HARVARD MEDICAL SCHOOL | BLAVATNIK INSTITUTE GLOBAL HEALTH & SOCIAL MEDICINE

Approaches for improving inference from observational multi-drug resistant tuberculosis (MDR-TB) treatment cohorts

RESIST-TB Webinar• January 27, 2020

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Associate Professor
Global Health and Social Medicine
Harvard Medical School

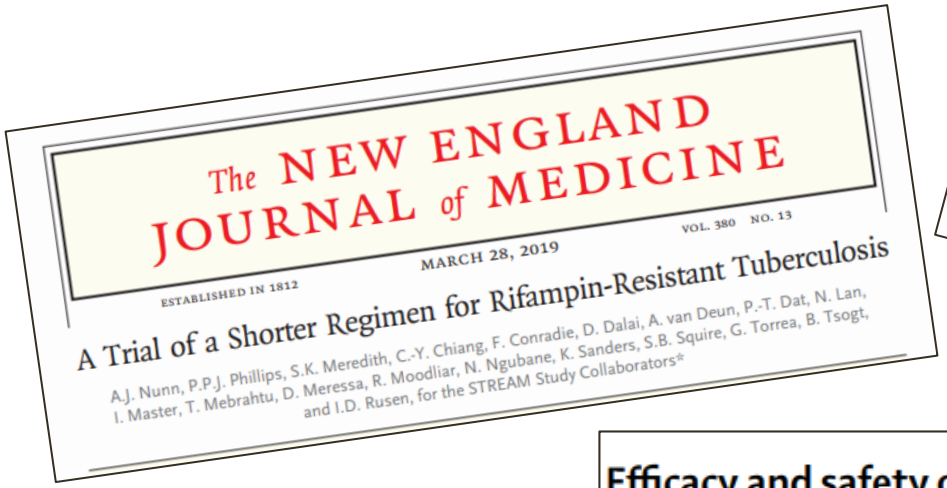
Overview

CONSIDERING REGIMEN CHANGES IN EVALUATING MDR-TB TREATMENTS:

Why is it important and what data do we need to do it?

1. Comment on generating data on optimal MDR-TB regimens
2. Evidence of regimen changes in MDR-TB regimens
3. Implications of not considering regimen changes
4. The “why”, “what” and “how” of accounting for regimen changes
5. Some friendly peer-pressure
6. Discussion / Conclusions

Trials of MDR-TB treatment are critically important.

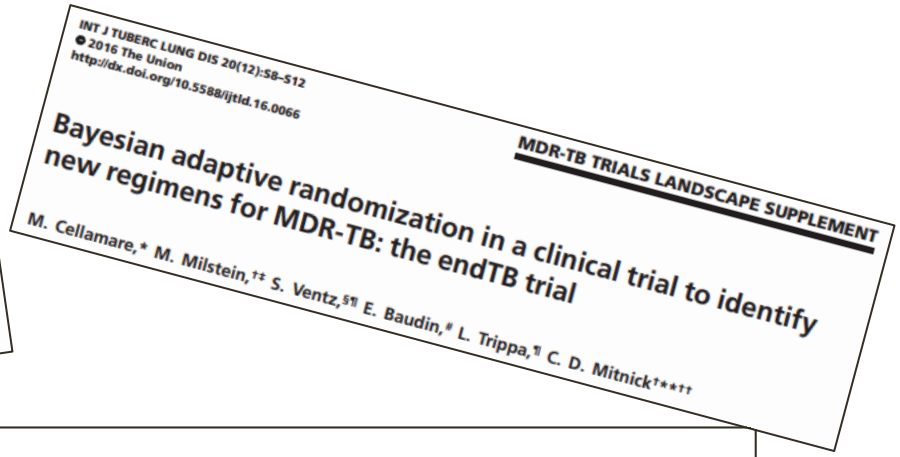


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 28, 2019 VOL. 380 NO. 13

A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis

A.J. Nunn, P.P.J. Phillips, S.K. Meredith, C.-Y. Chiang, F. Conradie, D. Dalai, A. van Deun, P.-T. Dat, N. Lan, I. Master, T. Mebrahtu, D. Meressa, R. Moodliar, N. Ngubane, K. Sanders, S.B. Squire, G. Torrea, B. Tsogt, and I.D. Rusen, for the STREAM Study Collaborators*



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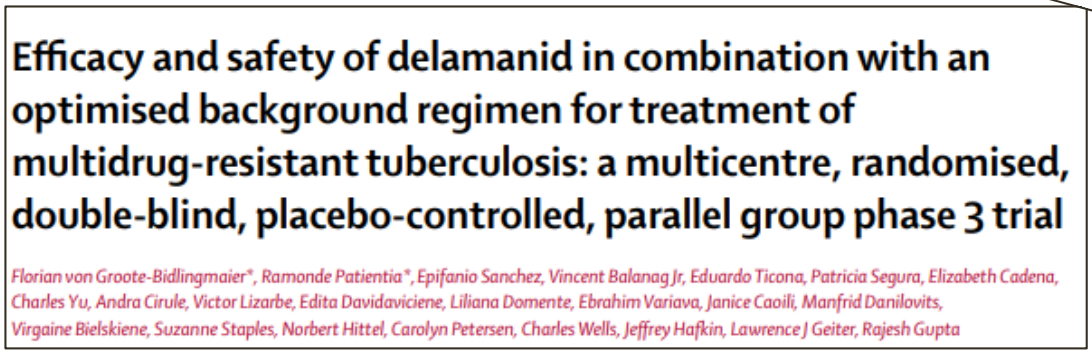
http://dx.doi.org/10.5588/ijtld.16.0066

MDR-TB TRIALS LANDSCAPE SUPPLEMENT

Bayesian adaptive randomization in a clinical trial to identify new regimens for MDR-TB: the endTB trial

M. Cellamare,* M. Milstein,†‡ S. Ventz,§¶ E. Baudin,# L. Trippa,¶ C. D. Mitnick†**††



Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial

Florian von Groote-Bidlingmaier, Ramonde Patientia*, Epifanio Sanchez, Vincent Balanag Jr, Eduardo Ticona, Patricia Segura, Elizabeth Cadena, Charles Yu, Andra Cirule, Victor Lizarbe, Edita Davidaviciene, Liliana Domente, Ebrahim Variava, Janice Caoili, Manfrid Danilovits, Virgaine Bielskiene, Suzanne Staples, Norbert Hittel, Carolyn Petersen, Charles Wells, Jeffrey Hafkin, Lawrence J Geiter, Rajesh Gupta*

Observational data are also critically important.

and children treated with longer MDR-TB regimens allows the study of useful correlates of outcome, including the regimen composition *(42–44)*. The evidence base for the effectiveness of many of the medicines used in MDR-TB regimens relies heavily on observational studies with only a few having been studied under randomized controlled conditions. As a result, the overall certainty in the evidence is often graded low or very low. The sources of data used by the GDG to address the two PICO

Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis *Lancet* 2018; 392: 821–34

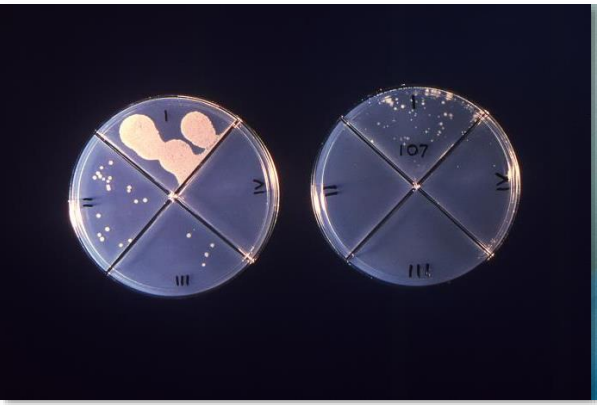
The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017; Nafees Ahmad, Shama D Ahuja,

RESEARCH ARTICLE

Treatment and outcomes in children with multidrug-resistant tuberculosis: A systematic review and individual patient data meta-analysis PLOS MEDICINE

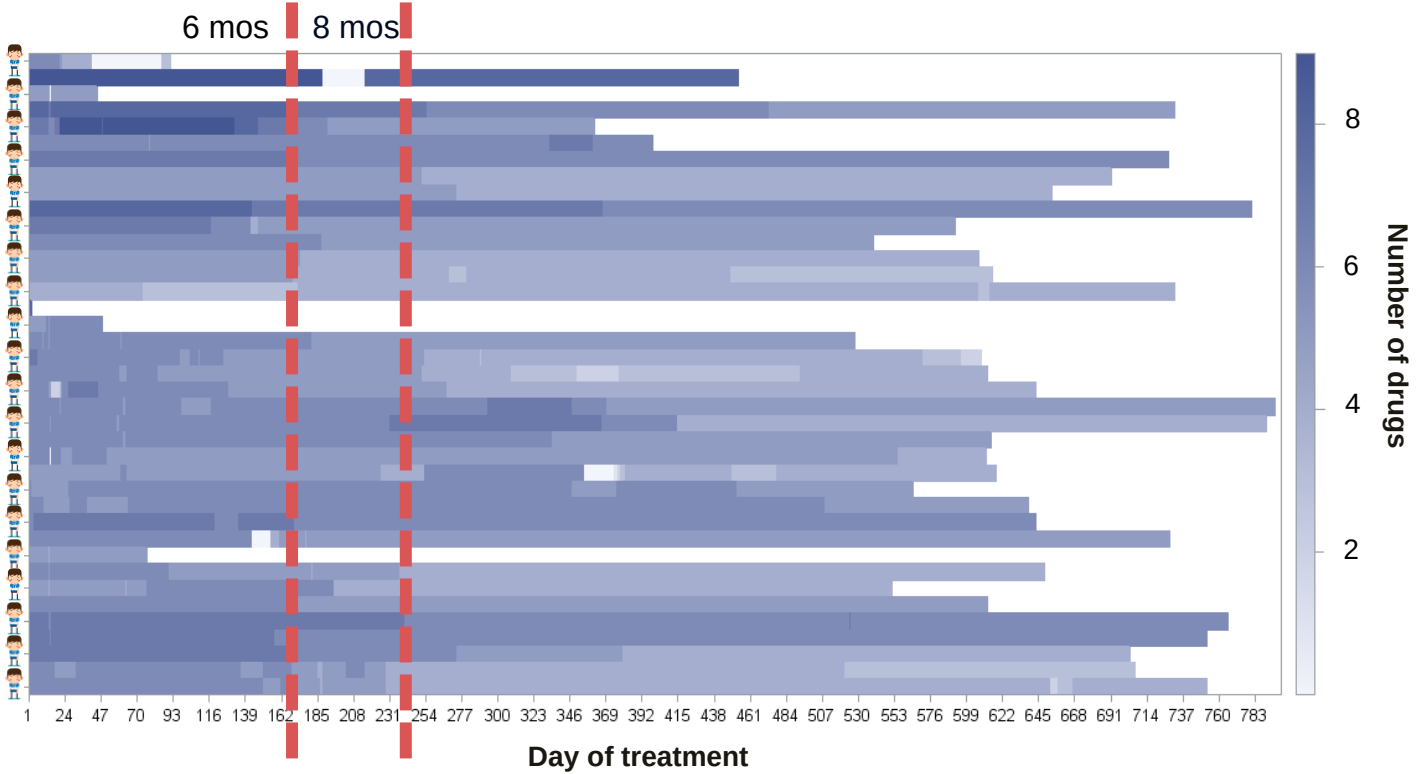
Elizabeth P. Harausz[1,2]*, Anthony J. Garcia-Prats[1], Stephanie Law[3], H. Simon Schaaf[1], Tamara Kredo[4], James A. Seddon[5], Dick Menzies[3], Anna Turkova[6], Jay Achar[7]

Longer MDR-TB regimens are dynamic.



Longer MDR-TB regimens are dynamic.

Heatmap of number of drugs received over time (39 patients)



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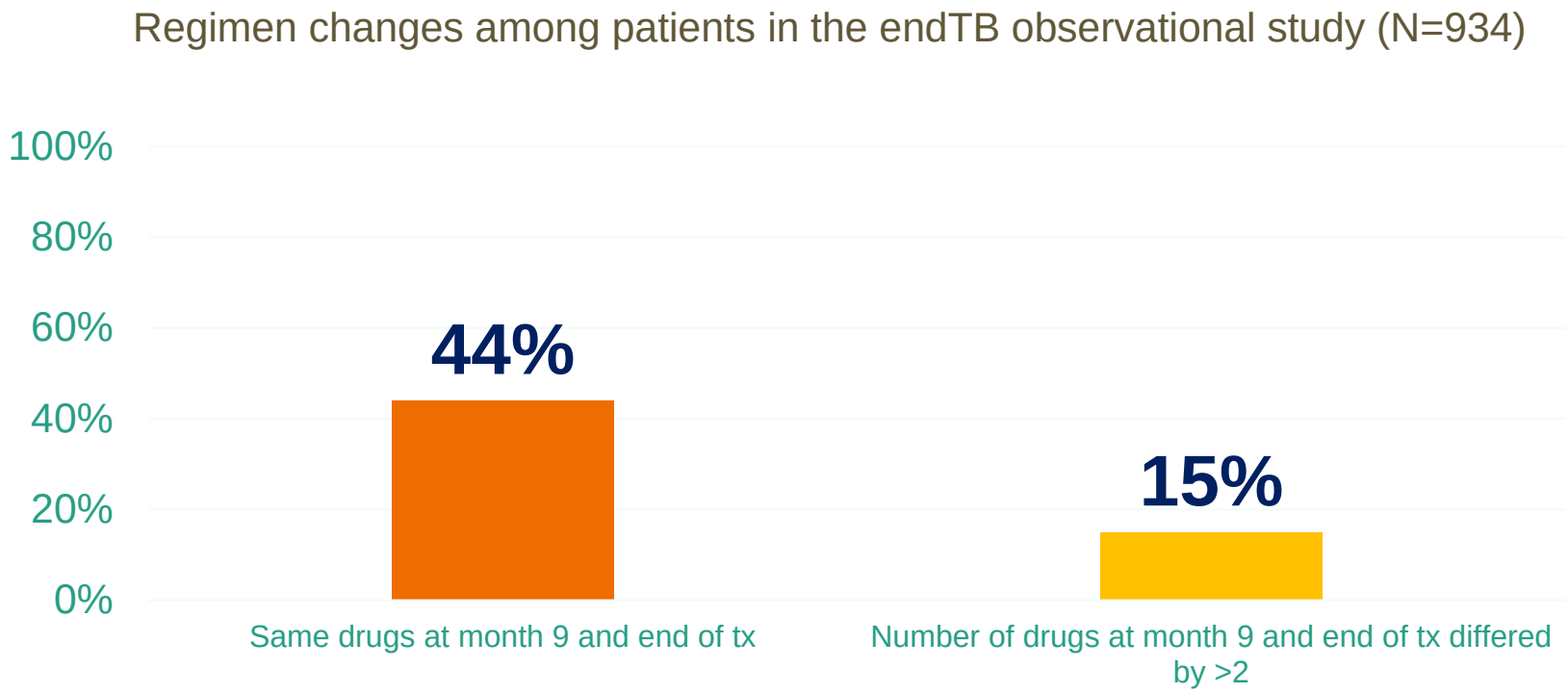


Longer MDR-TB regimens are dynamic.

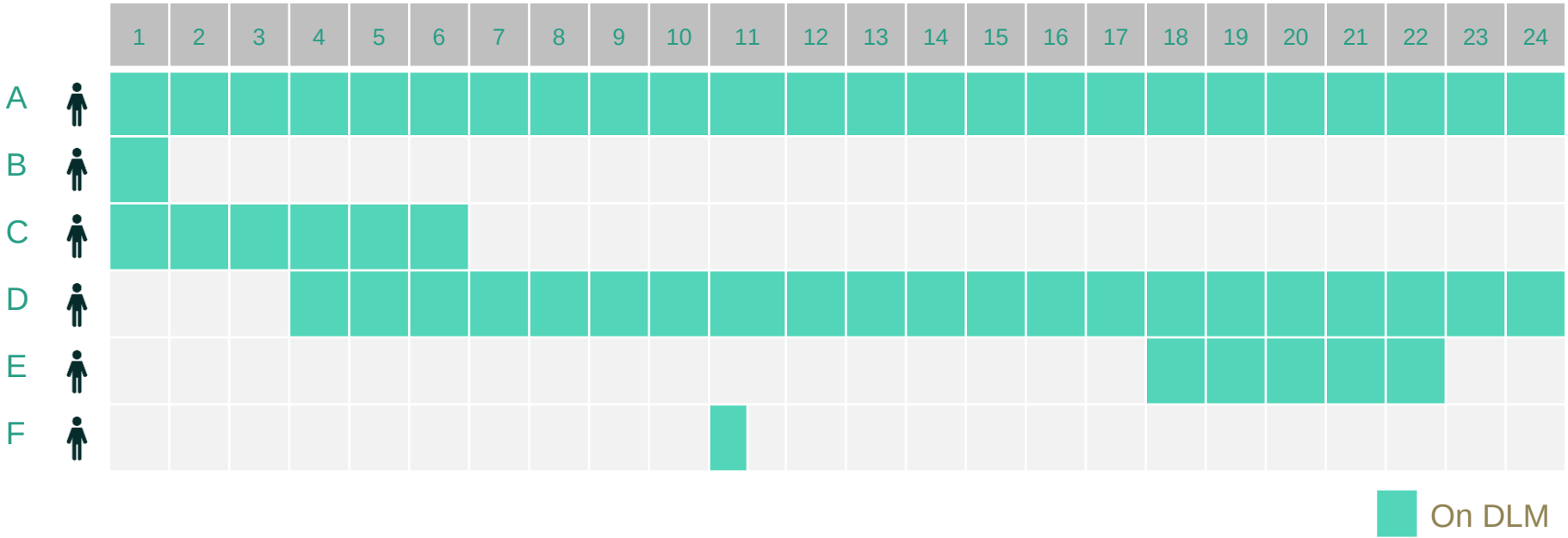
Regimen changes in the endTB observational study (N=1088)

Type of change	Median number of changes [IQR]
All changes (including dose adjustments, suspensions)	8 [5 to 11]
All changes, excluding dose adjustments	6 [4 to 9]
Unique regimen combinations	5 [3 to 7]

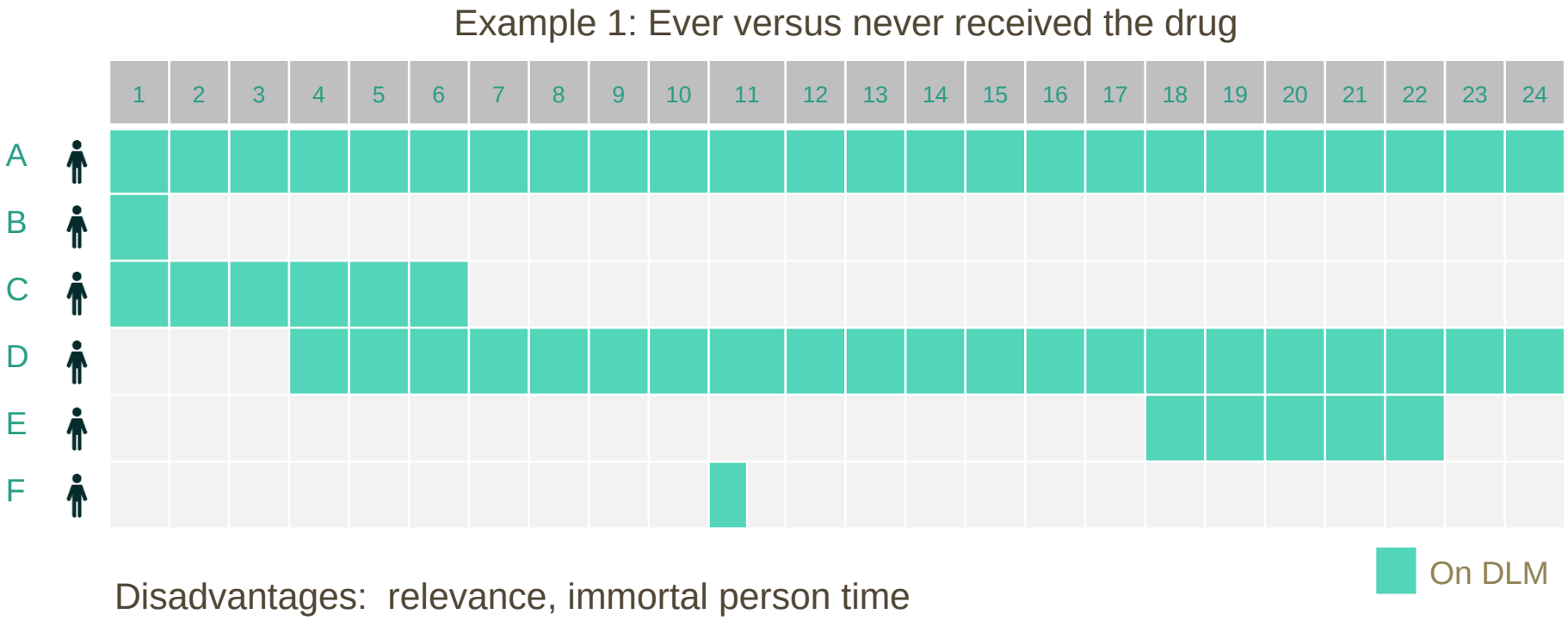
Historically we have lacked detailed longitudinal data on MDR-TB treatment.

So, we have to make tough decisions about classifying exposure.

Example: classifying exposure to DLM



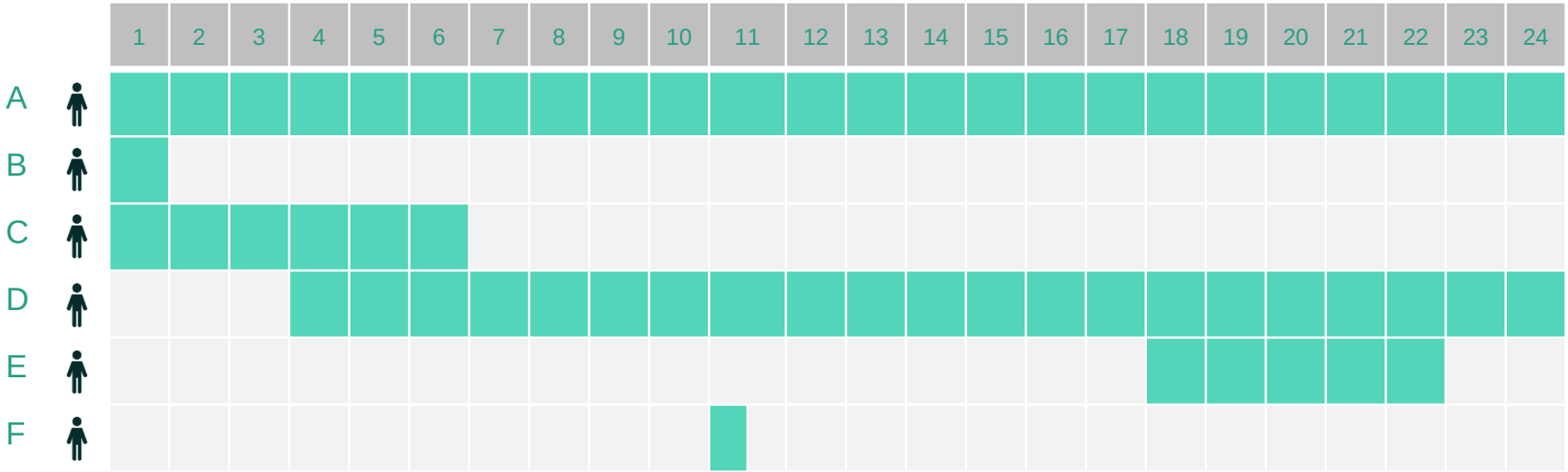
Example: classifying exposure to DLM



Disadvantages: relevance, immortal person time

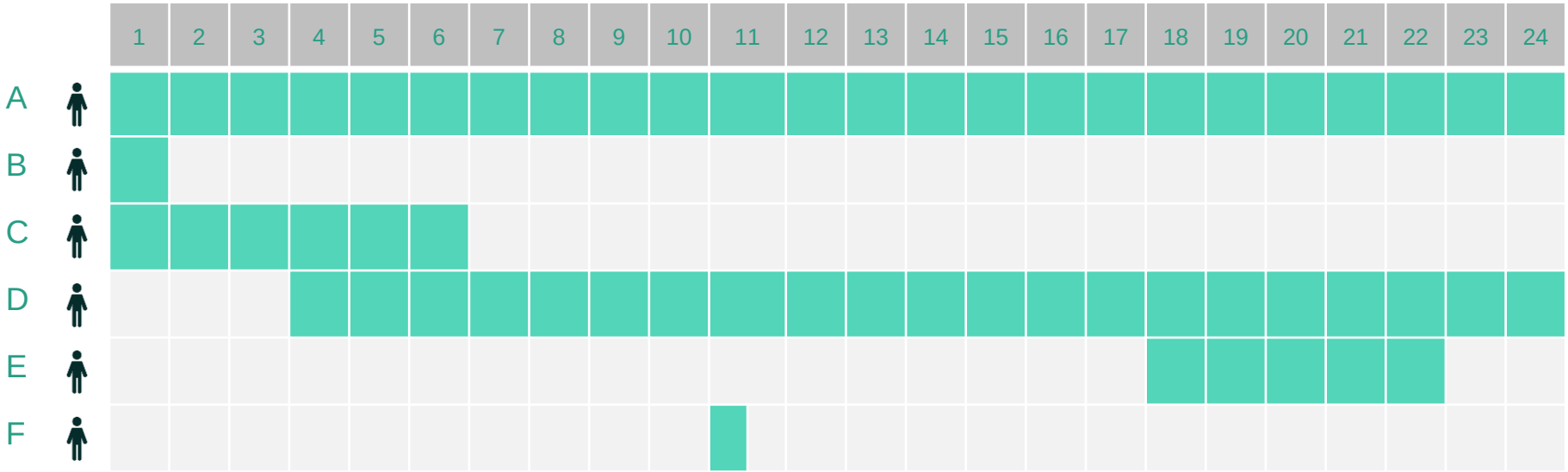
Example: classifying exposure to DLM

Example 2: Drugs received in the first month



Disadvantages: relevance, misclassification

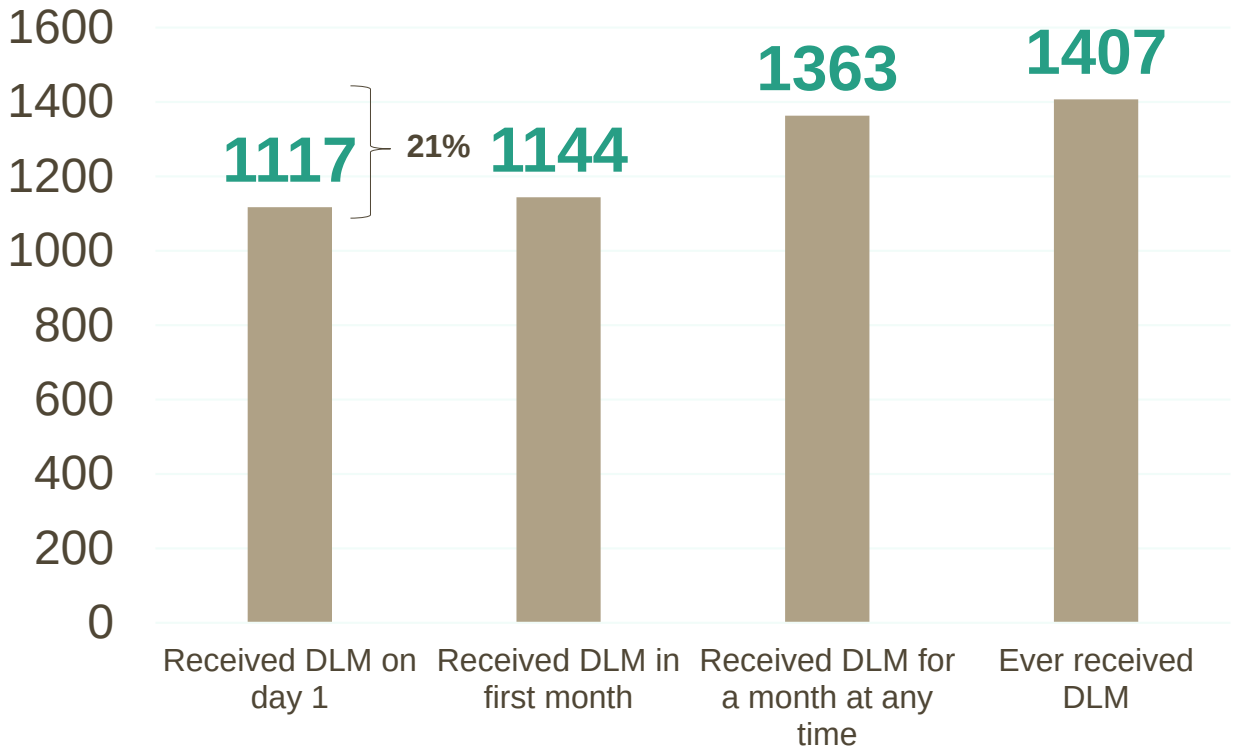
What if DLM is a confounder?



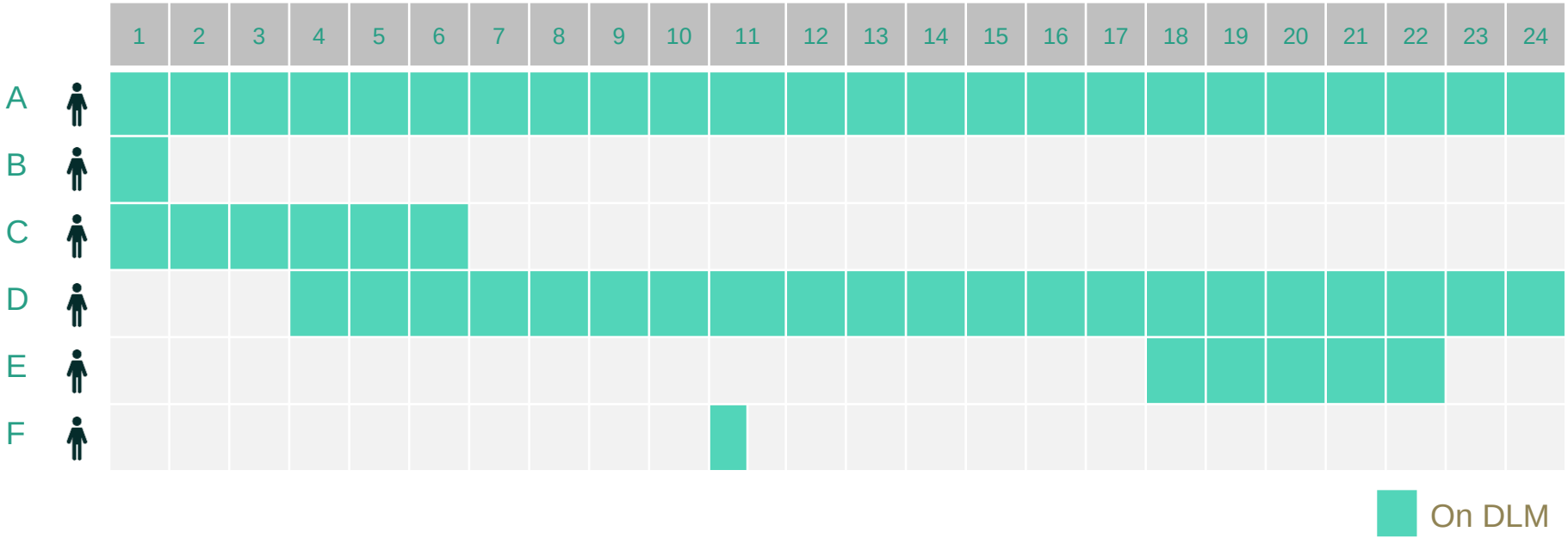
Residual confounding; Risk of over adjustment

DLM use, endTB observational study

- Use varied throughout the study
- Availability increased over time
- Added to or substituted into regimens

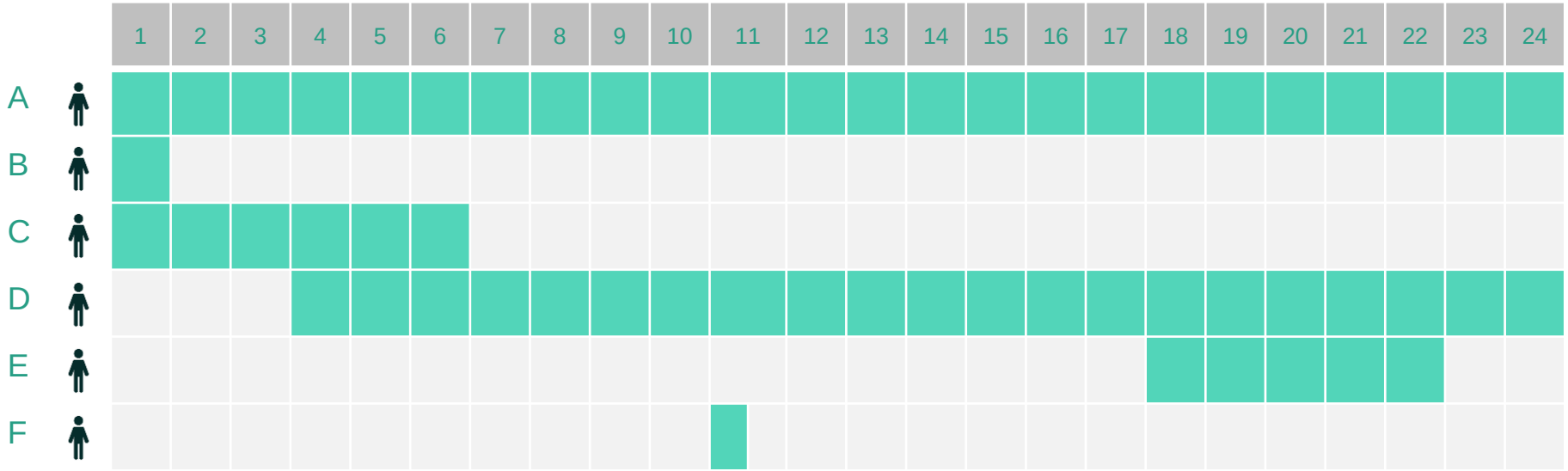


Why consider regimen changes?



- Improves relevancy of questions.
- This approach reduces bias (no assumptions about nature of exposure)

What data is needed to consider regimen changes?



- DLM start and stop dates
- Data on factors associated with DLM use at baseline and during follow-up
  - Cultures
  - Adverse events
  - Other drugs in the regimens

Presence and dates

On DLM

How do you do this?

- Use alternative statistical methods to adjust for confounding by both baseline and time-varying covariates.
  - e.g. Inverse probability weighting, G-formula

- Statistical code and methods paper increasingly available.

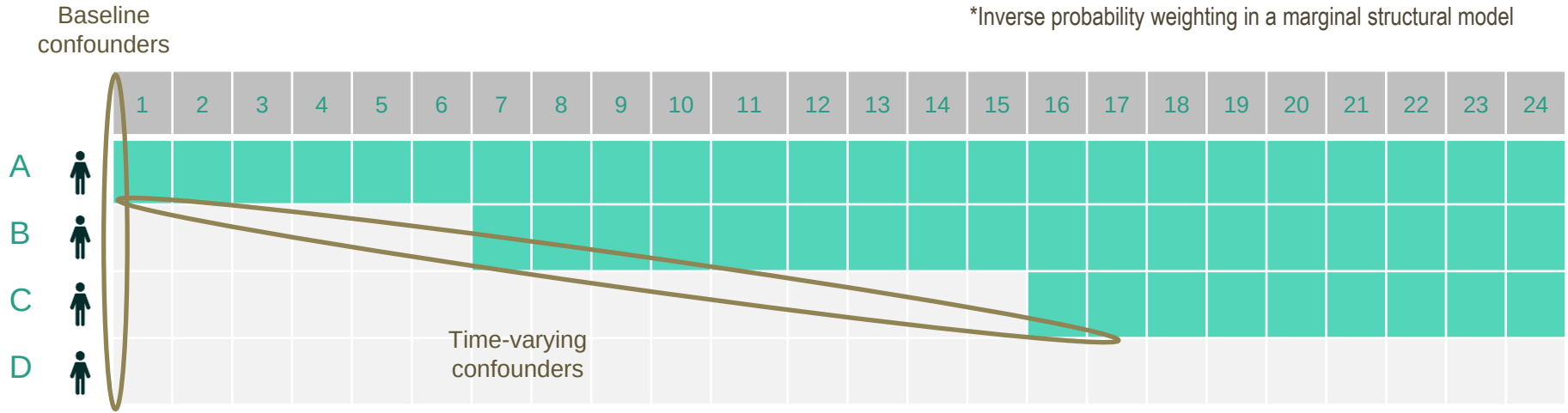
- Free text and analysis code available online:
  - https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/

How do you do this? An illustrative example in HIV

- Cohort of men living with HIV
- Estimate effect of AZT initiation on mortality

Analysis	RR	95% CI
Unadjusted	3.55	2.95 – 4.27
Baseline adjusted	2.32	1.92 – 2.81
Baseline and time-varying confounders*	0.74	0.57 – 0.96

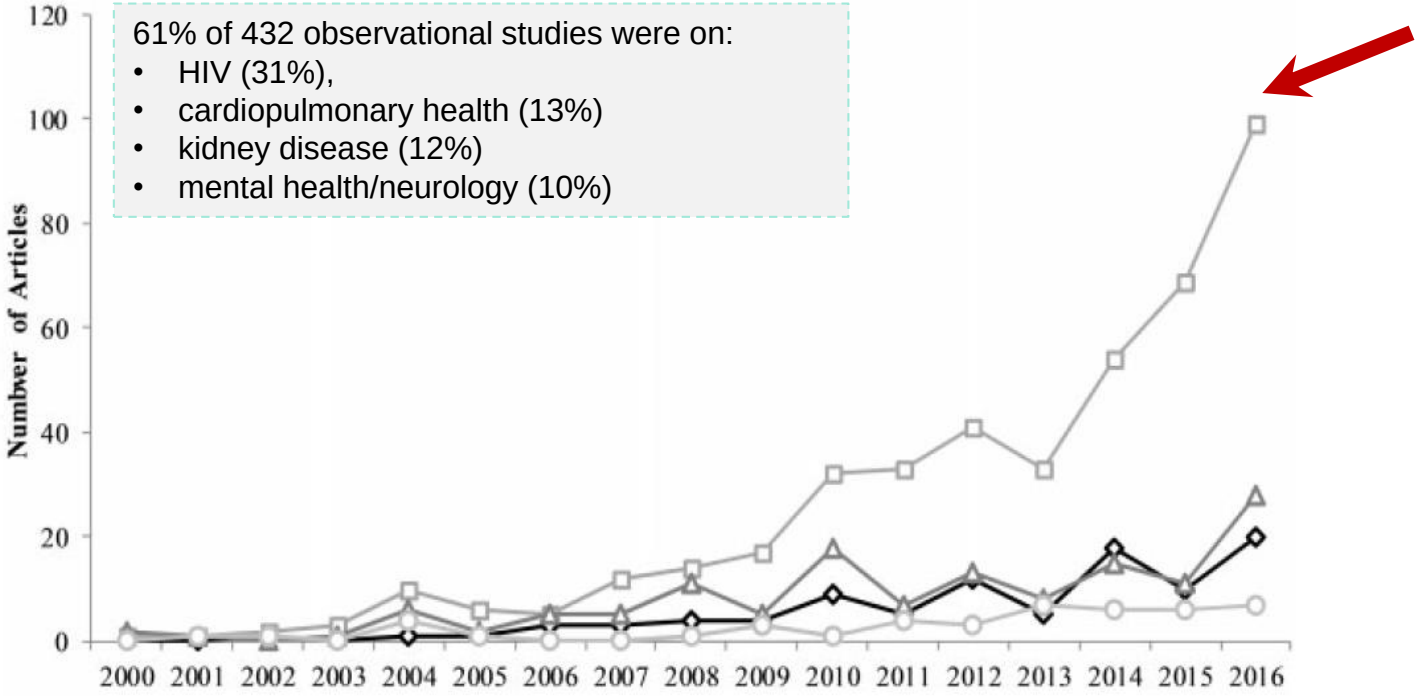
*Inverse probability weighting in a marginal structural model



Hernán et al. Epidemiology. 2000

On ART

These methods have become common.



Publications with discussion of theory or application of methods for time-varying mediation or confounding.

Clare et al. IJE, 2019

These methods have become common.

Key Messages

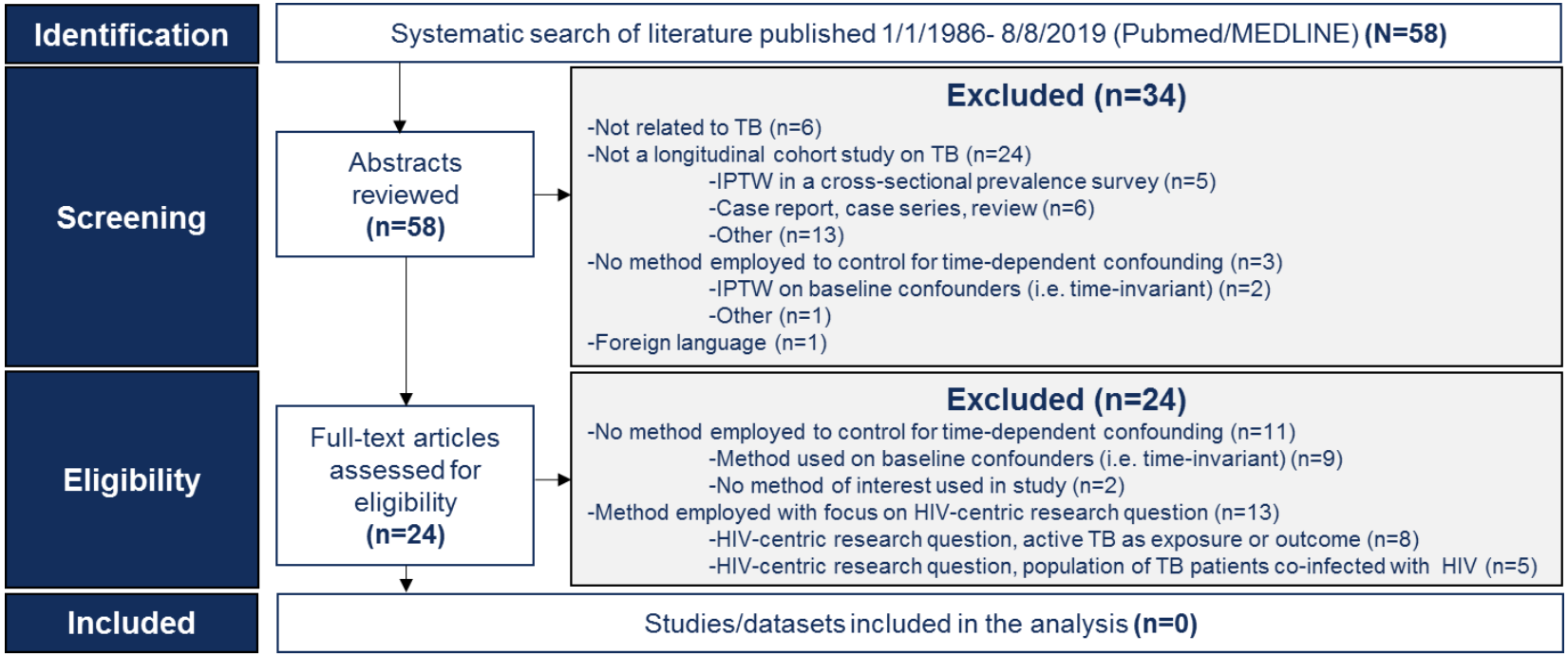
- "… time-varying confounding is an important issue in the analysis of non-randomized longitudinal data, and ignoring it can lead to false conclusions."

- "A number of techniques exist to adjust for … time-varying confounding; however, they remain under-used in the literature."

- "Effort is required to make existing methods accessible to researchers in order to make future analysis of longitudinal data more robust and more reliable."

Clare et al. IJE, 2019

No TB studies have used these methods.

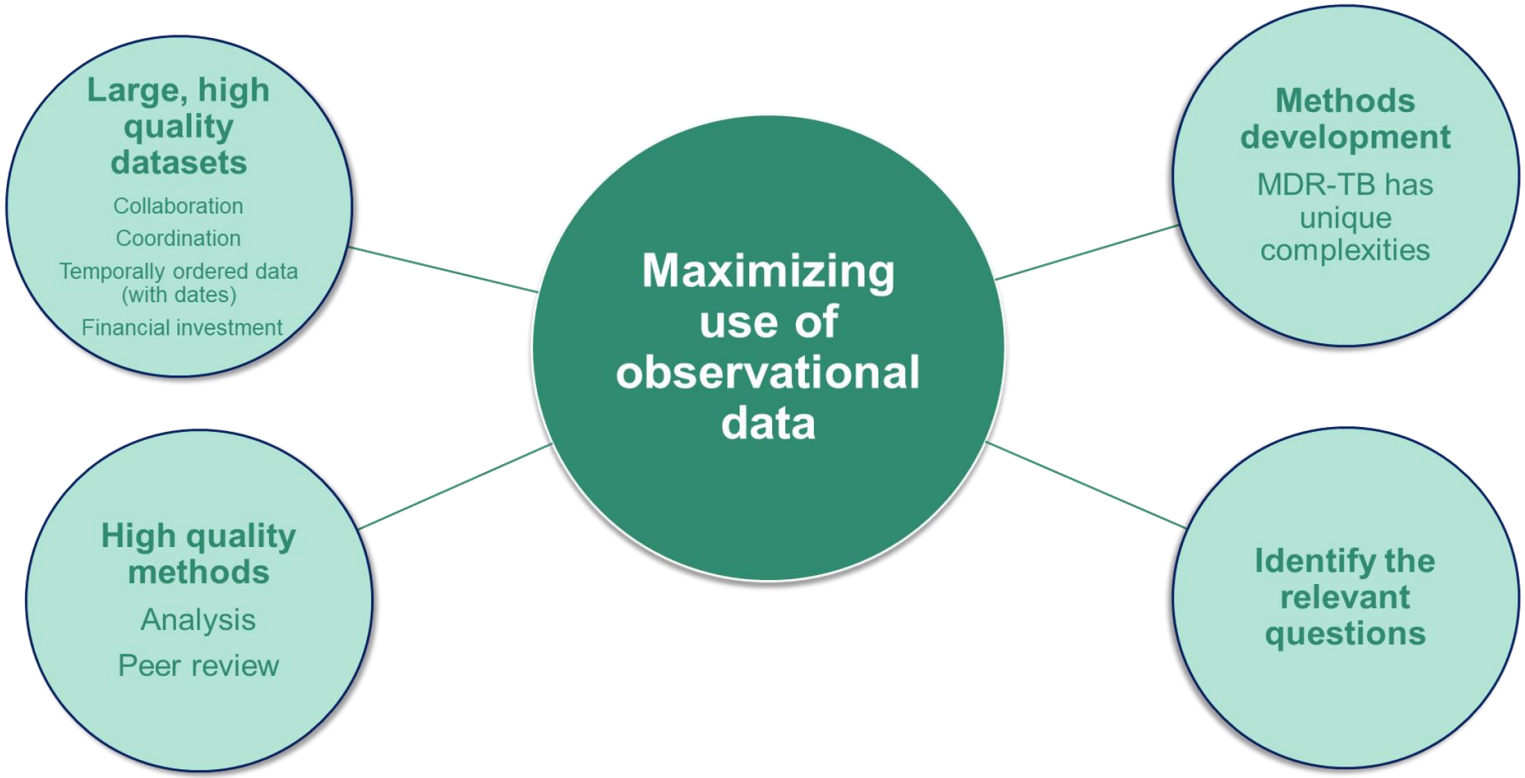


Carly Rodriguez et al. Unpublished data.

Summary

- Lack of detailed longitudinal data necessitates tough decisions and strong assumptions during analysis
- Unknown how these bias findings, affect patient care
  - We won't know until we do robust analyses on high-quality data.
  - Presence / directions of these biases can be hard to predict
  - Bias may be present in some cohorts but not others
- MDR-TB data limitations have precluded asking the most relevant questions and conducting the most robust analyses

Improving inferences from observational data:



ANSWERING THE RELEVANT QUESTION:

How we can analyze data from MDR-TB observational treatment cohorts to emulate randomized trials?

Carly Rodriguez, MPH

PhD Candidate, Department of Epidemiology, Boston University School of Public Health

Associate, Department of Global Health and Social Medicine, Harvard Medical School

BU Boston University School of Public Health

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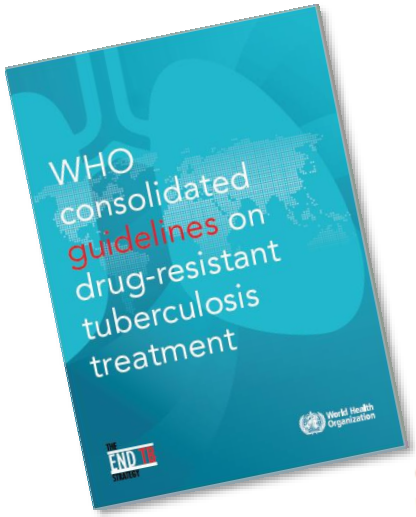
RANDOMIZED TRIALS AND OBSERVATIONAL DATA

- Randomized trials are the gold standard in assessing the causal effect of a treatment on an outcome
- However, randomized trials can be:
  - Untimely
  - Impractical
  - Expensive
  - Unethical

DATA FROM OBSERVATIONAL TREATMENT COHORTS IS OUR NEXT BEST CHOICE



Annex 1: PICO questions

1b. PICO questions from the *WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update*

Q1. *In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) is a shorter treatment regimen (9–12 months) more or less likely to safely improve outcomes than longer regimens conforming to WHO guidelines?*[43]

1a. PICO question from the *WHO treatment guidelines for isoniazid resistant tuberculosis, 2018*

Q1. *In patients with isoniazid-resistant tuberculosis (other than MDR-TB), which treatment regimen composition and duration, when compared with 6 or more months of rifampicin–pyrazinamide–ethambutol, leads to a higher likelihood of success with least possible risk of harm?*

Q2. *In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB), which individual agents are more likely to improve outcomes when forming part of a longer regimen conforming to WHO guidelines?*[44]

Q3. *In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) on longer regimens composed in accordance with WHO guidelines, are outcomes safely improved with fewer or more than five effective medicines in the intensive phase?*[49]

Q4. *In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) on longer regimens composed in accordance with WHO guidelines, are outcomes safely improved with an intensive phase shorter or longer than 8 months?*

Q5. *In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) on longer regimens composed in accordance with WHO guidelines, are outcomes safely improved with a total duration shorter or longer than 20 months?*

Q6. *In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) on longer regimens composed in accordance with WHO guidelines, what is the minimum duration of treatment after culture conversion that is most likely to improve outcomes?*

1d. PICO question from the *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update*

Q4. *Among patients on MDR-TB treatment, are the following two interventions (delay in start of treatment and elective surgery) likely to lead to the outcomes listed below?*[52]

Q7. *In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) treated with longer or shorter regimens composed in accordance with WHO guidelines, is monitoring using monthly cultures, in addition to smear microscopy, more likely to detect non-response to treatment?*

1c. PICO questions from the Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update

Q6. *In patients with HIV infection and drug-resistant TB receiving antiretroviral therapy, is the use of drugs with overlapping and potentially additive toxicities, compared with their avoidance, more or less likely to lead to the outcomes listed in Table 2?*

Q7. *Among patients with MDR-TB, is ambulatory therapy, compared with inpatient treatment, more or less likely to lead to the outcomes listed in Table 2?*

Q11. *Is decentralized treatment and care for MDR-TB patients more or less likely to lead to the outcomes listed below?*

1e. PICO questions from the *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update*

Q10. *In patients with TB, are any interventions to promote adherence to TB treatment more or less likely to lead to the outcomes listed below?*

THE TARGET TRIAL APPROACH

- An analysis of observational data can be viewed as an attempt to emulate a hypothetical pragmatic randomized trial, the **“target trial”**

- **Three (3) major steps**:
  1. Define the research question
  2. Describe, in detail, the target trial
  3. Explicitly emulate the target trial in the observational data

Hernan et al. *Am J Epidemiol*, 2016

THE TARGET TRIAL APPROACH

- **Three (3) major steps**:
  1. Define the research question
  2. Describe, in detail, the target trial:
     - **Eligibility criteria**
     - **Treatment strategies of interest**
     - **Assignment procedures**
     - **Follow-up period**
     - **Outcome**
     - **Analysis plan**
  3. Explicitly emulate the target trial in the observational data

Hernan et al. *Am J Epidemiol*, 2016

THE TARGET TRIAL APPROACH

Emulating a target trial of antiretroviral therapy regimens started before conception and risk of adverse birth outcomes

Ellen C. Caniglia[a], Rebecca Zash[b], Denise L. Jacobson[c], Modiegi Diseko[d], Gloria Mayondi[d], Shahin Lockman[e], Jennifer Y. Ch… Miguel …

Annals of the American Thoracic Society

Home > All AnnalsATS Issues > **Articles in Press**

Emulating a Novel Clinical Trial Using Existing Observational Data: Predicting Results of the PreVent Study

Andrew J Admon , John P Donnelly , Jonathan D Casey , David R Janz , Derek W Russell , Aaron M Joffe , Derek J … Stempek , James M. Dargin , Todd W Rice , Show All...

The value of explicitly emulating a target trial when using real world evidence: an application to colorectal cancer screening

Xabier García-Albéniz[1,2] · John Hsu[2,3] · Miguel A. Hernán[1,4,5]

American Journal of Epidemiology
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Vol. 183, No. 8
DOI: 10.1093/aje/kwv254
Advance Access publication: March 18, 2016

Practice of Epidemiology

Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available

Miguel A. Hernán* and James M. Robins

ELSEVIER Journal of Clinical Epidemiology 79 (2016) 70–75

Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses

Miguel A. Hernán[a,b,c,*], Brian C. Sauer[d], Sonia Hernández-Díaz[a], Robert Platt[e,f,g], Ian Shrier[g]

ELSEVIER Journal of Clinical Epidemiology 96 (2018) 12–22

ORIGINAL ARTICLE

Electronic medical records can be used to emulate target trials of sustained treatment strategies

Goodarz Danaei[a,b,*], Luis Alberto García Rodríguez[c], Oscar Fernández Cantero[c], Roger W. Logan[b], Miguel A. Hernán[b,d,e]

1. DEFINE THE RESEARCH QUESTION

PICO question:
In MDR/RR-TB patients, does concomitant use of bedaquiline and delamanid safely improve outcomes when compared with other treatment options in regimens otherwise conforming to current WHO guidelines?

Three (3) steps:

1. **Define the research question**
2. Describe the target trial
   a. Eligibility criteria
   b. Treatment strategies
   c. Assignment
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Does concomitant use of bedaquiline and delamanid for the first 6 months of treatment improve 6-month TB treatment outcome, compared to patients receiving bedaquiline-containing, delamanid-free regimens?

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2. DESCRIBE THE TARGET TRIAL

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   e. **Outcome**
   f. **Analysis plan**
3. Emulate the target trial

2. DESCRIBE THE TARGET TRIAL

Eligibility criteria	Patients with culture+ RR-, MDR-TB, XDR-TB
Treatment strategies	
Assignment	
Follow-up	
Outcome	
Analysis plan	

2. DESCRIBE THE TARGET TRIAL

Eligibility criteria	Patients with culture+ RR-, MDR-TB, XDR-TB
Treatment strategies	*Intervention*: **DLM** + BDQ + WHO-conforming longer regimen of 3 drugs likely to be effective *Control*: BDQ + WHO-conforming longer regimen of 3 drugs likely to be effective
Assignment	
Follow-up	
Outcome	
Analysis plan	

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Assignment	Random at treatment initiation
Follow-up	
Outcome	
Analysis plan	

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Assignment	Random at treatment initiation
Follow-up	From randomization to: week 24, death, or loss-to-follow up, whichever occurs first
Outcome	
Analysis plan	

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Outcome	Sputum culture conversion at wk 24
Analysis plan	

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Outcome	Sputum culture conversion at wk 24
Analysis plan	Across treatment arms: % with culture conversion at wk 24, time-to-culture conversion

3. EMULATE THE TARGET TRIAL

- Assume multi-country **observational cohort** of patients with RR-, MDR-, and XDR-TB treated under programmatic conditions with bedaquiline, delamanid, or both

Three (3) steps:

1. Define the research question
2. Describe the target trial
   a. Eligibility criteria
   b. Treatment strategies
   c. Assignment
   d. Follow-up period
   e. Outcome
   f. Effect of interest
   g. Analysis plan
3. **Emulate the target trial**

	TARGET TRIAL	OBSERVATIONAL COHORT
Eligibility criteria	Patients with culture+ RR-, MDR-TB, XDR-TB	Same
Treatment strategies	*Intervention*: **DLM** + BDQ + WHO-conforming longer regimen of 3 drugs likely to be effective *Control*: BDQ + WHO-conforming longer regimen of 3 drugs likely to be effective	
Assignment	Random at treatment initiation	
Follow-up	From randomization to: week 24, death, or loss-to-follow up, whichever occurs first	
Outcome	Sputum culture conversion at week 24	
Analysis plan	Across treatment arms: % with culture conversion at week 24, time-to-culture conversion	

	TARGET TRIAL	OBSERVATIONAL COHORT
Eligibility criteria	Patients with culture+ RR-, MDR-TB, XDR-TB	Same
Treatment strategies	*Intervention*: **DLM** + BDQ + WHO-conforming longer regimen of 3 drugs likely to be effective *Control*: BDQ + WHO-conforming longer regimen of 3 drugs likely to be effective	Same. *Note, this requires excluding patients with <3 drugs likely to be effective, >3 drugs likely to be effective (not counting BDQ/DLM)*
Assignment	Random at treatment initiation	
Follow-up	From randomization to: week 24, death, or loss-to-follow up, whichever occurs first	
Outcome	Sputum culture conversion at week 24	
Analysis plan	Across treatment arms: % with culture conversion at week 24, time-to-culture conversion	

	TARGET TRIAL	OBSERVATIONAL COHORT
Eligibility criteria	Patients with culture+ RR-, MDR-TB, XDR-TB	Same
Treatment strategies	*Intervention*: **DLM** + BDQ + WHO-conforming longer regimen of 3 drugs likely to be effective *Control*: BDQ + WHO-conforming longer regimen of 3 drugs likely to be effective	Same. *Note, this requires excluding patients with <3 drugs likely to be effective, >3 drugs likely to be effective (not counting BDQ/DLM)*
Assignment	Random at treatment initiation	Regimen received on day 1 of treatment based on site, provider preference, etc.
Follow-up	From randomization to: week 24, death, or loss-to-follow up, whichever occurs first	
Outcome	Sputum culture conversion at week 24	
Analysis plan	Across treatment arms: % with culture conversion at week 24, time-to-culture conversion	

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Assignment	Random at treatment initiation	Regimen received on day 1 of treatment based on site, provider preference, etc.
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Outcome	Sputum culture conversion at week 24	Same
Analysis plan	Across treatment arms: % with culture conversion at week 24, time-to-culture conversion	Inverse probability (IP) treatment weighting for baseline confounders and IP censoring weights for treatment switches

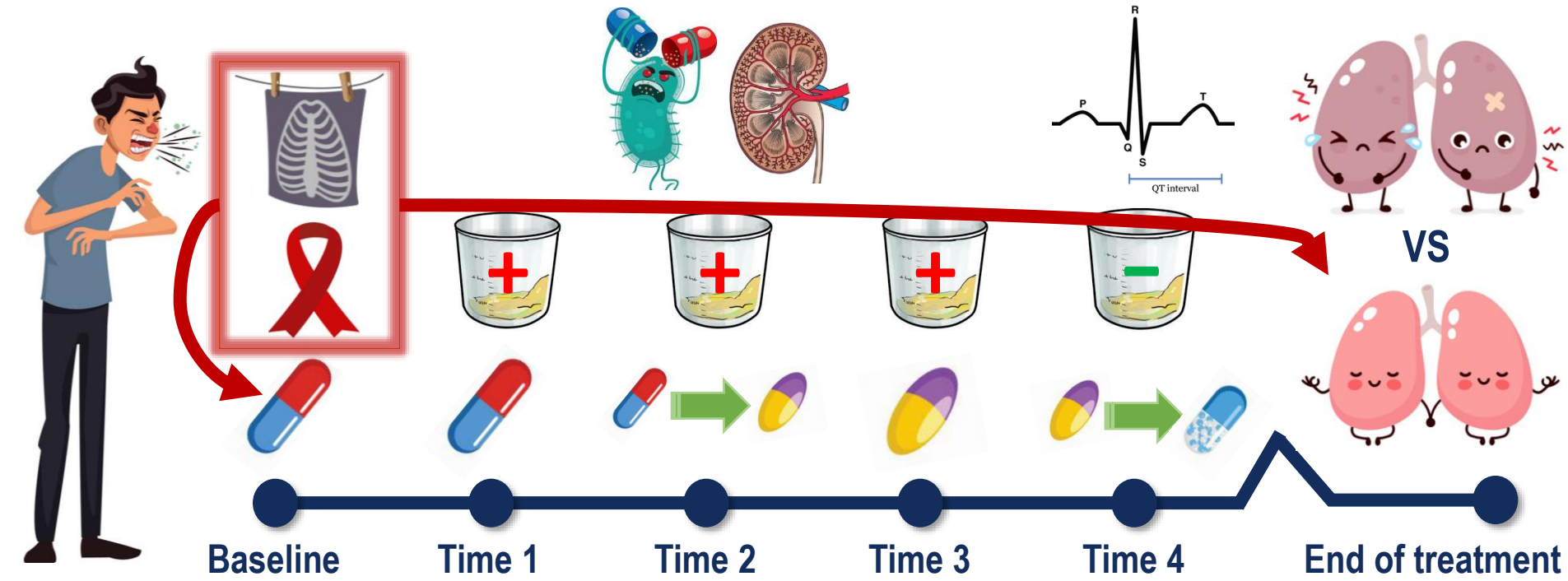
3. EMULATE THE TARGET TRIAL

- Analysis plan
  - MDR-TB treatment is complex
  - Treatment regimens often change dependent on other time-varying factors such as bacteriologic response, toxicity, and resistance

Three (3) steps:

1. Define the research question
2. Describe the target trial
   a. Eligibility criteria
   b. Treatment strategies
   c. Assignment
   d. Follow-up period
   e. Outcome
   f. Effect of interest
   g. Analysis plan
3. **Emulate the target trial**

TIME-DEPENDENT CONFOUNDING IN MDR-TB COHORTS



3. EMULATE THE TARGET TRIAL

- Analysis plan
  - MDR-TB treatment is complex
  - Treatment regimens often change dependent on other time-varying factors such as bacteriologic response, toxicity, and resistance
  - **Simple adjustment methods, such as regression on baseline factors and propensity score matching, likely does not completely resolve bias**
  - **Methods that can account for complex longitudinal data are needed (inverse probability weighting, g-formula)**

Three (3) steps:

1. Define the research question
2. Describe the target trial
   a. Eligibility criteria
   b. Treatment strategies
   c. Assignment
   d. Follow-up period
   e. Outcome
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   g. Analysis plan
3. **Emulate the target trial**

CONCLUSION

- Observational treatment cohorts can be used to draw inferences on the treatment and management of MDR-TB when evidence from randomized trials is not available
- The target trial approach is a powerful tool to design analyses in observational cohort data
  - Forces clear statement of research question
  - Structured approach to identify and avoid common pitfalls and potential sources of bias
  - Improves transparency and allows others to critically examine the design of observational analyses and the validity of their estimates