

Estimating Direct Effects of New HIV Prevention Methods. Focus: the MIRA Trial

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Overview of Talk

- Motivation: In randomized, controlled trials of new HIV prevention methods, the Intention 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.
- Present supplemental analysis tool, requiring more assumptions than the ITT, to help answer some of these public health questions.
- We focus on the MIRA trial in this talk.
- Bonus Features at the End

Summary of MIRA Trial:

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

Most Important Public Health Questions:

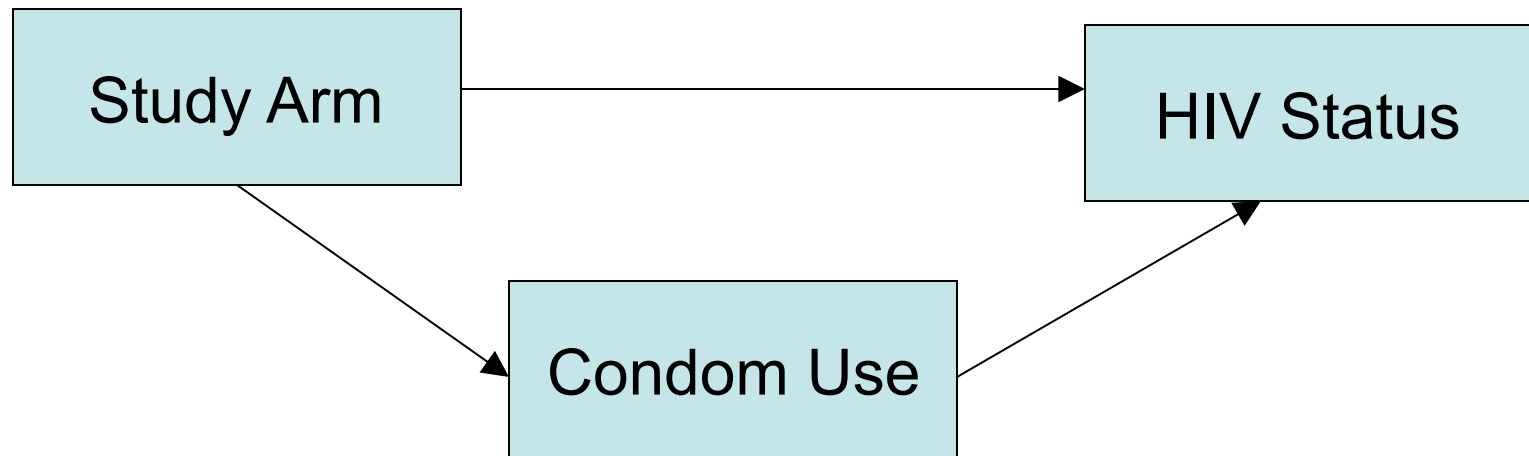
1. What is the effectiveness of providing study product in environment of country-level standard condom counseling?
(in environment of no condom counseling?)
2. How does providing study product alone compare to consistent condom use alone in reducing HIV transmission?
3. How does providing the study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

None of these answered by ITT.

Results of MIRA Trial

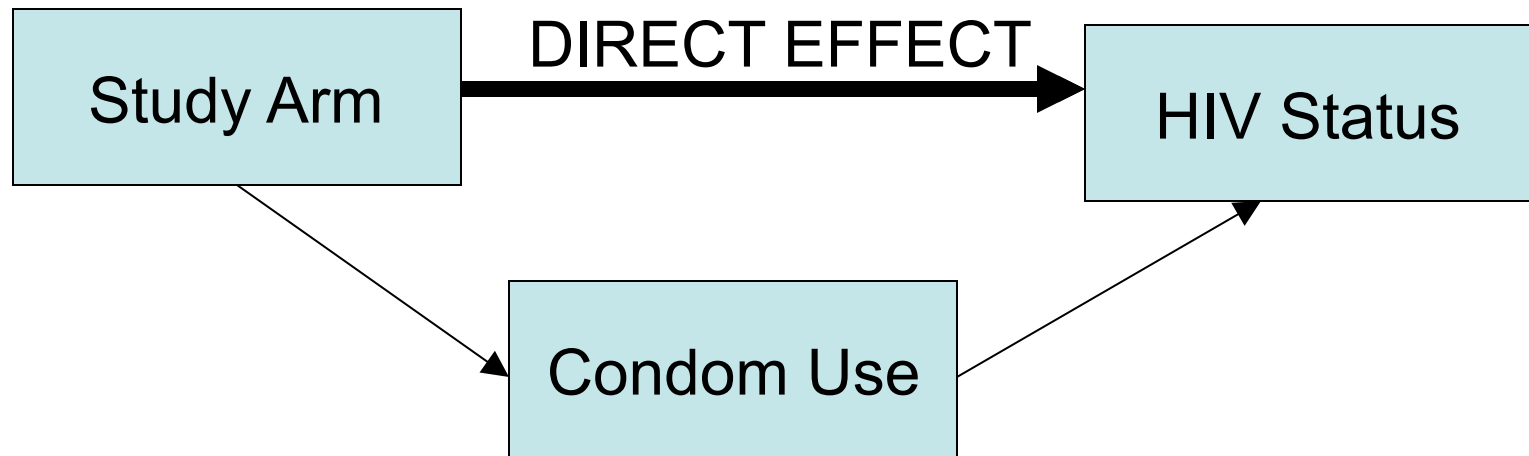
- Intention to Treat Analysis:
 - 158 new HIV infections in Diaphragm Arm
 - 151 new HIV infections in Control Arm
- But Avg. Reported Condom use (at last sex)
 - 53.5% in Diaphragm Arm
 - 85.1% in Control Arm
- To make sense of this—we'd like to understand the role of condom use in mediating the effect of treatment assignment on HIV infection.

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.

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



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Direct Effect Definition, using Counterfactuals

We consider 3 condom use categories:

never users ($c=0$), sometimes users ($c=1/2$),
always users ($c=1$)

- Direct Effect defined to be:

Probability of HIV infection for those given diaphragms and gel, were they to constrained to use condoms at frequency c , minus

the probability of HIV infection for those not given diaphragm and gel, were they constrained to use condoms at frequency c .

Public Health Questions in terms of Direct Effects

3. How does providing diaphragms and gel alone compare to unprotected sex, in terms of risk of HIV infection?

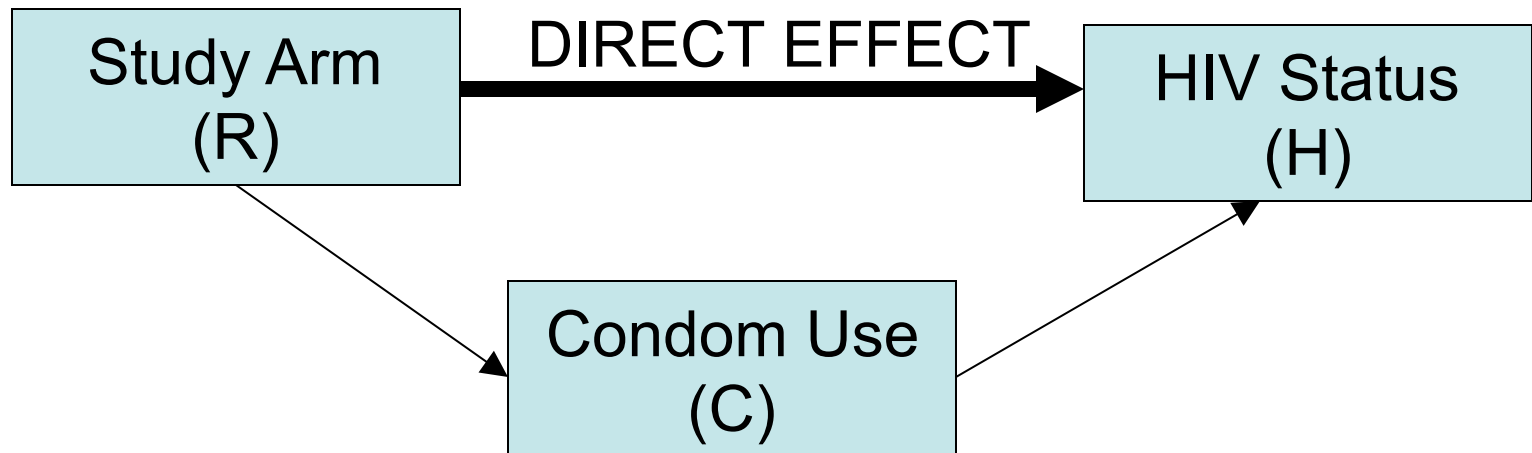
Equivalent to:

What is direct effect of providing diaphragms, with condom use set at at “never use.”

Estimation of Direct Effect When There Are **No** Confounders

- Direct Effect Estimate:

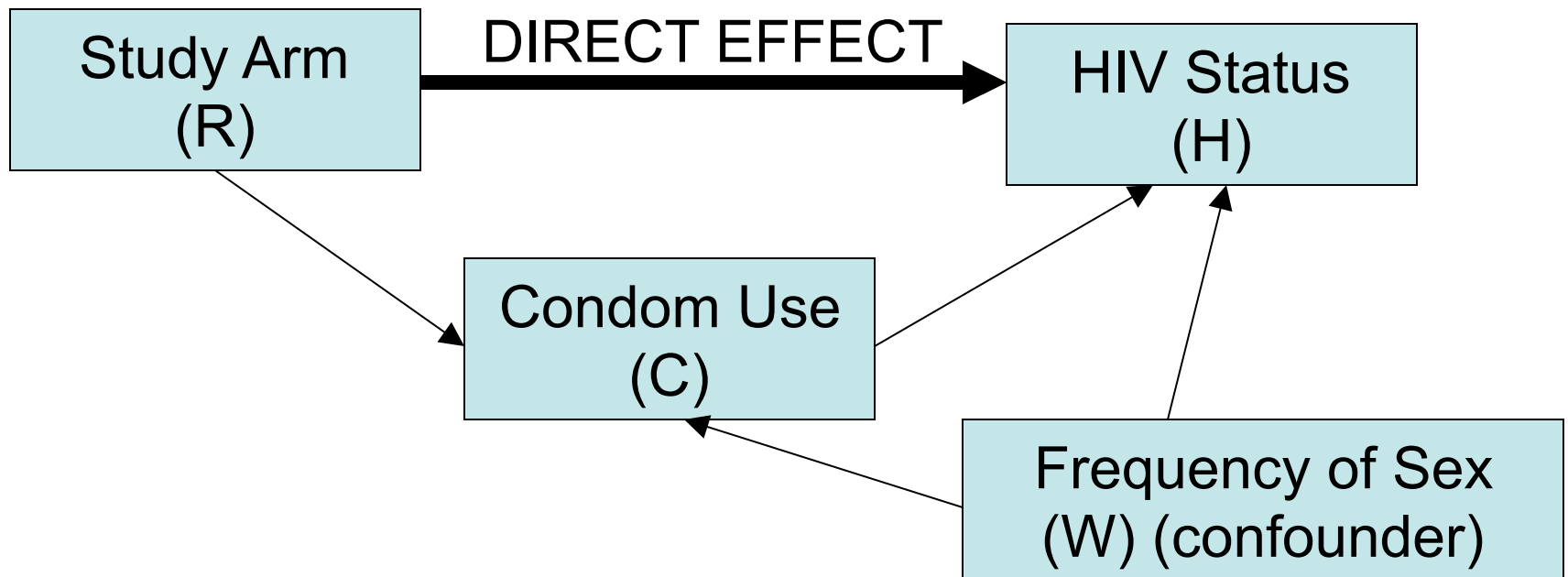
$$\begin{aligned} & P(\text{HIV Positive} \mid \text{Arm} = \text{Diaphragm}, C = c) / \\ & P(\text{HIV Positive} \mid \text{Arm} = \text{Control}, C = c) \\ & = P(H=1 \mid R = 1, C = c) / P(H=1 \mid R=0, C=c) \end{aligned}$$



Estimation of Direct Effect When There Are Confounders

Direct Effect Estimate =

$$E_W[P(H=1 | R=1, C=c, W)] / E_W[P(H=1 | R=0, C=c, W)]$$



Estimation of Direct Effect When There Are Confounders

- Direct Effect Estimate = $E_W[P(H=1 | R=1, C=c, W)] / E_W[P(H=1 | R=0, C=c, W)]$

For high dimensional W , we need to model

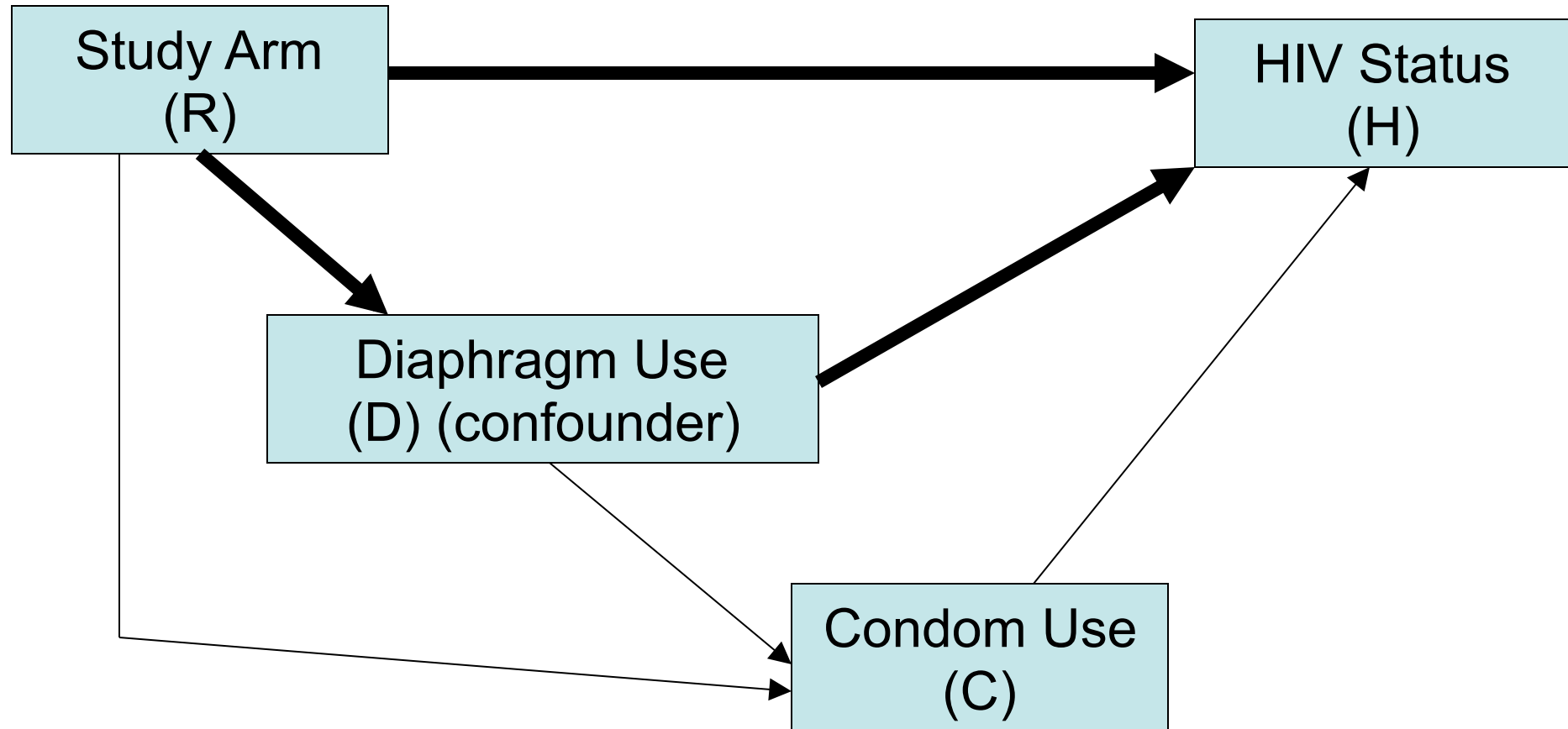
$P(H = 1 | R, C, W)$. For example,

$P(H = 1 | R, C, W) =$

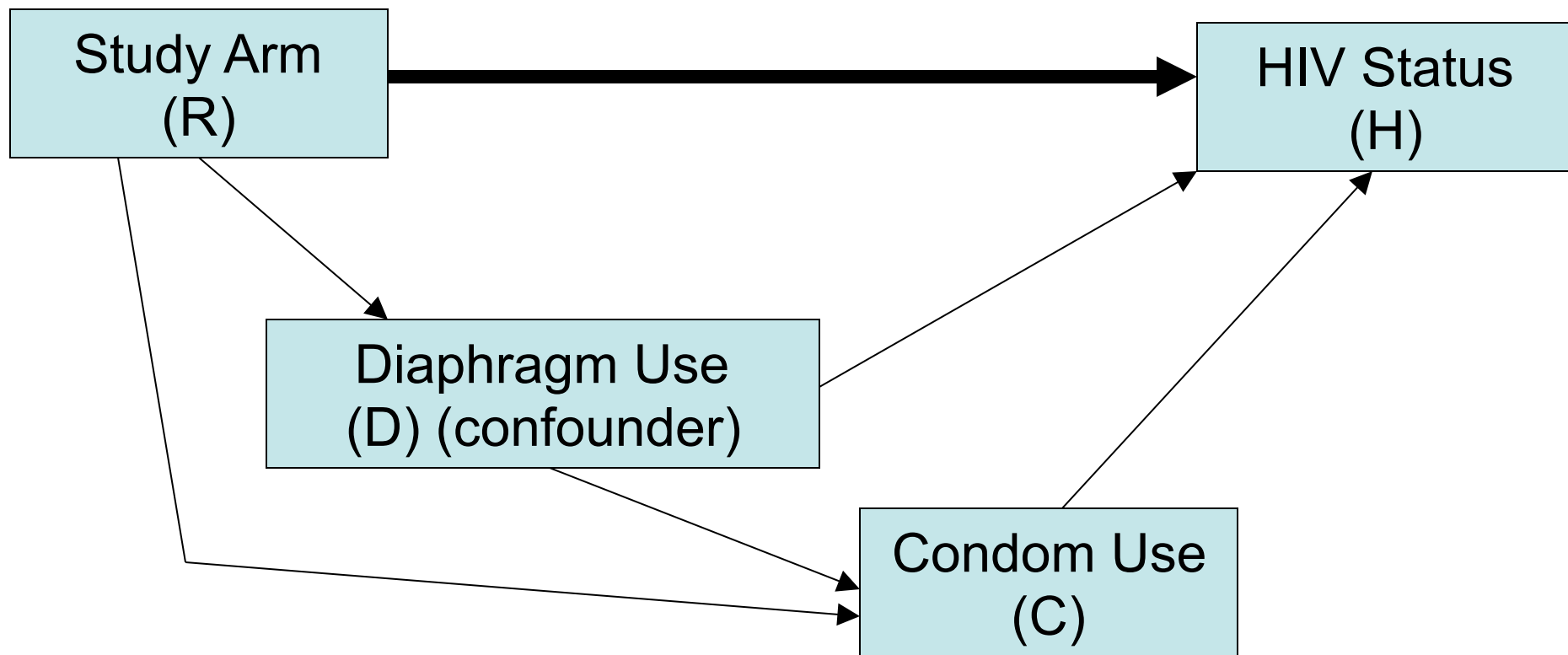
$$\text{logit}^{-1}(a_0 + a_1 R + a_2 C + a_3 R \cdot C + a_4 W)$$

Fit the model, take empirical means with respect to W , and take ratio to get direct effect estimate.

Estimation of Direct Effect When There Are Confounders as Causal Intermediates



Why Regression Gives Biased Estimates When There Are Confounders as Causal Intermediates



Using Regression, if we control for D, we don't get the direct effect that we want.

Solution: Use Inverse Probability of Treatment Weighted (IPTW) Estimator:

Estimated Probability of Infection for R=r,C=c:

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

Estimated Direct Effect = $\hat{P}_{r=1,c} / \hat{P}_{r=0,c}$

Limitations of Our Analysis

Bias could result from:

1. Unmeasured confounders (e.g. characteristics of male partners).
2. Models not correctly specified
3. Measurement error
4. Intensive condom counseling affecting HIV risk factors other than condom use
5. Experimental Treatment Assignment Violation

Results of Direct Effects Analysis

- Relative Risk of HIV infection between Diaphragm arm and Control arm by end of Trial, with Condom Use Fixed at “**Never**”: **0.59 (95% CI: 0.26, 4.56)**
- Relative Risk of HIV infection between Diaphragm arm and Control arm by end of Trial, with Condom Use Fixed at “**Always**”: **0.96 (95% CI: 0.59, 1.45)**

Conclusion: No evidence from direct effects analysis that diaphragms prevent (or don't prevent) HIV.

But then how do we explain:

- Intention to Treat Analysis:
 - 158 new HIV infections in Diaphragm Arm
 - 151 new HIV infections in Control Arm
- But Avg. Reported Condom use (at last sex)
 - 53.5% in Diaphragm Arm
 - 85.1% in Control Arm
- Would number of infections prevented by adding 31.6% condom use in Diaphragm arm be enough to get a statistically significant result?

CRUDE ADJUSTMENT FOR CONDOM USE

Would number of infections prevented by adding $(85.1\% - 53.5\%) = 31.6\%$ condom use be enough to get a statistically significant difference?

Adding 31.6% condom use in Diaphragm arm, assuming reported condom use 46% protective, would have prevented

$$31.6\% \times 46\% \times 158 = 23 \text{ infections.}$$

“Crudely adjusting for condom use,” we have
158-23=135 new HIV infections in Diaphragm Arm
151 new HIV infections in Control Arm

But need a difference of 41 prevented infections to get statistical significance. ☹️

Conclusion:

Because the ITT doesn't answer some questions of most public health importance for the MIRA trial, we propose a direct effects analysis as a supplementary tool.

Bonus Feature 1: Targeted Maximum Likelihood

- Work by Mark van der Laan, Dan Rubin, Kelly Moore (all at U.C. Berkeley)
- Goal: Leverage Information in Baseline Covariates to Estimate ITT Effects with Maximum Precision, while Making No Model Assumptions
- For example, for $T = \text{Treatment}$, $W = \# \text{ partners}$, First fit a model $m(T, W, \beta)$ for $P(\text{HIV} \mid T, W)$.

Then estimate marginal treatment effect relative

risk by
$$\sum_{i=1}^n m(1, W_i, \hat{\beta}) / \sum_{i=1}^n m(0, W_i, \hat{\beta})$$

Bonus Feature 2: Regression Based Hypothesis Tests

- Work by Rosenblum and van der Laan
- Goal: Hypothesis Tests for **mean treatment effects within strata of baseline covariates.**
- Valid Inference Making No Model Assumptions
- Regression-based Hypothesis Tests

For example, for $T = \text{Treatment}$, $W = \# \text{ partners}$, fit a model $m(T, W, \beta)$ for $P(\text{HIV} \mid T, W)$.

such as
$$m(T, W, \beta) = \beta_0 + \beta_1 T + \beta_2 W + \beta_3 TW$$

Then reject null if estimate of β_1 more than 1.96 robustly estimated standard errors from 0.