




Statistical Aspects of HIV Prevention Trials

Helen Weiss

London School of Hygiene &
Tropical Medicine



“Statistical analysis is limited in being able to compensate for ineligible patients being entered, for noncompliance to intervention, for unreliable outcome measures, for missing data and for underpowered trials”.

(De Mets, J Int Med 2004)

DeMets: Statistical issues in interpreting clinical trials.

J Int Medicine. 2004;255:529-537

- Intention-to-treat principle (*use it*)
- Surrogate endpoints (*don't use them*)
- Subgroup analyses (*interpret with caution*)
- Missing data (*minimise it*)
- Non-inferiority trials (*challenging!*)

Some key statistical issues in HIV prevention trials

- Sample size & power
 - Choice of study population
 - Choice of endpoint
- Methods of analysis
- Factors influencing measured efficacy
 - Adherence
 - Withdrawal
- Some issues in studies among HIV+ individuals
- Alternative designs – alternative analyses

Randomised controlled trials of interventions to prevent HIV

Intervention	Number of trials		Impact on HIV incidence
	Complete	Ongoing	
Behaviour change	7	3	Little overall impact
Bacterial STD tx	5	0	Impact in one trial
Herpes suppressive tx	1	2	No overall impact
Male circumcision	3	0	50-60% reduction in risk in all 3 trials
Female diaphragm & gel	1	0	No overall impact
Oral pre-exposure prophylaxis	1	3	No overall impact
Vaginal microbicides	8	5	No overall impact
HIV vaccine	4	1	No overall impact

Possible reasons for lack of impact:

- No true effect
- Study too small to detect significant effect
- Poor adherence → reduced efficacy in trial



Ensuring adequate power: Key factors in choosing trial population

Individual RCT

- High HIV incidence
- Low HIV prevalence at baseline
- High follow-up rate
- High adherence with intervention

Cluster RCT

As above, plus:

- Low intra-cluster correlation
- Small risk of contamination between clusters

Sample size assumptions in MC trials

	South Africa	Kenya	Uganda
Age range	18 – 24	18 – 24	15 – 49
Assumed incidence	2.2 per 100 pyr	2.5 per 100 pyr	1.8 per 100 pyr
Effect size	0.5	0.5	0.5
Follow-up assumed	85%	85%	85%
Adherence	100%	95%	90%
Number enrolled	Control = 1,582 Int = 1,546	Control = 1,393 Int = 1,391	Control = 2,522 Int = 2,474
Observed incidence	2.1 per 100 pyr	2.1 per 100 pyr	1.3 per 100 pyr

Measuring impact at community level

- Community randomised trials
 - STD treatment trials; VCT; behavioural
 - Larger sample size than individual
 - May be only feasible intervention
- Series of cross-sectional studies
 - Impact of male circumcision on HIV in community
 - Project ACCEPT (community VCT)

Methods of analysis for HIV incidence

■ Kaplan-Meier analysis:

- Non-parametric
- Estimates cumulative risk of infection per arm

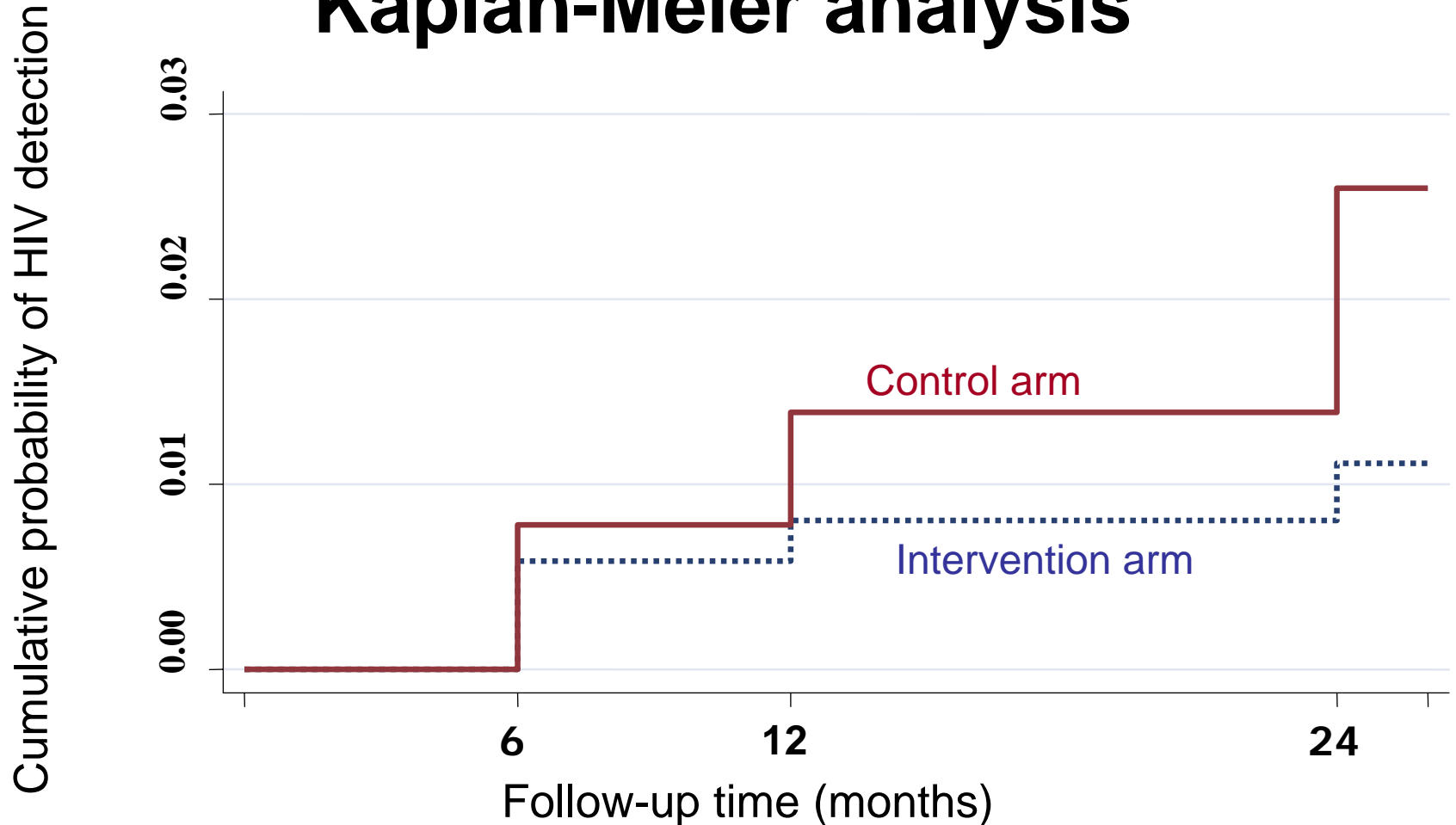
■ Cox regression:

- Assumes proportional hazards over time
- Estimates hazard ratio

■ Poisson regression:

- Number of events / person-time at risk
- Assumes that the HIV incidence is constant within specified age/time periods
- Estimates rate ratio

Rakai male circumcision trial: Kaplan-Meier analysis



Cases/total

Cont

19/2430

14/2279

12/980

Int

14/2387

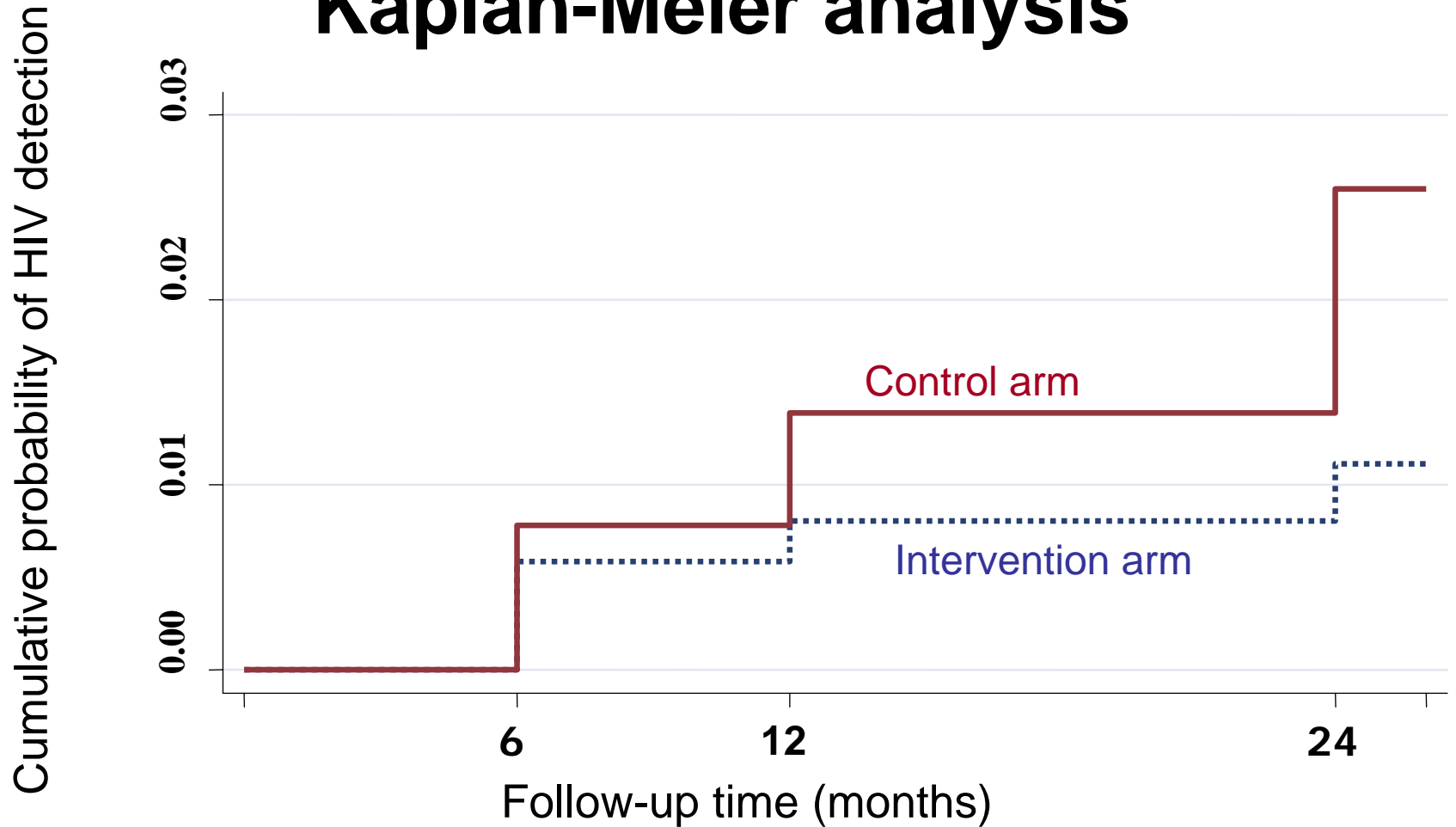
5/2274

3/964

No weighting by number at risk

Assumes all events occurred at exactly 6, 12, 24 months – not true in practice

Rakai male circumcision trial: Kaplan-Meier analysis



Cumulative risk ratio: 0.43 (95%CI 0.24-0.75)

Primary analysis: Poisson regression

Intervention	0-6 months	6-12 months	12-24 months
HIV events/py	14/1172	5/1191	3/990
Incidence/100 py	1.19	0.42	0.30
Control			
HIV events/py	19/1207	14/1176	12/1009
Incidence/100 py	1.58	1.19	1.19
Rate ratio (95%CI)	0.76 (0.35-1.60)	0.35 (0.10-1.04)	0.25 (0.05-0.94)

Overall Poisson rate ratio: 0.49 (0.28-0.84)

Intent-to-treat analysis

- Subjects compared in the treatment arms to which they were originally randomised
- Advantages
 - Preserves randomisation – minimises bias
 - Captures ‘real-life’ effectiveness
- Disadvantages
 - Does not allow for ineligible recruits, poor adherence or cross-overs

‘Modified’ intent-to-treat analysis

e.g. Kisumu male circumcision trial

Analyses	Risk ratio (95% CI)
Intent-to-Treat	0.47 (0.28-0.78)
Modified ITT (excluding 4 men HIV positive at baseline)	0.41 (0.24-0.70)
Modified ITT also excluding 4 early seroconvertors	0.32 (0.18-0.58)
Modified as-treated (allowing change in arm)	0.40 (0.23-0.68)

Adherence

- Frequency and correctness of product use (with infected partners)
- How measured?
 - Questionnaires
 - Coital logs
 - Product counts
 - Routine or ad-hoc visits
 - Validation with biological measure

Example: Mwanza HSV suppressive therapy trial *(Watson-Jones, IAS 2007)*

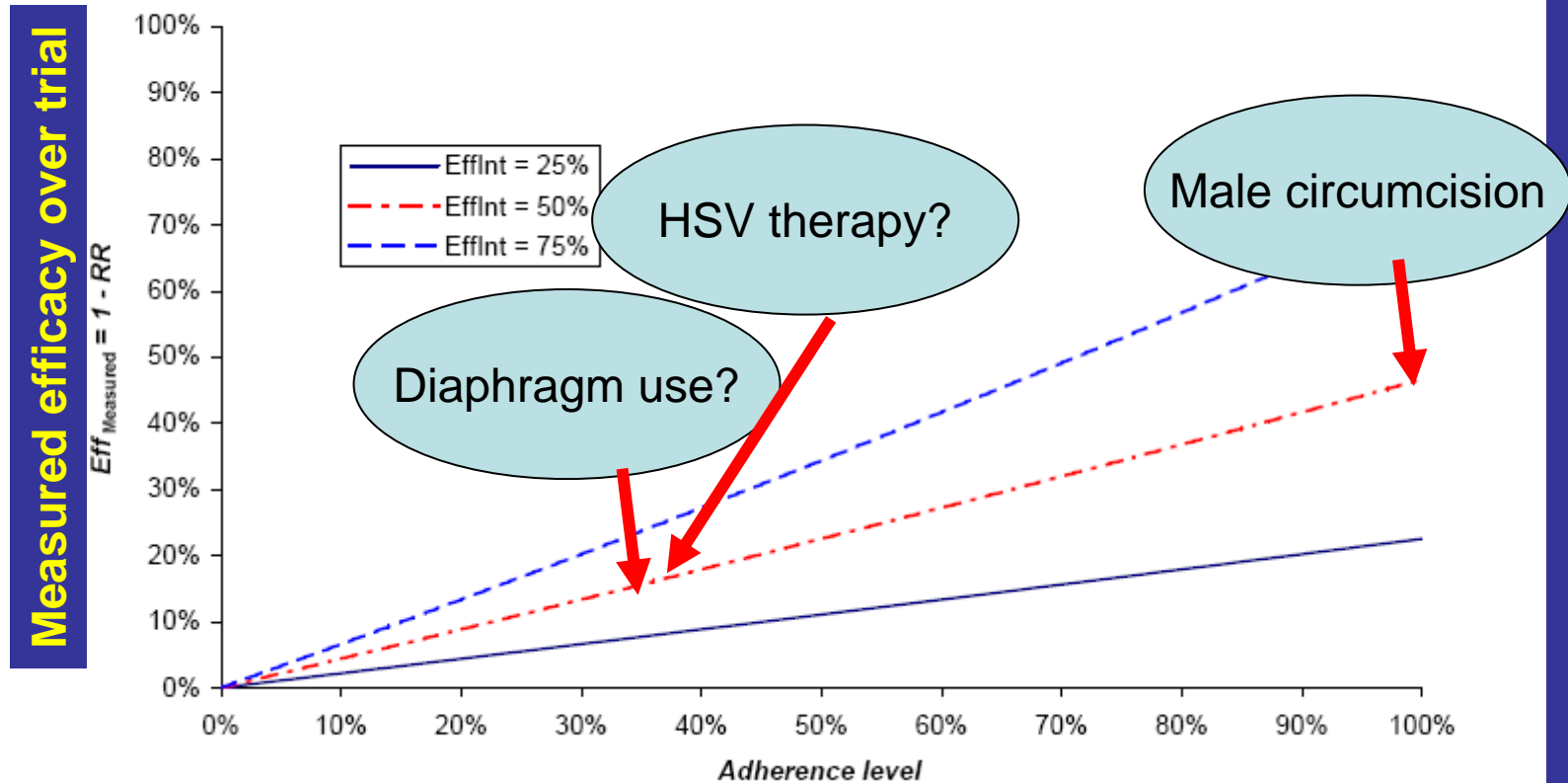
- Mobile population of high risk women
- Asked to take two 400mg tablets of aciclovir twice daily for up to 30 months
- Adherence estimated by pill count every 3 months; and at additional ad-hoc visits
- Problem of unknown adherence if women did not return tablets or reported them lost, stolen or destroyed

Adherence in Mwanza HSV trial (by pill counts)

	Person- years in placebo arm	Person- years in aciclovir arm	Incidence rate ratio (95% CI)
>90% adherence	348 (51%)	318 (52%)	0.58 (0.3-1.4)
75-90% adherence	126 (19%)	97 (16%)	1.09 (0.3-3.6)
<75% adherence	89 (13%)	90 (15%)	2.48 (0.5-12.8)
Unknown adherence	113 (17%)	101 (15%)	2.52 (0.8-8.2)

Impact of adherence on measured trial efficacy

Figure 1



Assumes 18 month follow-up, 10 coital acts per month, transmission probability 0.0015 per coital act

Dealing with sub-optimal adherence

- Anticipate adherence levels and impact of efficacy at design stage
- Measure adherence accurately during trial, with validation using biomarkers where possible
- Consider powering study for subgroups, or dose-response, by adherence level
- Note that lack of impact may reflect poor adherence, not lack of efficacy
- Can carry out analyses to allow for non-adherence (instrumental variance/causal models)

Non-adherence due to pregnancy

- Product may be contra-indicated in pregnancy (aciclovir; certain microbicides)
- Should women intending to become pregnant be excluded from the trial?
- Should women be censored at first positive pregnancy test?
- Should censored women be re-included following pregnancy/breast-feeding?

■ Mwanza HSV trial

- 20% of women became pregnant and taken off study drug. Pregnant women censored at time of first pregnancy test. No re-entry.

■ HPTN039 (suppressive therapy) & SAVVY (microbicide)

- Pregnant women discontinued from study medication but included in primary analysis

■ MIRA trial (diaphragm & gel)

- Pregnant women continued with intervention and included in primary analysis

Censoring within an RCT: analysis issues

- Specify method of analysis in advance
- Present baseline characteristics of those censored and not censored

- Disadvantages of censoring
 - No longer intention-to-treat analysis
 - Could cause bias if
 - intervention is associated with pregnancy rates, and
 - pregnancy is associated with risk of HIV
- Advantages of censoring
 - As-treated analysis gives closer measure of efficacy if censoring is unbiased w.r.t exposure & outcome

Interventions to reduce HIV transmission

- Measuring HIV viral shedding in genital secretions
 - E.g. Impact of aciclovir on genital & plasma HIV viral load
- Recruiting HIV-negative partners (*discordant partners study*)
 - E.g. Rakai MC trial of impact on M-F transmission
 - Partners in Prevention trial of impact of aciclovir on HIV transmission

ANRS 1285: Burkina Faso HSV suppressive therapy trial

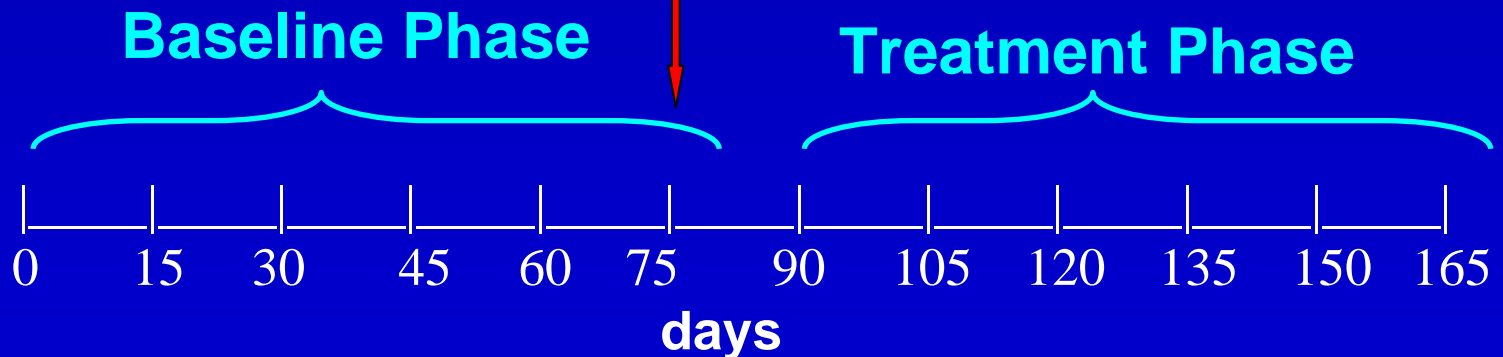
Sex workers
cohort (n=650)

PLWHA NGOs

Screening 1: HIV, HSV2, pregnancy
Screening 2: CD4+ count, creatinin

HIV+, HSV2+, ineligible for HAART

Randomised to placebo or valacyclovir

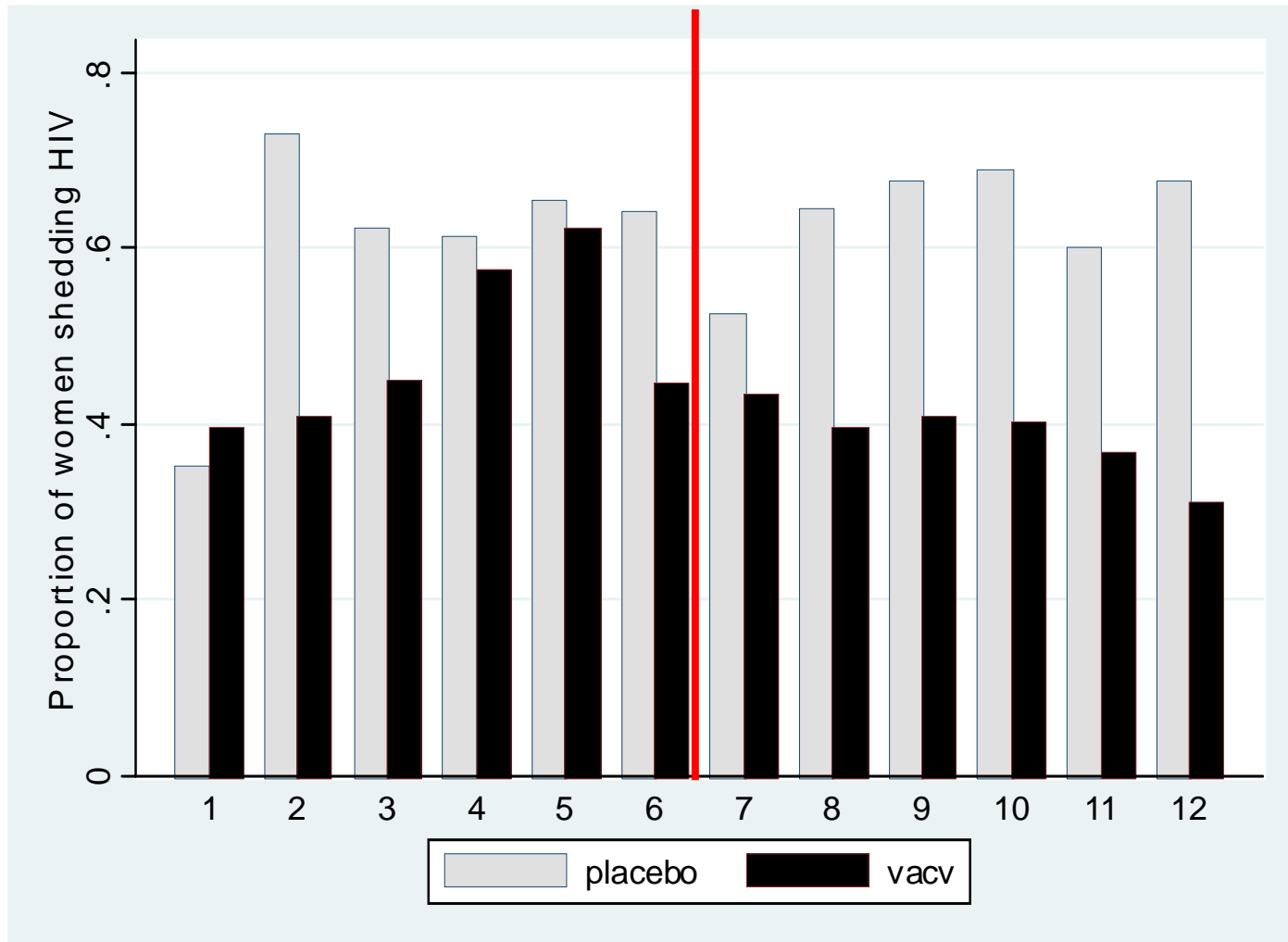


Statistical analysis issues in ANRS 1285a trial

- Risk ratio vs odds ratio
- Adjustment for baseline imbalance
- Summary measures vs repeated measures

Nagot et al, NEJM 2007

ANRS 1285a: Genital HIV viral load over time

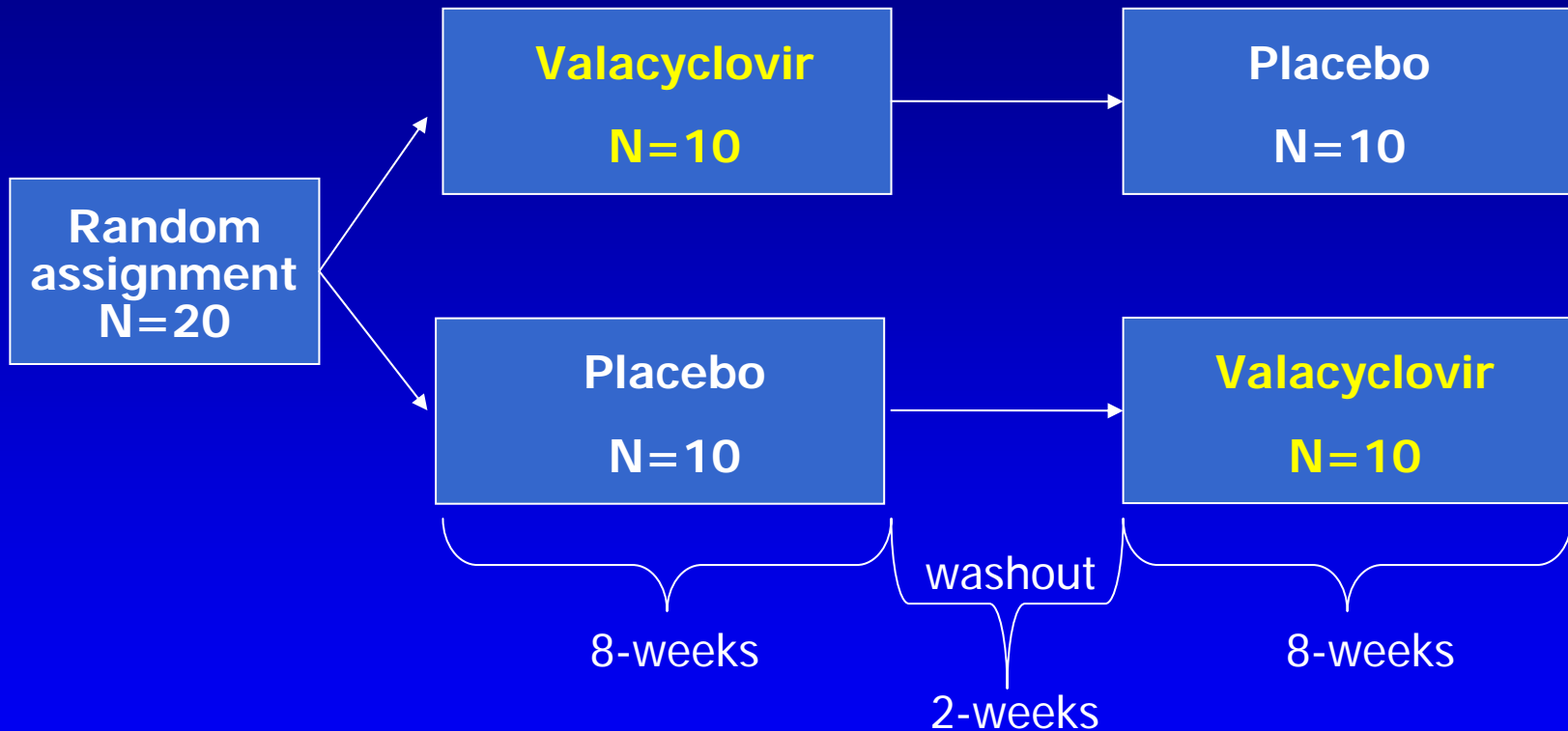


Measures of impact

- Odds ratio vs Risk ratio
 - Unadjusted OR=0.46, 95%CI 0.2-1.1
 - Unadjusted RR=0.86, 95%CI 0.7-1.0
- Adjustment for baseline imbalance in HIV shedding
 - Adjusted RR=0.93, 95%CI 0.8-1.1
- Repeated measures analysis
 - Unadjusted RR=0.62, 95%CI 0.5-0.8
 - Adjusted RR=0.77, 95%CI 0.6-0.9

Cross-over trials

Peru valaciclovir trial



HIV genital shedding detected in **4%** vs 22% of visits

Stepped wedge design: 12 clusters

	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sep	Oct	Nov	Dec
1	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
2	White	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
3	White	White	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
4	White	White	White	Green	Green	Green	Green	Green	Green	Green	Green	Green
5	White	White	White	White	Green	Green	Green	Green	Green	Green	Green	Green
6	White	White	White	White	White	Green	Green	Green	Green	Green	Green	Green
7	White	White	White	White	White	White	Green	Green	Green	Green	Green	Green
8	White	White	White	White	White	White	White	Green	Green	Green	Green	Green
9	White	White	White	White	White	White	White	White	Green	Green	Green	Green
10	White	White	White	White	White	White	White	White	White	Green	Green	Green
11	White	White	White	White	White	White	White	White	White	White	Green	Green
12	White	White	White	White	White	White	White	White	White	White	White	Green

Intervention in place

**Clusters act as controls
Random implementation order**

Pre-/Post-intervention Comparison

- Requires baseline data.
- Interpretation strengthened by pre-/post-intervention comparisons of risk factors under intervention as well as outcomes.
- Impact plausible if outcome improved and prevalence of risk factor diminished.
- However, without concurrent controls, rarely provides compelling evidence - independent secular trends in outcome &/or exposure can rarely be ruled out.

Adopters vs Non-adopters Comparison

- Carried out at individual or household level, even for cluster RCT
- Essentially a risk factor study
- Controlling confounding factors very important - since adopters may differ in many respects, including exposure to infection
- Magnitude of this problem can be assessed by comparing non-adopters in intervention area(s) with persons in control areas.
- Informs on how intervention is working – useful for extrapolation to other settings

Summary

- RCT is gold standard
- Trials must be powered adequately
- Tempting to be over-optimistic in sample size assumptions (to get funding!)
- Allow for reduced HIV incidence within trial
- Adherence major issue in most HIV prevention strategies
- Need to improve methods of estimating adherence
- ITT is least biased – but often informative to also allow for as-treated analyses
- Causal models allow for non-adherence



Beyond ITT analyses: Structural models / causal inference / instrumental variable

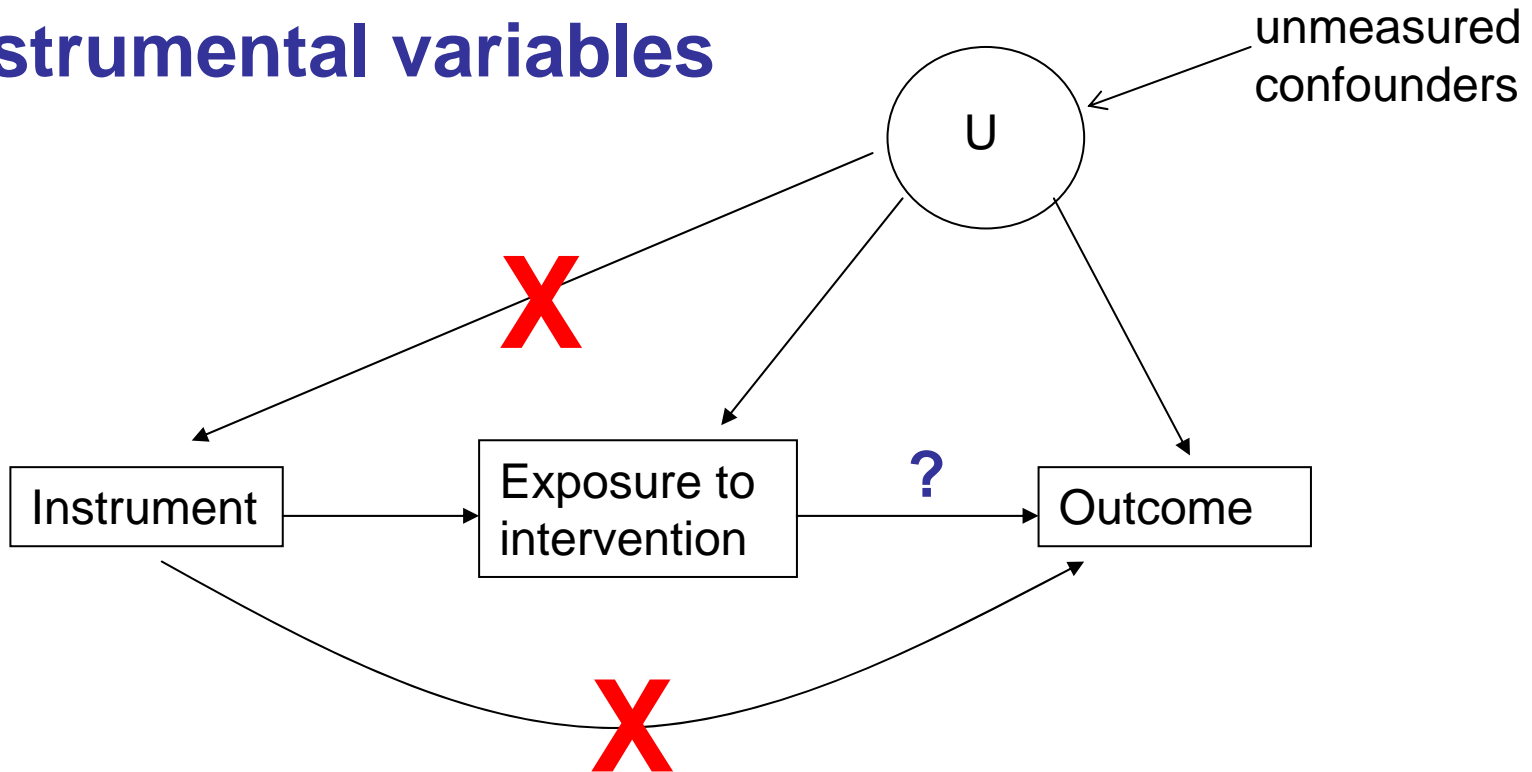
- Models the effects of actual exposure that is latent in the data

Goetghebeur & Loeys, Epi Reviews 2002

- Can estimate treatment effects with incomplete adherence

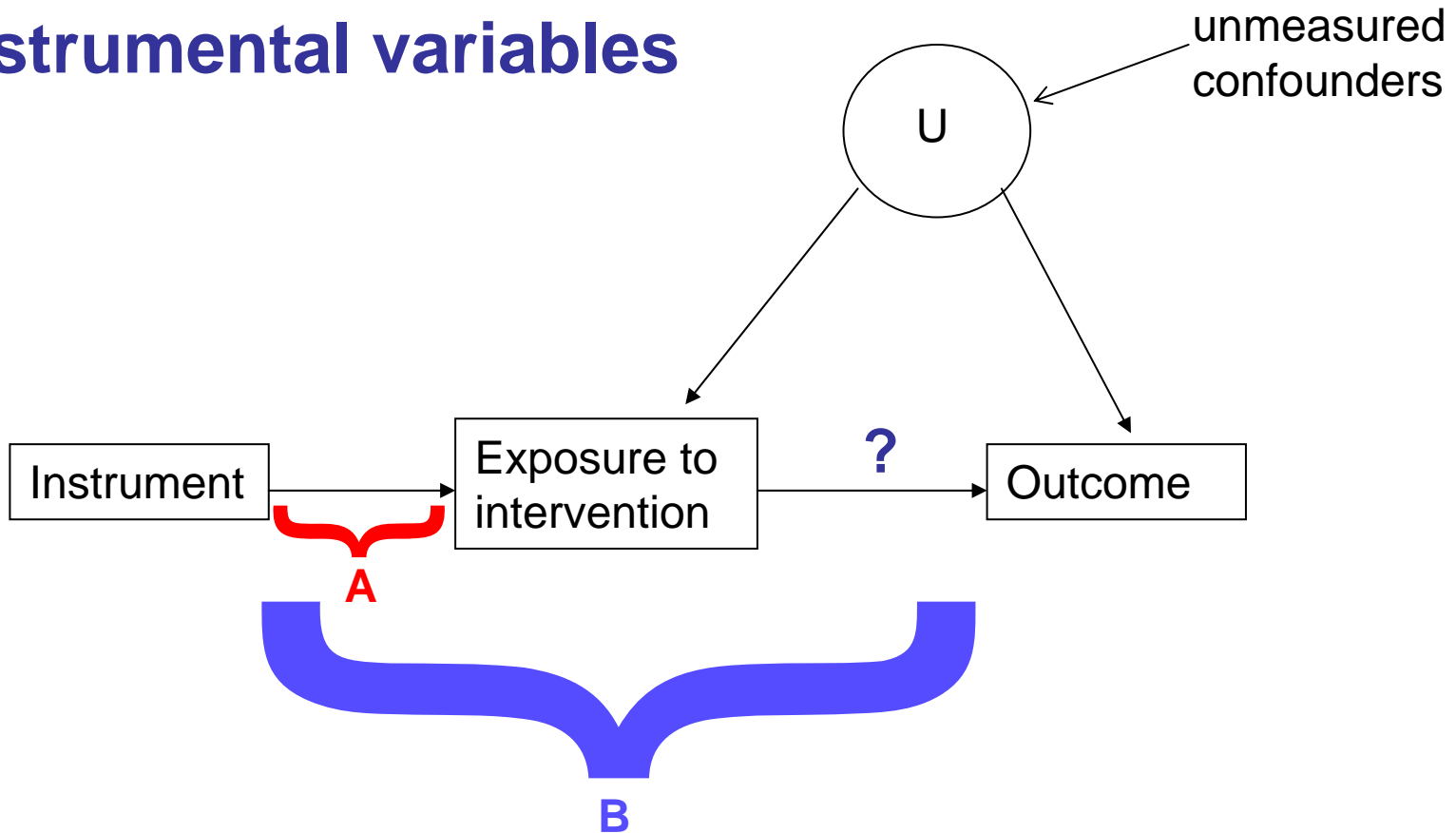
Greevy et al, JASA, 2004

Instrumental variables



- an “instrument” is a variable that precedes and is related to exposure but not directly related to the outcome or the unmeasured confounders

Instrumental variables



- by comparing **A** with **B**, such an “instrument” enables estimation of the causal effect of exposure to the intervention, unconfounded by the unmeasured confounders