UC Berkeley Biostatistics

Estimating Direct Effects of New HIV Prevention Methods
Focus: the MIRA Trial. Are Latex Diaphragms and Gel Protective Against HIV?

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Overview

Motivation: In randomized, controlled trials of new HIV prevention methods, the Intent to Treat (ITT) analysis may not answer the most important public health questions, due to an effective secondary intervention: intensive condom counseling in both study arms. We present a method, requiring more assumptions than the ITT, for answering some of these public health questions. We focus on the MIRA trial, which investigates the effectiveness of a female-controlled barrier method, the latex diaphragm, in preventing HIV acquisition among women.

Background: the MIRA Trial (Methods for Improving Reproductive Health in Africa)

- Two arm, randomized, controlled trial, in South Africa and Zimbabwe
- Primary intervention: diaphragm and gel provision to diaphragm arm (not to control arm).
- Secondary Intervention: Intensive condom provision and counseling given to both arms.
- Main Outcome: HIV infection
- Trial is not blinded
- Motivating Question: What is effectiveness of providing diaphragms and gel for women who cannot get their partners to use condoms?

The Intent to Treat (ITT) Estimate May Not Answer Most Important Public Health Question

Most Important Public Health Questions

1. What is the effectiveness of providing study product in an environment of country-level standard condom counseling? (also, in environment of no condom counseling?)
2. How does providing study product alone compare to consistent condom use alone in reducing HIV transmission?
3. How does providing the study product alone compare to unprotected sex, in terms of risk of HIV infection?

The effectiveness (as measured by 1-relative risk of HIV infection) of a study product in an environment of intensive condom counseling may be quite different from its effectiveness in an environment of country-level standard condom counseling.
Therefore, the Intent to Treat Estimator (ITT) may not answer questions 1-3 above, if trial is done in environment of secondary intervention: intensive condom counseling.

Reasons effectiveness may be different in environment of intensive condom counseling vs. environment of country-level standard condom counseling:

Reason A: In trials without blinding, effects of intensive condom counseling may be different for treatment arm and control arm.
Reason B. Even in trials with blinding (e.g. microbicide trials), effects of intensive condom counseling may be different for those who adhere to assigned treatment and those who don't.
Reason C. Intensive condom counseling may itself affect adherence to assigned treatment.

Illustration of Reason A

Consider the following two hypothetical randomized trials: The first trial is carried out in an environment of no condom counseling; for simplicity, assume the following: 75% of the subjects in both arms of this trial adhere to the study product, the product is 20% protective against HIV infection, and no one in the trial uses condoms. This information is depicted below, where represents patients who adhere to the study product. In this scenario, the relative risk of infection is RR = 170/200 = 0.85.

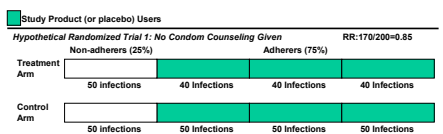

Illustration of Reason A (continued)

The second hypothetical randomized trial is carried out in an environment of ***intensive*** condom counseling; for simplicity, assume the following: 75% of the subjects in both arms of this trial adhere to the study product, the product is 20% protective against HIV infection, and condoms are 80% protective. This information is depicted below, where represents patients who adhere to the study product, and represents subjects who use condoms. The relative risk of infection in this hypothetical trial is RR = 106/80 = 1.33. This is quite different from the RR=0.85 in the first hypothetical trial, in which no condom counseling was given. Note that in unblinded trials with secondary interventions, even under the null hypothesis that the study product has no effect, even for large sample sizes there may be a large difference in infection rates between the two arms (for example, due to differential condom use between the arms).

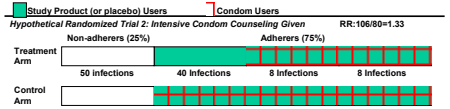

Illustration of Reason B for why a study product could be more (or less) effective, depending on whether the product is given in an environment of no condom counseling vs. intensive condom counseling.

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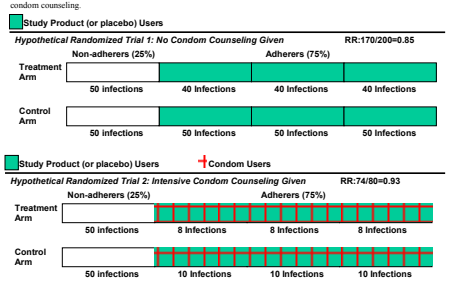
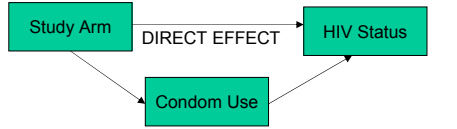


Estimating Direct Effects: Adjusting for a Mediator (condom use)

We want to estimate the effect of diaphragm provision, at a set level of condom use.
We call this the direct effect of treatment assignment.

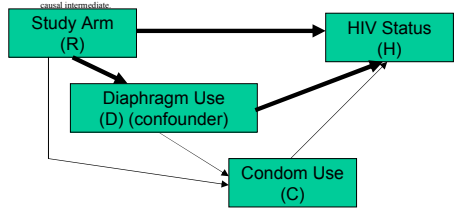


Direct Effect Definition, in terms of Counterfactuals

We consider 3 condom use categories: never users (c=0), sometimes users (c=1/2), always users (c=1)
The Direct Effect is defined to be the probability of HIV infection for those given diaphragms and gel, were their condom use set at frequency c, divided by the probability of HIV infection for those not given diaphragm and gel, were their condom use also set at frequency c.

Estimation of Direct Effects

When there are no confounders of the effect of condom use on HIV infection, the direct effect of treatment arm assignment on HIV status, for condom use set at level c, is simply
P(HIV Positive | Arm = Diaphragm, Condom use = c) / P(HIV Positive | Arm = Control, Condom Use = c).
However, since condom use is not randomly assigned, there are likely confounders of its effect on HIV status, such as number of partners and STI's. Some such confounders may be causal intermediates, meaning they are influenced by treatment arm assignment; for example, diaphragm use, depicted in the causal diagram below, is a causal intermediate.



One cannot use straightforward regression to estimate direct effects in the presence of causal intermediates, such as Diaphragm Use in the above causal diagram, since controlling for diaphragm use would leave out an important causal pathway one would like to capture, while not controlling for diaphragm use would expose one to unmeasured confounding of the effect of condom use on HIV status. One option for estimating direct effects in the presence of causal intermediates is to use an inverse probability of treatment weighted (IPTW) estimator.

Inverse Probability of Treatment Weighted (IPTW) Estimator of Direct Effect

In the MIRA trial of the effectiveness of latex diaphragms in preventing HIV, for the point treatment setting (ignoring longitudinal data, which can be handled by a similar, but more complicated, IPTW estimator), the IPTW estimator is given below, where R represents (randomized) arm assignment, C represents condom use, H represents HIV status, D represents diaphragm use, and W represents baseline confounders. P(CR,D,W) is the estimated probability of condom use being at frequency c, given arm assignment R, diaphragm use D, and baseline confounders W. We assume each subject has 50% probability of being assigned to either arm.

$$\hat{P}_{r,c} = \frac{1}{n}\sum_{i=1}^{n} \frac{1\{R_i = r, C_i = c, H_i = 1\}}{\hat{P}(C = c \mid R = r, D = D_i, W = W_i)/2}$$

Here, the direct effect of arm assignment on HIV outcome is the ratio: $\hat{P}_{r=1,c} / \hat{P}_{r=0,c}$

Assumptions Needed for IPTW to be a Consistent Estimator of Direct Effect

The IPTW could be biased if any of the following hold:

1. There are unmeasured confounders (e.g. characteristics of male partners). Note: one advantage of randomized trial over observational study for computing direct effects: There cannot be confounders of R and H.
2. The models for condom use or hazard of HIV infection not correctly specified
3. Measurement error in condom use and/or confounders; missing data values not missing at random
4. Experimental Treatment Assignment Violation: Very Low or very high probability of condom use given specific values of past covariates and past condom use.

Also, note that if intensive condom counseling affects diaphragm adherence or HIV risk factors other than condom use, then the direct effects estimates will not generalize to environments with different levels of condom counseling.

Conclusions

Because the intent to treat (ITT) estimate of diaphragm effectiveness doesn't answer the questions of most public health importance for the MIRA trial, we propose a direct effects analysis to answer the following questions:
How does providing diaphragms and gel alone compare to consistent condom use alone in reducing HIV transmission?
How does providing diaphragms and gel alone compare to unprotected sex, in terms of risk of HIV infection?
These methods can be used in other clinical trials of new HIV prevention methods, in which the effectiveness of the new method may be affected by intensive condom counseling.

Selected References

J. Trussell and R. Dominik. Will microbicide trials yield unbiased estimates of microbicide efficacy?.*Contraception* 72(6):408-413, December 2005.
M. J. van der Laan and M.L. Petersen, "Direct Effect Models" (August 2005). *U.C. Berkeley Division of Biostatistics Working Paper Series*. Working Paper 187. http://www.bepress.com/ucbbiostat/paper187

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