

# Alternatives to Intention to Treat: Direct effects of HIV Prevention Methods in the MIRA Study

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NIAID & The Gates Foundation

# References

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- S. Shiboski, M. Rosenblum and N. P. Jewell, “The impact of secondary condom interventions on the interpretation of results from HIV intervention trials,” submitted.
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# Purpose of Talk

- The application of causal inference techniques to randomized trials
  - the basic Intention to Treat (ITT) analysis may not answer the most important public health questions
  - Why are causal methods needed?
  - What questions do they answer?
  - Are these the right questions?
- We present ideas, requiring more assumptions than the ITT, for answering some of these questions.
- Two major applications
  - the MIRA trial on HIV intervention
  - pain trials and (unmasking) side effects

# The MIRA Trial

- Gates Foundation study to determine the effectiveness of a latex diaphragm in the reduction of heterosexual acquisition of HIV among women
- Two arm, randomized, controlled trial
- Primary intervention: diaphragm and gel provision to diaphragm arm (nothing to control arm).
- Secondary Intervention: Intensive condom provision and counseling given to both arms, plus treatment of STIs
- Trial is not blinded
- 5000 women seen for 18 months in three sites in Zimbabwe and South Africa

# MIRA Trial: Basic Intention to Treat Results

- Basic Intention to Treat Analysis:
  - 158 new HIV infections in Diaphragm Arm
  - 151 new HIV infections in Control Arm
- ITT estimate of Relative Risk is 1.05 with a 95% CI of (0.84, 1.30)
- End of story . . . . .?

# MIRA Trial: Basic Intention to Treat Results

- However condom use differed between the two arms:
  - 53.5% in Diaphragm Arm (by visit)
  - 85.1% in Control Arm (by visit)
- Could this mean that the diaphragm was more effective than it appeared from the basic analysis?
- 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.

# Is the Variation in Condom Usage Enough to Make a Difference?

- In the diaphragm arm, observed infection rate amongst non-condom users is 4.2 new HIV infections per 100 woman years
- To increase the condom use in the diaphragm arm to equal that in the control arm would require a change for about 1250 woman years
- Amongst these 1250 woman years we would therefore expect about 52 new infections absent condom use
- With condom use being about 80% effective, this would remove  $.8 \times 52 = 42$  infections amongst this group had condoms been used
- 116 HIV infections (Tx arm) vs 151 (control arm) would just achieve statistical significance . . . .

# 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 questions are answered by basic ITT analysis**

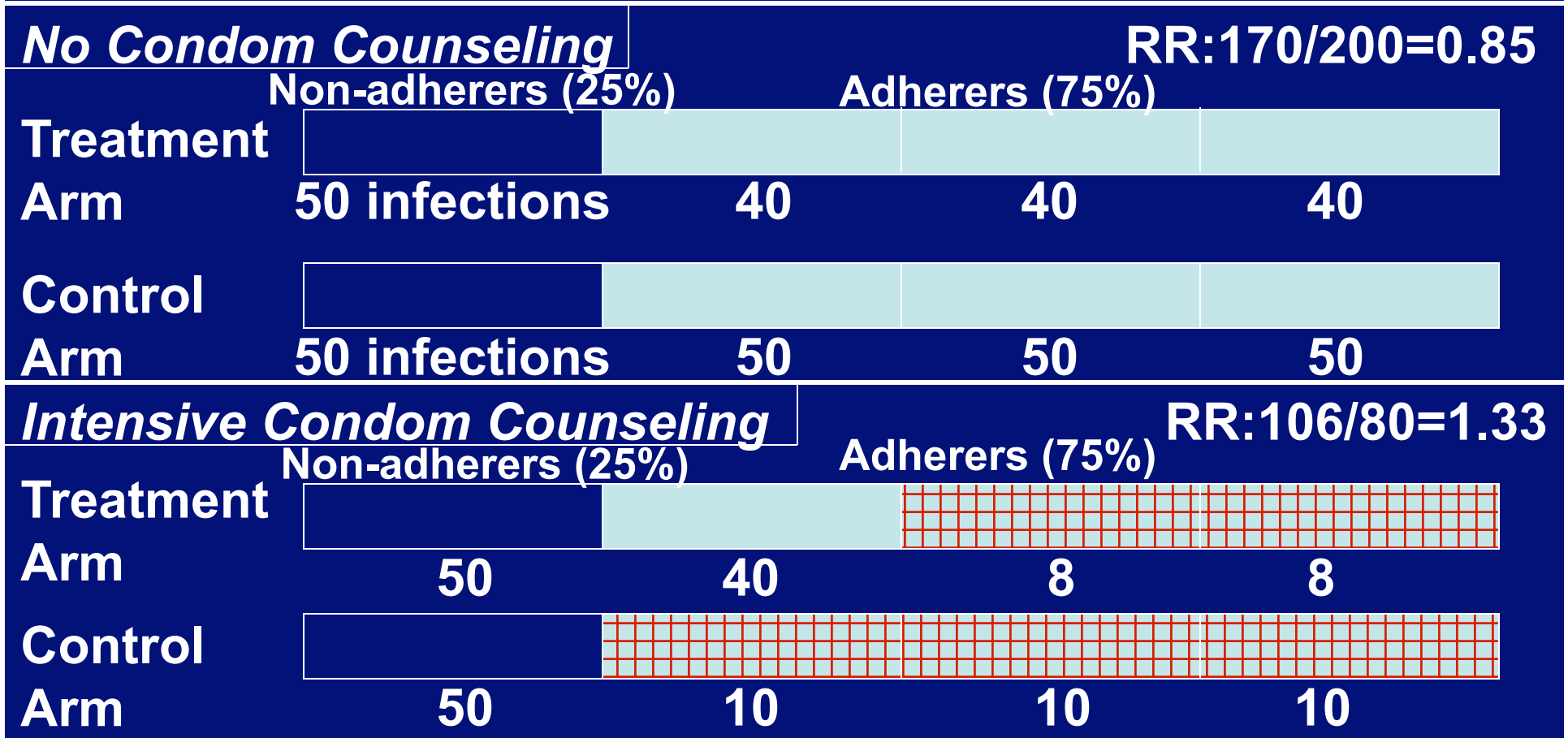
## Reasons effectiveness may be different in environment of intensive condom counseling vs. environment of country-level standard condom counseling

- A. In trials without blinding, effect of intensive condom counseling may be different for treatment arm and control arm.
- B. Effects of intensive condom counseling may be different for those who adhere to assigned treatment and those who don't.
- C. Intensive condom counseling may itself affect adherence to assigned treatment.

# Reason A: In unblinded trials, effect of intensive condom counseling may be different for treatment arm and control arm.

Assume: Condoms 80% protective, Study Product 20% efficacy, and Intensive Condom Counseling less effect in treatment arm

Study Product (or placebo) Users
  Condom Users

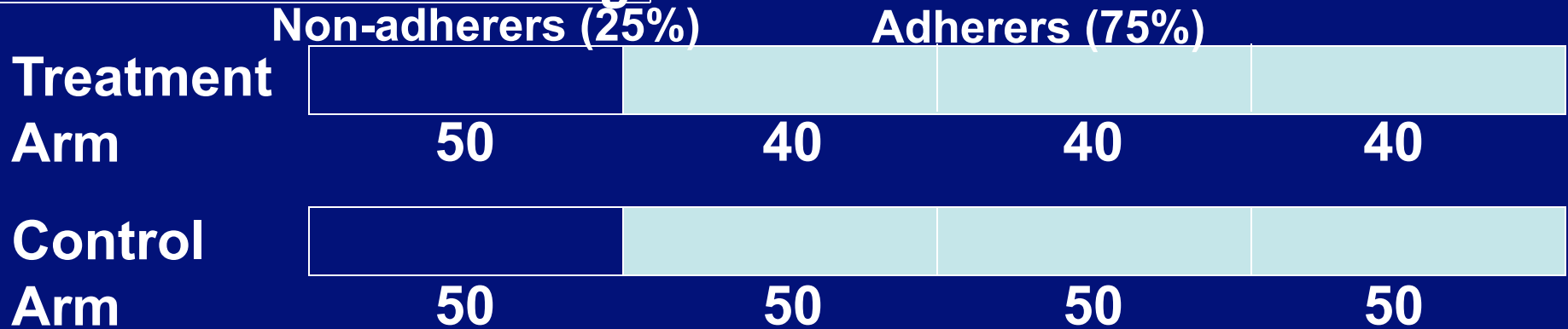


# Reason B: Effects of intensive condom counseling may be different for adherers to assigned treatment and for non-adherers

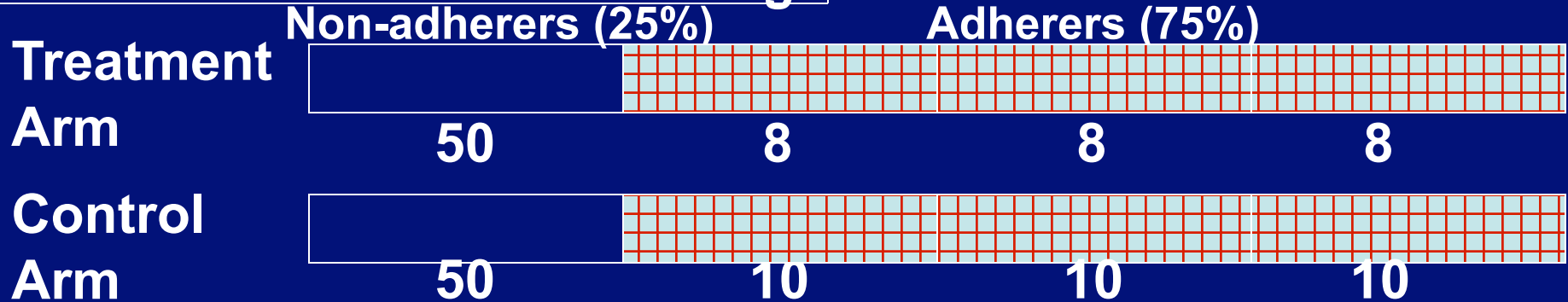
Assume Condoms 80% protective, Study Product 20% efficacy

Study Product (or placebo) Users
  Condom Users

**No Condom Counseling** RR: 170/200 = 0.85



**Intensive Condom Counseling** RR: 74/80 = 0.93



# Reason C: Intensive condom counseling may affect adherence to assigned treatment

Assume: Condoms 80% protective, Study Product 20% efficacy, and Intensive Condom Counseling Reduces Study-Product Use

Study Product (or placebo) Users
  Condom Users

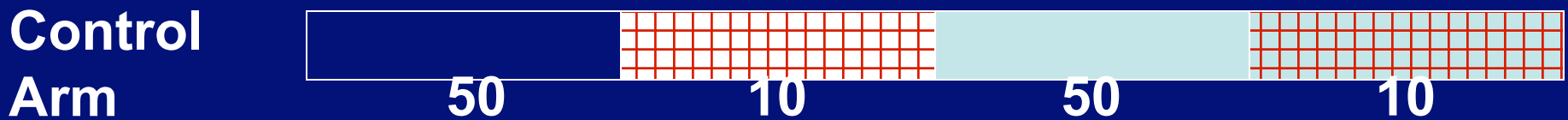
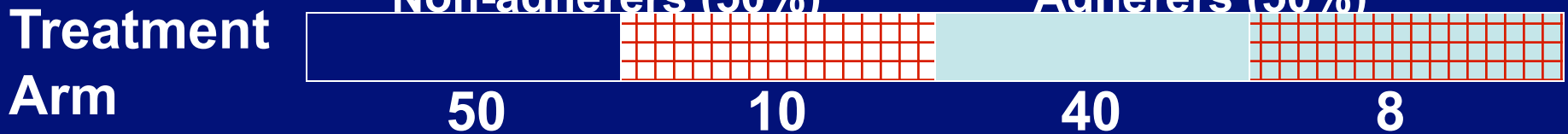
**No Condom Counseling** RR: 170/200 = 0.85

Non-adherers (25%) Adherers (75%)



**Intensive Condom Counseling** RR: 108/120 = 0.90

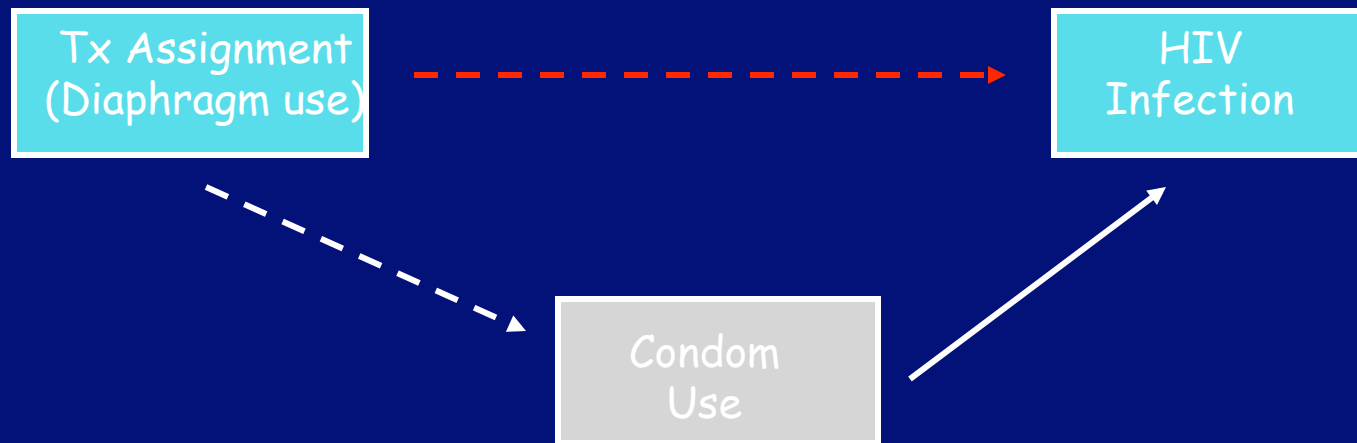
Non-adherers (50%) Adherers (50%)



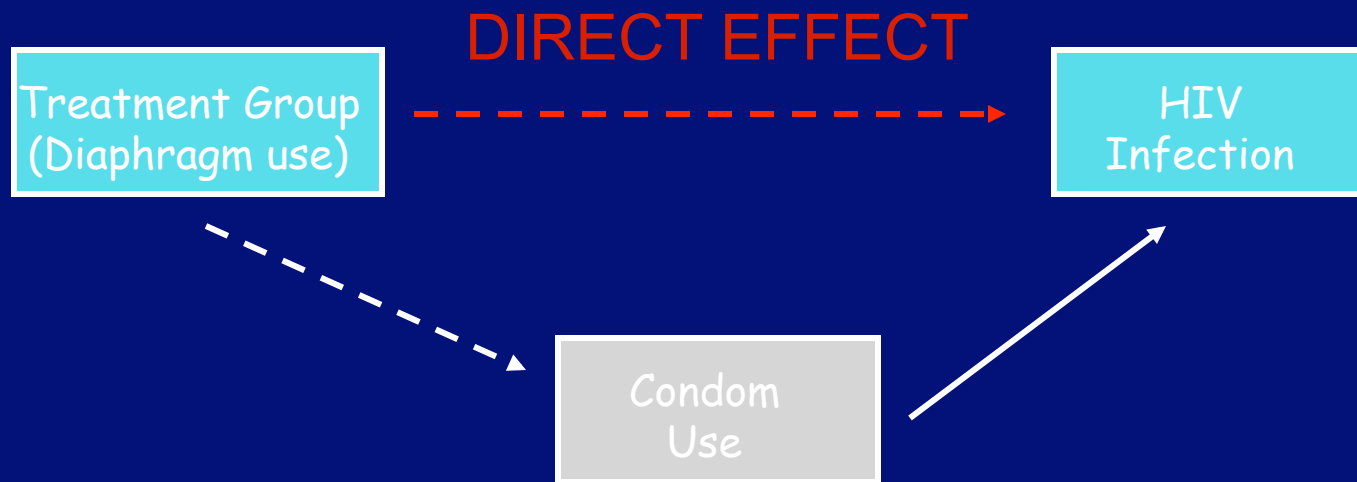
## Reason C: Intensive condom counseling may affect adherence to assigned treatment

- Because the ITT doesn't answer the questions of most public health importance for the MIRA trial, we propose a direct effects (ITT) 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?

# MIRA Trial—Randomization of Diaphragm



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



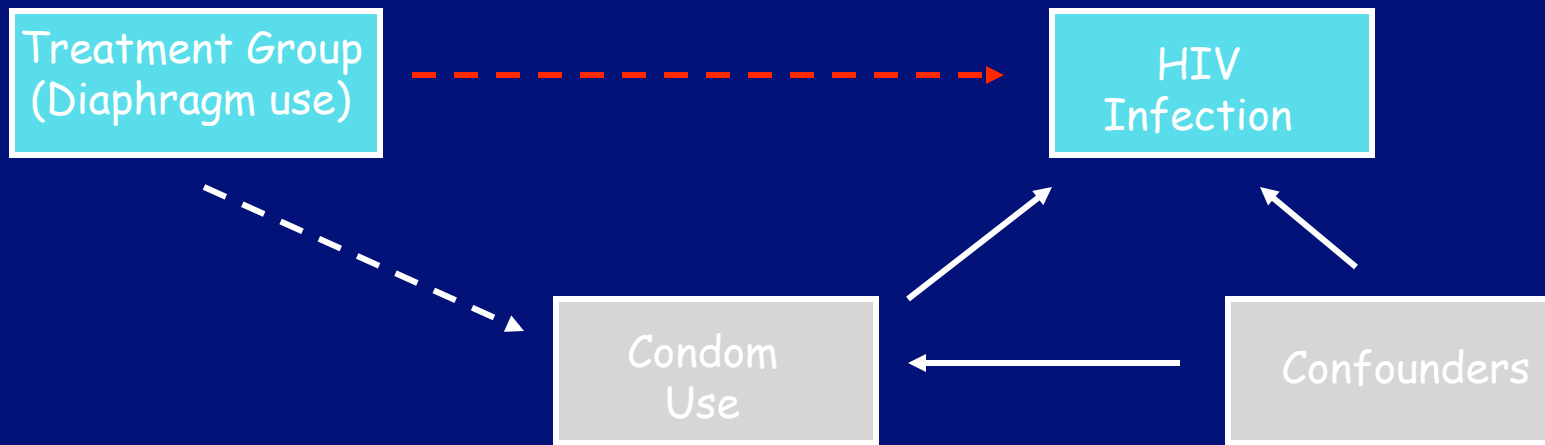
- We want to estimate the direct effect of diaphragm provision, at a set level of condom use. (Petersen et al. 2006, Robins and Greenland 1992, Pearl 2000, Rosenblum et al. 2009)
- Still ITT interpretation
- Requires Stronger Assumptions than basic ITT

# Direct Effect Definition, using Counterfactuals

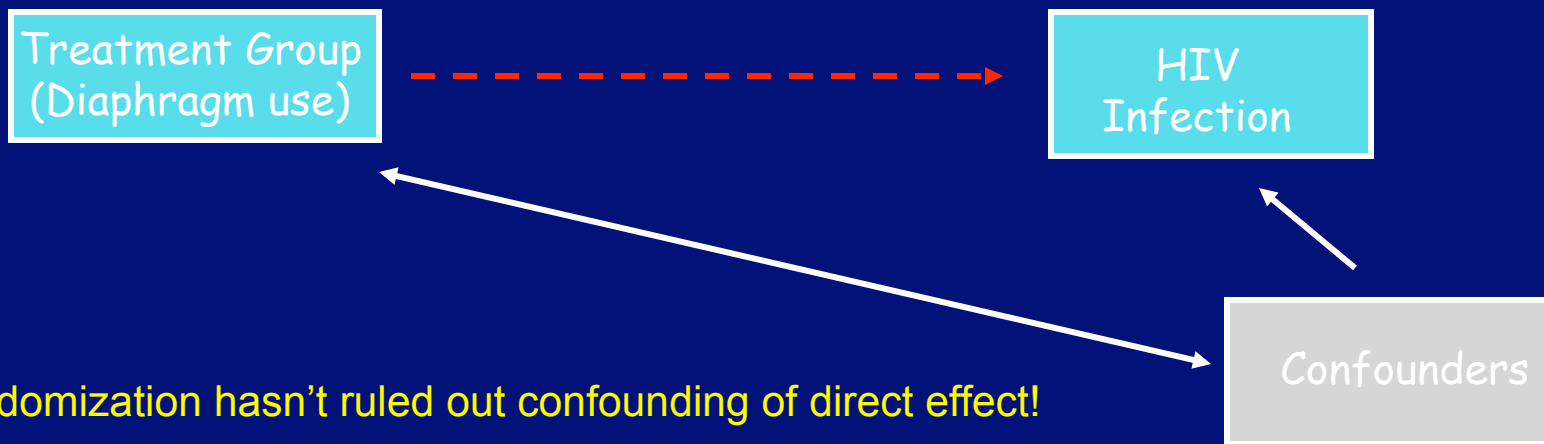
- We consider 3 condom use categories: never users ( $c=0$ ), sometimes users ( $c=1/2$ ), always users ( $c=1$ )
- Direct Effect defined to be:  
Probability of HIV infection for those given diaphragms and gel, were participants to use condoms at frequency  $c$ , divided by the probability of HIV infection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

# Estimating Direct Effects: Stratify on condom use?

(danger: condom use is not randomized)



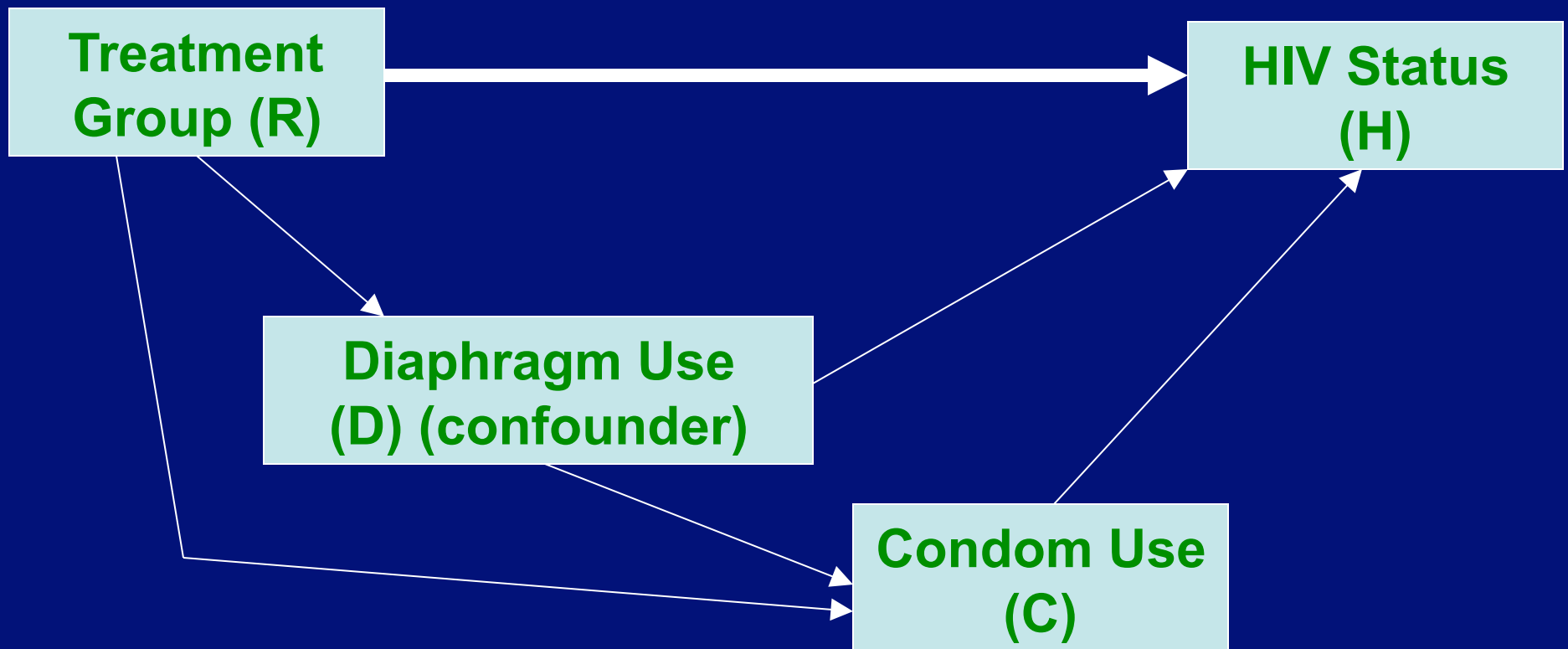
after stratification on condom use



randomization hasn't ruled out confounding of direct effect!

Now have to adjust for confounders (but we are still ITT)

# Why Stratification/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.

# Analysis Details

- We allow for diaphragm use to be a confounder of condom use
- Inverse probability weighted estimators
  - (in future, targeted maximum likelihood?)
- Allow for time-varying measures of all variables

# 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 definitive evidence from direct effects analysis that diaphragms prevent (or don't prevent) HIV.

## 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 23 infections.

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

151 new HIV infections in Control Arm

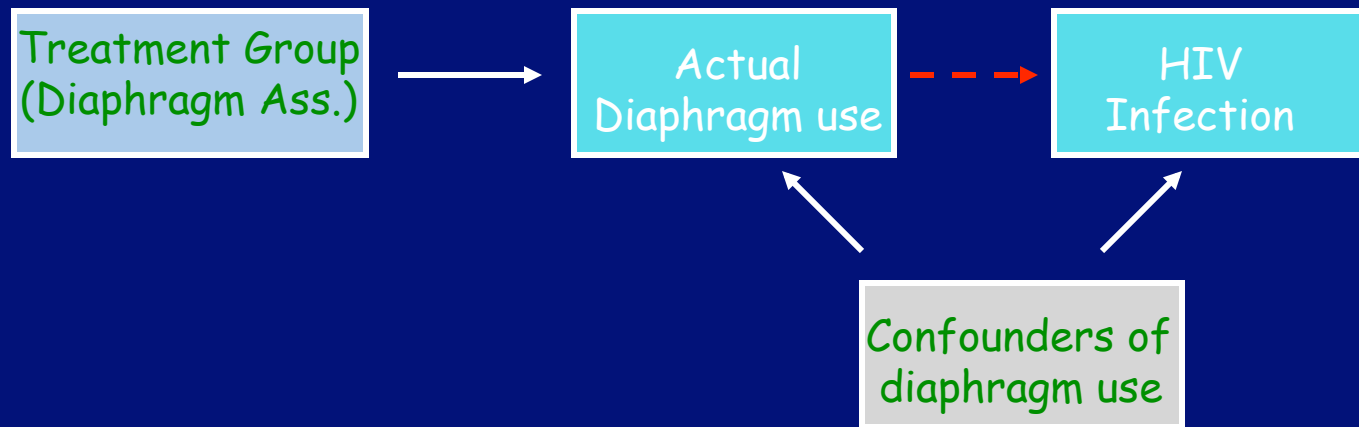
But need a difference of 41 prevented infections to get statistical significance. ☹️

# Limitations of Our Analysis

## Bias could result from:

- Unmeasured confounders (e.g. characteristics of male partners).  
Note: one advantage of randomized trial over observational study for computing D.E.: There cannot be confounders of R and H.
- Measurement error in condom use (currently being assessed) and/or confounders; missing data values
- Experimental Treatment Assignment Violation: Very Low or very high probability of condom use given specific values of past covariates and past condom use.

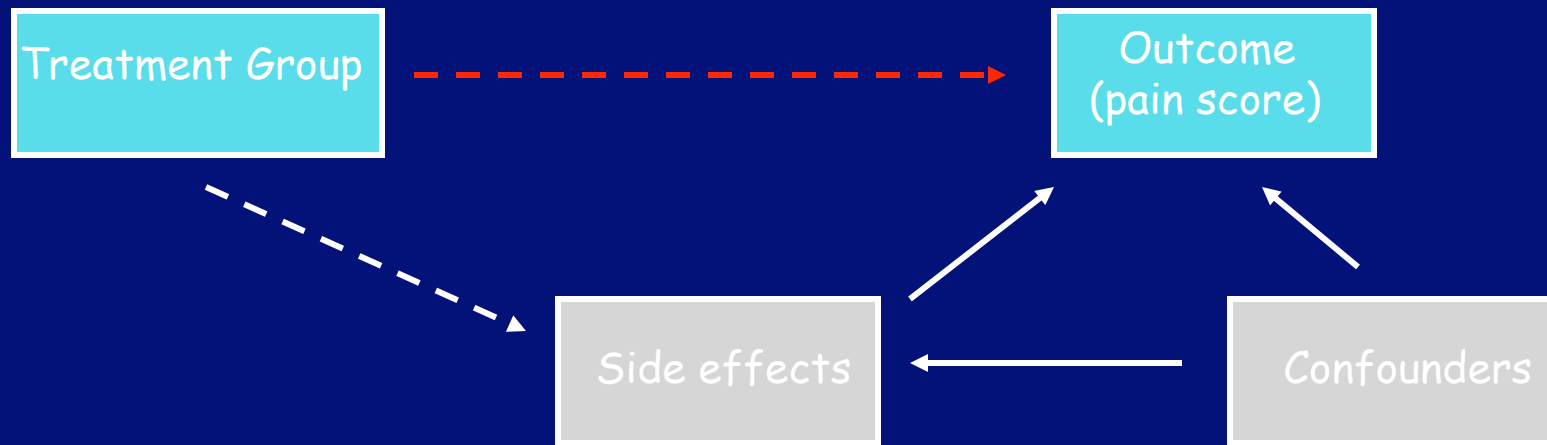
# Further Complication: Assessing Effects of D itself (non-ITT:compliance)



Non-compliance with assigned treatment  
(but have instrumental variables across three sites)

On-going work

# Application to Unmasking of Blinded Treatment Assignment Due to Side Effects



- side effects are treatment-related and therefore potentially unmasking
- outcome is measured subjectively
- actual use of the drug (adherence) is a potential confounder

## Advantages/Differences of Blinded Trials

- Different causal diagrams in each arm
- Testing the null is appropriate even with differential rate of side effects amongst adherents/non-adherents
- ITT analysis will not 'reverse' effects

# Implications for Design/Analysis?

- Causal methods help us think about what we want to estimate and appropriate methods to collect data to achieve this goal
- Ethics of intensive condom counseling--human subjects review?
- Alternative (adaptive) designs (focus on non-condom users, adherents etc)
- How do we measure use of condoms effectively?
- Need to think about measurement of potential confounders even with randomization?
- Blinded analysis?
- Use of surrogate outcomes (eg in this case HSV?) and comparison with outcomes of interest