Targeting interventions: transporting subgroup analyses of RCTs to inform implementation

Megha Mehrotra, MPH, PhD(c)
NRSA Fellow, National Institute of Mental Health

University of California, San Francisco
Department of Epidemiology and Biostatistics

28 September 2018

Introduction

Subgroup analyses of RCTs inform implementation of new interventions

- Efficient resource prioritization
- Avoid causing harm

Introduction

Subgroup analyses of RCTs inform implementation of new interventions

- Efficient resource prioritization
- Avoid causing harm

However, trial populations rarely resemble the target population of interest!

Pre-Exposure Prophylaxis (PrEP)

Thor Smith for the New York Times

- Daily oral Truvada (FTC/TDF)
- $>$ 90% efficacy under high adherence

The WHO has recommended the use of PrEP for all at-risk individuals.

iPrEx

2499 participants:

- 2174 men
- 325 transgender women

ITT analysis: 44% reduction in HIV incidence among those randomized to PrEP compared to placebo.

Subgroup analysis found no benefit of randomization in transgender women, likely due to low drug concentrations.

iPrEx

What does that tell us about PrEP for transgender women?

iPrEx

What does that tell us about PrEP for transgender women?

- In the context of limited resources, should we prioritize adherence support for trans women over MSM?
- Is PrEP cost-effective in trans women?

iPrEx

What does that tell us about PrEP for transgender women?

- In the context of limited resources, should we prioritize adherence support for trans women over MSM?
- Is PrEP cost-effective in trans women?

iPrEx


San Francisco
Boston
Iquitos
Guayaquil
Lima
Rio de Janeiro
Sao Paulo
Cape Town
Chiang Mai

iPrEx

The iPrEx study population is unlikely to represent any realistic target population!

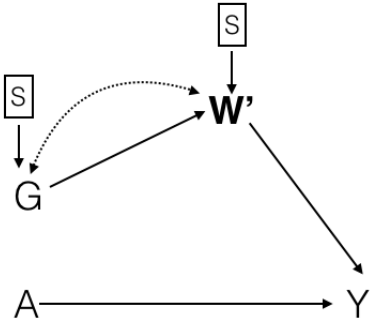
Target Populations: HIV-negative participants from Latino MSM Community Involvement Study

- 473 Latino MSM and transgender women (San Francisco:; Chicago:) recruited via respondent-driven sampling
- Computer assisted self-administered interviews collected information about sexual behavior, substance use, HIV testing, and demographics
- Chicago and San Francisco treated as distinct target populations

Question and Target Parameter

What would the effect heterogeneity between transgender women and MSM have been had the iPrEx trial been conducted in each of our target populations

Selection Diagram



Where *A* is treatment assignment, *Y* is incident HIV infection, *G* is gender, and **W'** is a vector of baseline covariates that comprises age, education, number of partners in the past 6 months, preferred sexual role, and alcohol use.

Notation

We use $S = 0$ to denote the target population(s) and $S = 1$ for the iPrEx study population, and we use $G = 1$ for MSM and $G = 0$ for transgender women.

We define the average causal effect of randomization to PrEP in the iPrEx study population as:

$$\Delta^1 = \mathbb{E}(Y \mid do(A = 1), S = 1) - \mathbb{E}(Y \mid do(A = 0), S = 1)$$

and effect hetergeneity across strata of gender on the additive scale as:

$$\Psi^1 = \mathbb{E}(\Delta^1 \mid G = 1) - \mathbb{E}(\Delta^1 \mid G = 0)$$

Target Parameter

The average causal effect in the target population is therefore:

$$\Delta^0 = \mathbb{E}(Y \mid do(A = 1), S = 0) - \mathbb{E}(Y \mid do(A = 0), S = 0)$$

And the target parameter is:

$$\Psi^0 = \mathbb{E}(\Delta^0 \mid G = 1) - \mathbb{E}(\Delta^0 \mid G = 0)$$

Identifiability

Population exchangeability (s-admissibility):

After accounting for gender and baseline covariates, the target and trial populations are exchangeable.

$$P(Y \mid do(A), G, W', S = 0) = P(Y \mid do(A), G, W', S = 1)$$

Identifiability

Population positivity:

Every combination of covariates within strata of gender in the target population must be represented in the study population.

$$P(S = 1, G \mid W') > 0 \text{ whenever } P(W' \mid G, S = 0) > 0$$

Identifiability

Given the prior selection diagram and the assumptions stated, the target parameter is identified by:

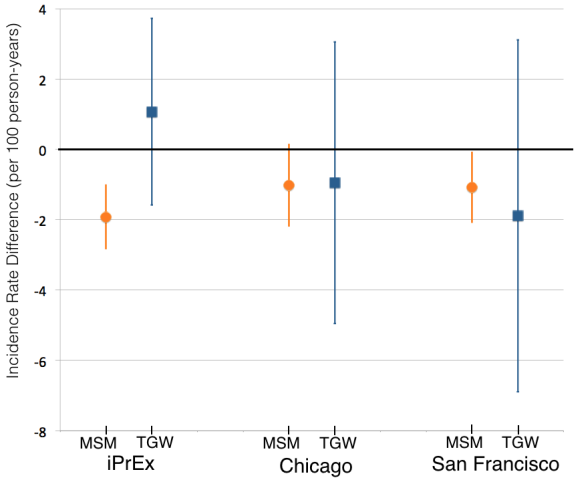
$$\sum_{W'} \mathbb{E}(Y \mid A, G, W', S = 1) P(W' \mid G, S = 0)$$

Estimation

Inverse odds of selection weighted Poisson regression to transport to each target population:

$$IOSW_i = \begin{cases} \frac{P(S_i=0|W_i'G_i)}{P(S_i=1|W_i',G_i)} * \frac{P(S_i=1,G_i)}{P(S_i=0,G_i)} & \text{if } S_i = 1 \\ 0 & \text{if } S_i = 0 \end{cases}$$

Effectiveness of randomization to PrEP by gender and population



Conclusions

- Had the iPrEx study been conducted in a population that shared the same distribution of covariates as the MSM and transgender women in the Latino MSM Community Involvement Study, we would not have observed meaningful effect heterogeneity by gender.

- To best use subgroup analyses of RCTs to inform implementation of interventions, the analyses should be transported to the desired target population.

Acknowledgements

Dissertation Committee:

- David Glidden
- Elvin Geng
- Maria Glymour
- Daniel Westreich

Other mentors:

- Bob Grant
- Maya Petersen

Funding: Ruth L. Kirschstein National Research Service Award (NRSA) Fellowship: F31MH111346

S. R. Cole and E. A. Stuart. “Generalizing Evidence From Randomized Clinical Trials to Target Populations: The ACTG 320 Trial”. en. In: *American Journal of Epidemiology* 172.1 (July 2010), pp. 107–115. ISSN: 0002-9262, 1476-6256. DOI: 10.1093/aje/kwq084. (Visited on 09/01/2015).

Madeline B Deutsch et al. “HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial”. en. In: *The Lancet HIV* (Nov. 2015). ISSN: 23523018. DOI: 10.1016/S2352-3018(15)00206-4. (Visited on 11/09/2015).

Robert M. Grant et al. “Preexposure chemoprophylaxis for HIV prevention in men who have sex with men”. eng. In: *N. Engl. J. Med.* 363.27 (Dec. 2010), pp. 2587–2599. ISSN: 1533-4406. DOI: 10.1056/NEJMoa1011205.

Robert M. Grant et al. “Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study”. eng. In: *Lancet Infect Dis* 14.9 (Sept. 2014), pp. 820–829. ISSN: 1474-4457. DOI: 10.1016/S1473-3099(14)70847-3.

Judea Pearl and Elias Bareinboim. *Transportability across studies: A formal approach*. Tech. rep. DTIC Document, 2011.

Jesus Ramirez-Valles et al. "HIV Infection, Sexual Risk Behavior, and Substance Use Among Latino Gay and Bisexual Men and Transgender Persons". In: *Am J Public Health* 98.6 (June 2008), pp. 1036–1042. ISSN: 0090-0036. DOI: 10.2105/AJPH.2006.102624.

Tyler J. VanderWeele and Mirjam J. Knol. "Interpretation of subgroup analyses in randomized trials: heterogeneity versus secondary interventions". ENG. In: *Ann. Intern. Med.* 154.10 (May 2011), pp. 680–683. ISSN: 1539-3704. DOI: 10.7326/0003-4819-154-10-201105170-00008.

Daniel Westreich et al. "Transportability of trial results using inverse odds of sampling weights". eng. In: *Am. J. Epidemiol.* (May 2017). ISSN: 1476-6256. DOI: 10.1093/aje/kwx164.