event analysis.

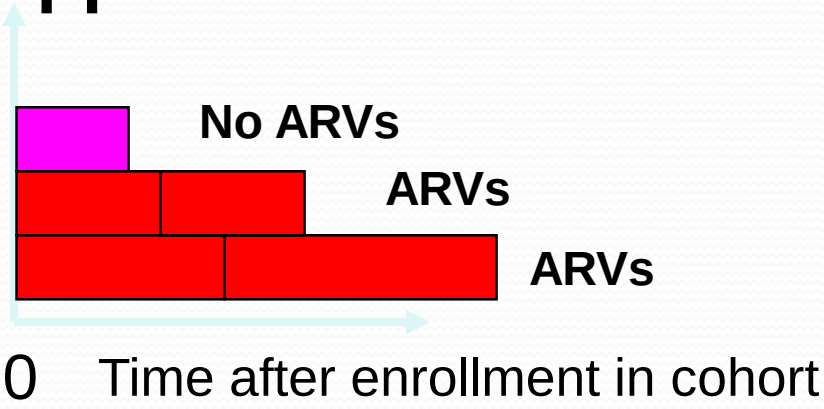
Immortal Time Bias

Time to event analysis

Time-varying (actual data)



Time-fixed approach



Bias can be introduced if analyzed as received ARVs or received no ARVs.

Adapted from:
biostat.mc.vanderbilt.edu/wiki/pub/Main/GCRCNoonWorkshops/COPD_statin_time_immortal_bias.ppt

Examples in the Literature

(1) Do inhaled corticosteroids after hospitalization for chronic obstructive pulmonary disease (COPD) reduce the time to readmission or death? (Suissa S. Am J Respir Crit Care Med. 2003; 168: 49-53)

Rate Ratio

Time – fixed	**Time-varying**
0.69 (95%CI: 0.55, 0.86)	**1.00 (95%CI: 0.79, 1.26)**

(2) Do Oscar winners live longer than less successful peers? A reanalysis of the evidence. (Sylvestre MP, Huszti E, Hanley JA. Ann Intern Med. 2006; 145: 361-363)

Reduction in Mortality Rate

Time – fixed	**Time-varying**
26% (95%CI: 8%, 40%)	**15% (95%CI: -5%, 32%)**

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