UNION GRADUATE COLLEGE

Ethical and Scientific Issues in Prevention Research

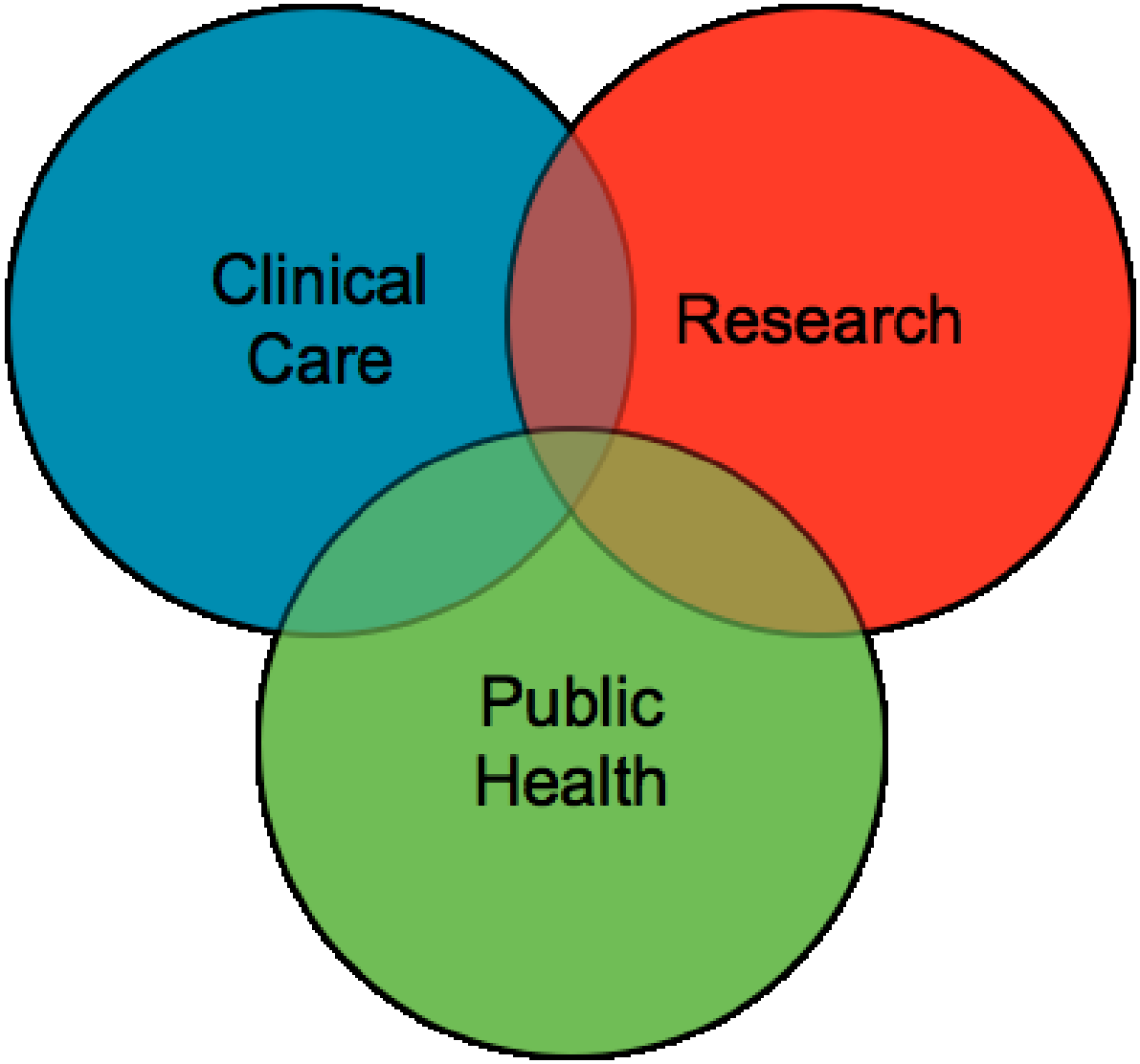
Sean Philpott, PhD, MSBioethics

The Bioethics Program

Union Graduate College-Mt. Sinai School of Medicine

UNION GRADUATE COLLEGE

Overlapping Frameworks



UNION GRADUATE COLLEGE

Medicine vs. Public Health

Medicine

- Autonomy
  - Right to decline care.
- Non-maleficence
  - Do no harm.
- Beneficence
  - Help patients.
- Justice
  - Provide equal care to all.

Public Health

- Interdependence
  - Individual actions affect others.
- Participation
  - Input from the public.
- Evidence
  - Facts, not beliefs or conjecture.

UNION GRADUATE COLLEGE

Research vs. Public Health

Research

- Respect for Persons
  - Get consent.
  - Protect the vulnerable.
- Beneficence
  - Maximize benefits.
  - Minimize risks.
- Justice
  - Fair subject selection.

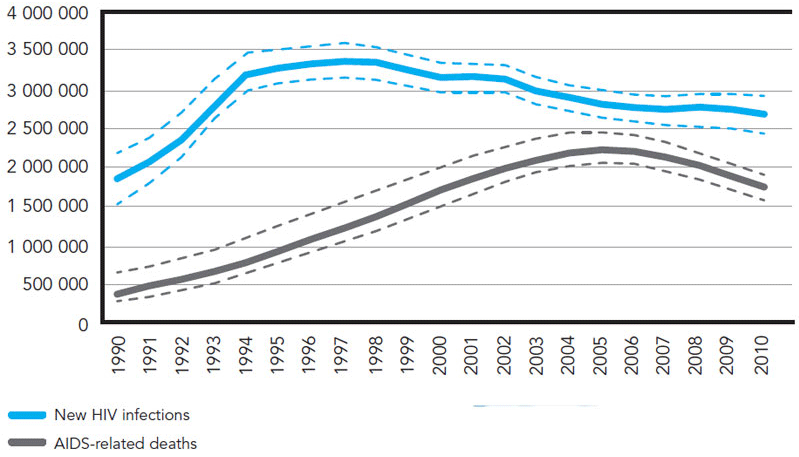
Public Health

- Interdependence
  - Individual actions affect others.
- Participation
  - Input from the public.
- Evidence
  - Facts, not beliefs or conjecture.

UNION GRADUATE COLLEGE

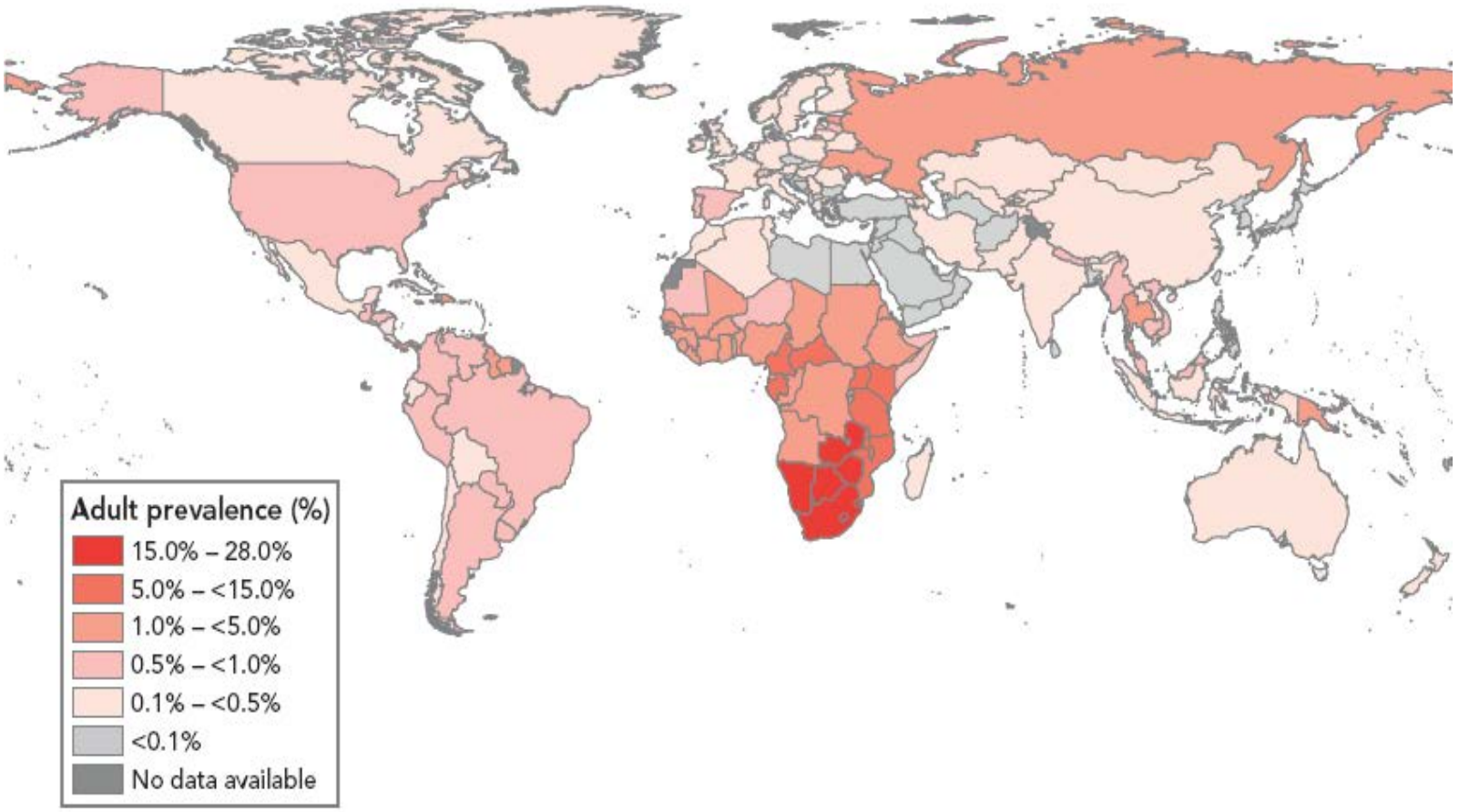
Reversing the Epidemic

- HIV/AIDS is now a largely preventable disease as well as a chronic manageable condition.
  - Behavioral interventions.
  - New prevention modalities.
    - Pre-exposure prophylaxis; and
    - Treatment as prevention.
  - Advances in treatment.



A global view of HIV infection

33.3 million people [31.4–35.3 million] living with HIV, 2009



UNION GRADUATE COLLEGE

HIV Prevention Trials

- Complex clinical trial designs.
- Healthy volunteers - “at risk”.
- Results affected by user behavior.
- Sensitive issues (e.g. sex, power, gender).
- Stigma associated with HIV and sexual activity.
- Multiple trial sites and transnational collaborations.

UNION GRADUATE COLLEGE

Vulnerability and HIV Research

- Challenge 1: HIV disproportionately affects vulnerable populations.
  - Generally, the people at greatest risk are also those who are:
    - Impoverished;
    - Less educated;
    - Stigmatized (drug users, sex workers, MSM);
    - Lack access to health care.

UNION GRADUATE COLLEGE

Inequity and HIV Research

- Challenge 2: Most HIV prevention research is done in resource-poor settings
  - "Standard of care" in HIV trials has been the subject of intense debate:
    - What package of prevention services should be provided to participants in the control arm?
    - What types of ancillary care should be provided to trial participants?

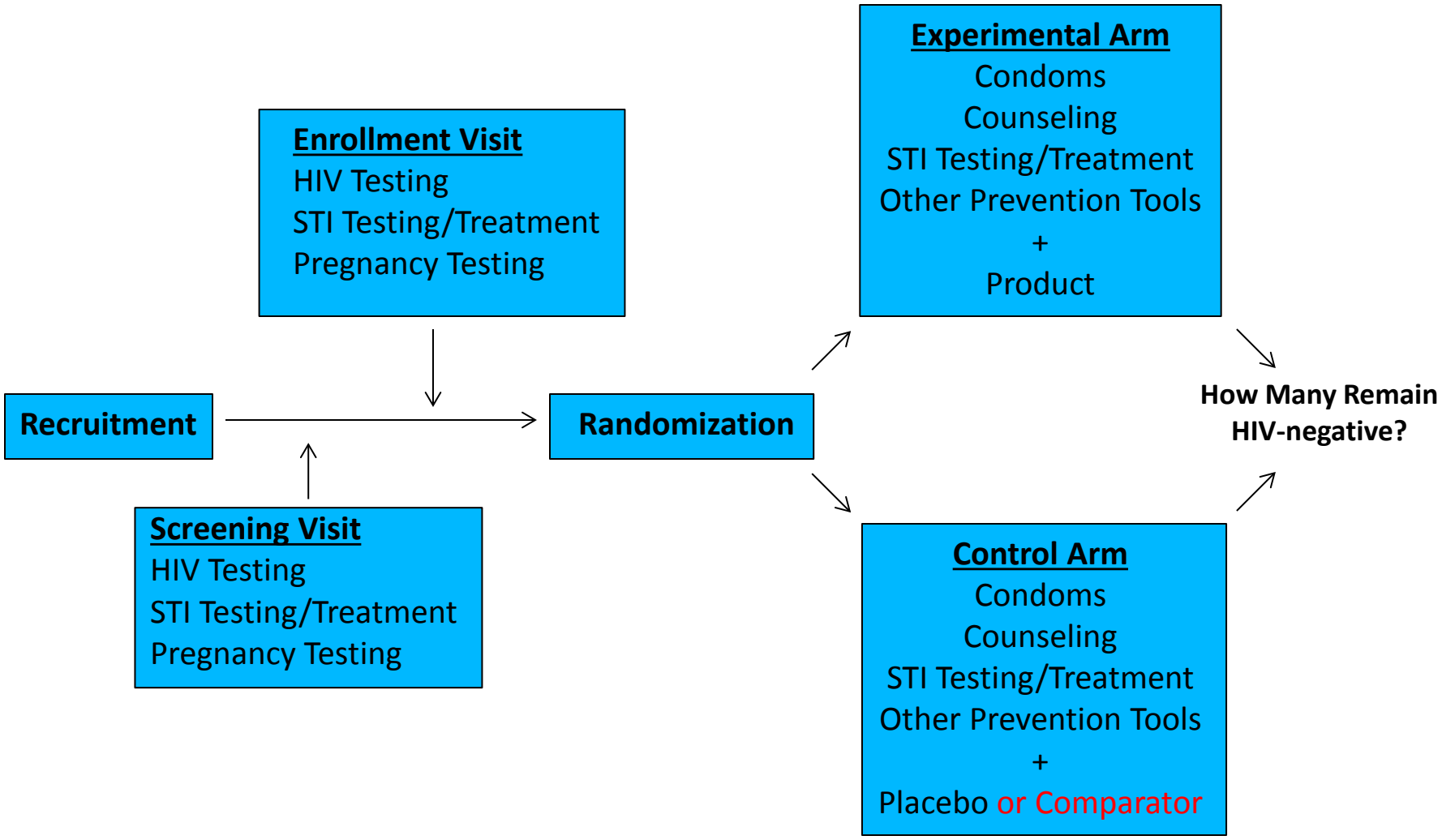
UNION GRADUATE COLLEGE

Treatment and HIV Research

- Challenge 3: Infection with HIV is a necessary study endpoint.
  - Many researchers and ethicists would argue that HIV infection occurs despite trial participation, not because of it.
  - Should these participants be offered lifelong access to HIV care and treatment?

UNION GRADUATE COLLEGE

Basic Trial Design



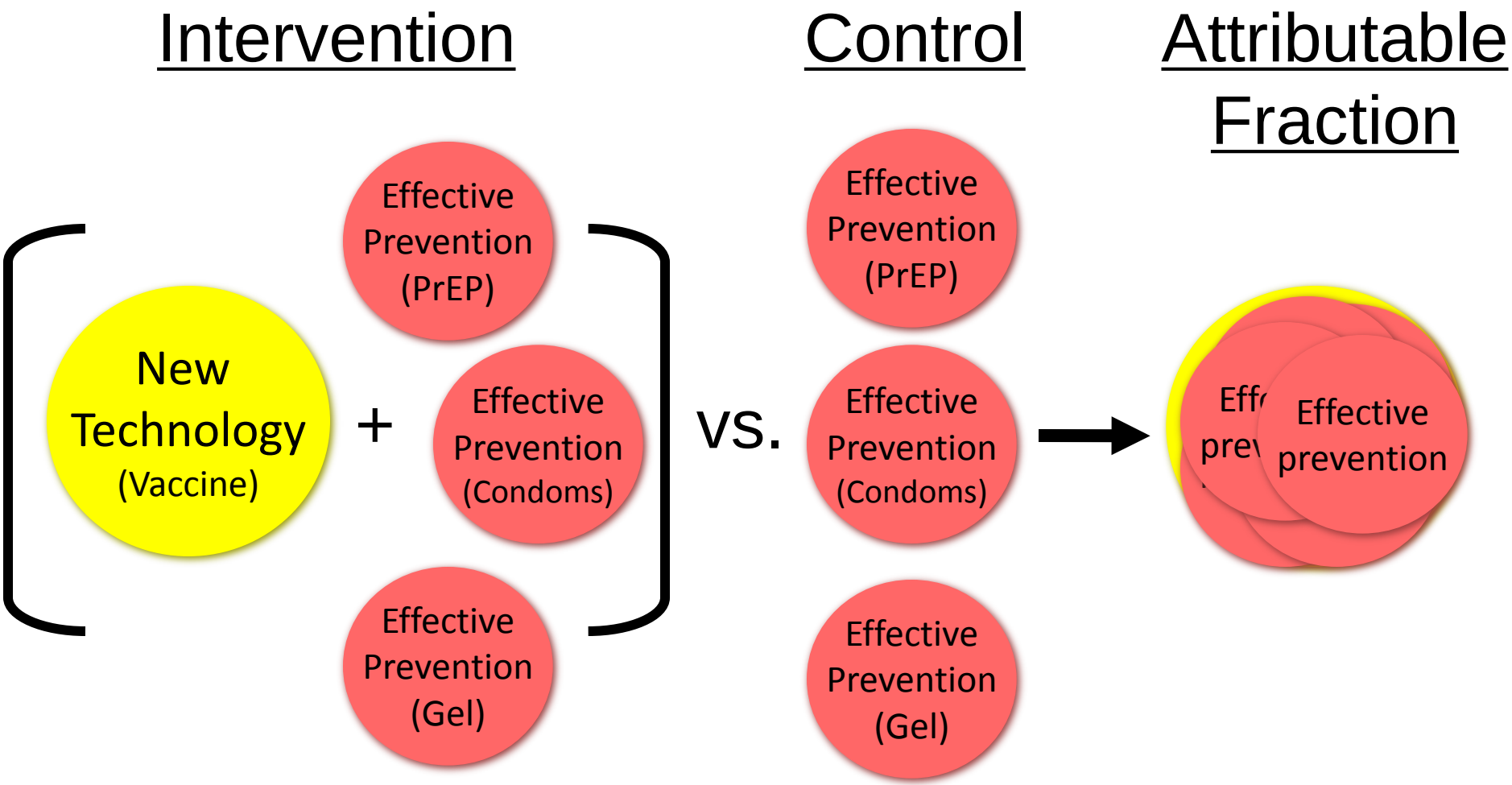
UNION GRADUATE COLLEGE

Scientific Issues

- Prevention packages don't address the needs of many participants, and may be unsustainable once a trial ends
- Prevention packages make also it difficult to assess experimental interventions.
  - Social desirability bias.
  - Complications of poor measurement.
  - Attenuation of power.
- When does it become unethical to use a placebo?

UNION GRADUATE COLLEGE

Evaluating Efficacy



UNION GRADUATE COLLEGE

Sample Size

- Assumptions:
  - Background HIV rate: 4.5%
  - Effectiveness of standard package: 0%
  - Effectiveness of new intervention: 55%
  - 12 month follow-up with 10% attrition
  - 300 HIV endpoints required

Number of Participants: 10,218

Estimated Cost of Trial: $71m US

UNION GRADUATE COLLEGE

Sample Size (2)

- Assumptions:
  - Background HIV rate: 4.5%
  - Effectiveness of standard package: 50%
  - Effectiveness of new intervention: 55%
  - 12 month follow-up with 10% attrition
  - 300 HIV endpoints required

Number of Participants: 20,435

Estimated Cost of Trial: $142m US

UNION GRADUATE COLLEGE

Trial Incidence

Trial	HIV Incidence per 100 Person-Years	
	Pre-Trial Estimate	During Trial
Cameroon (1995-97)	14.0	6.7
Nairobi (2000-02)	6.0	3.7

UNION GRADUATE COLLEGE

Sample Size (3)

- Assumptions:
  - Pre-trial HIV rate: 4.5%
  - Estimated HIV rate during trial: 2.0%
  - Effectiveness of standard package: 50%
  - Effectiveness of new intervention: 55%
  - 12 month follow-up with 10% attrition
  - 300 HIV endpoints required

Number of Participants: 50,731

Estimated Cost of Trial: $267m US

UNION GRADUATE COLLEGE

Sustainability

- Survey of condom use by participants enrolled in a randomized controlled trial of N-9 in Cameroon (Wong et al. 2005):

	During Study	Post-Study
% of acts with condoms	82 - 84%	57%
% of participants reporting consistent condom use	64 – 67%	35%

UNION GRADUATE COLLEGE

Established and Proven

- If we accept the argument that researchers should provide all state-of-the-art interventions to study participants, we must ask:
  - When is something “proven” to be effective?
  - Once proven effective, when does it become an “established” intervention?

UNION GRADUATE COLLEGE

Established Preventions

- Does an intervention become an established when it is:
  - Recommended by a normative agencies?
  - Added to a national prevention strategy?
  - Available in the community?
  - Common practice?

UNION GRADUATE COLLEGE

Ethics and Placebo Controls

- Study participants may randomized to receive a placebo control only when there is (Freedman 1987):
  - No standard therapy;
  - Standard therapy is no better than placebo;
  - Standard treatment is placebo;
  - There is doubt about the net therapeutic advantage of standard therapy; or
  - Standard treatment is unavailable (e.g. because of cost or supply).

UNION GRADUATE COLLEGE

Ethics and Placebo Controls (2)

- Study participants may also randomized to receive a placebo control if:
  - The study only enroll participants who refractory to standard treatment (Solomon 1995); or
  - When the placebo is added on top of standard treatment (Gilbert 1995).

UNION GRADUATE COLLEGE

Current Dilemma

Given that PrEP has been shown to work, can we test the effectiveness other formulations using a placebo-controlled trial design?

UNION GRADUATE COLLEGE

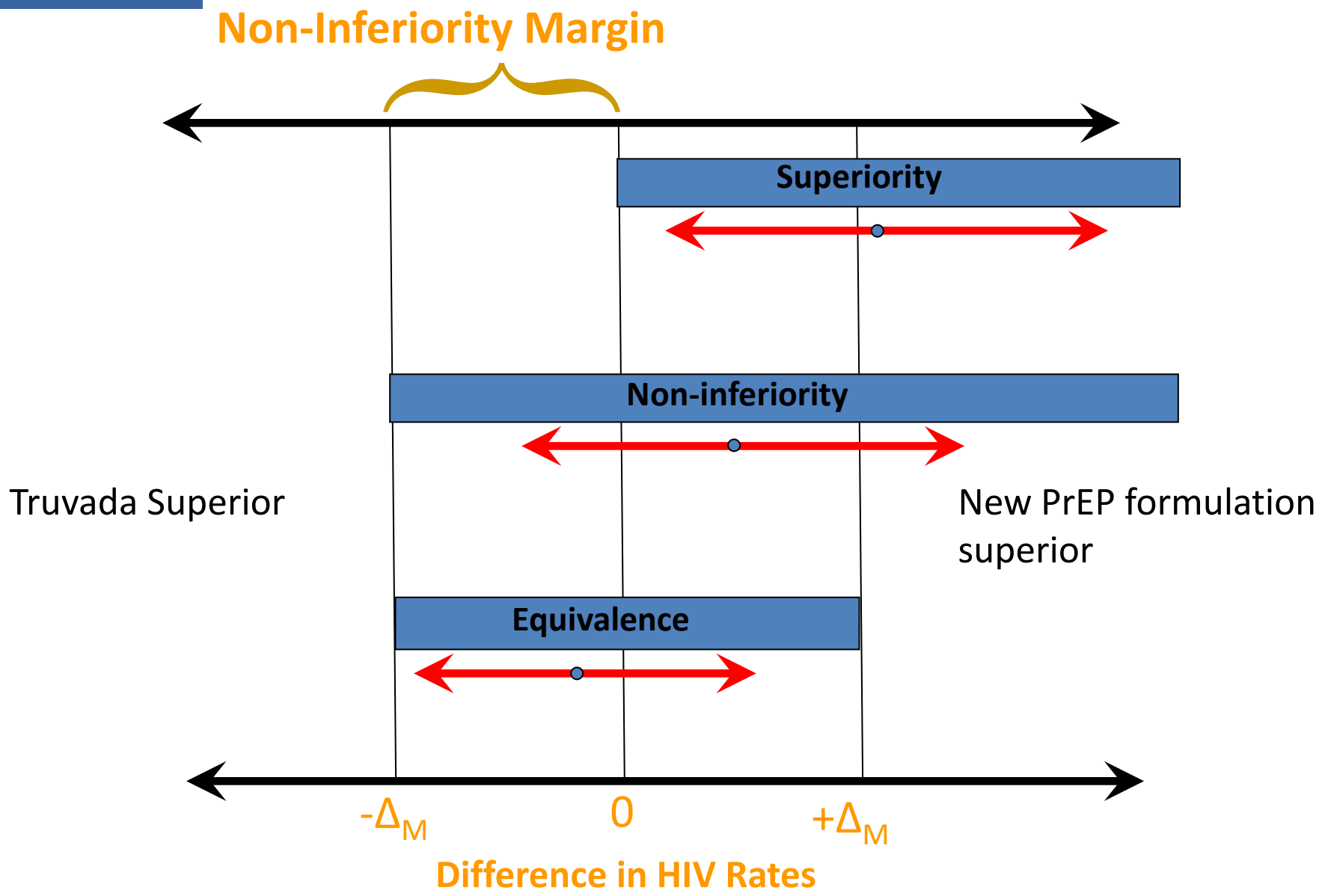
Studies Using Active Controls

- If we want to test new formulations of PrEP against Truvada, we have to use one of two study designs:
  - Test if the new formulation of PrEP is superior to Truvada (a superiority trial)

  or
  - Test if the new formulation is equivalent or not worse (by an amount X) than Truvada (a non-inferiority trial)

UNION GRADUATE COLLEGE

Studies Using Active Controls (2)



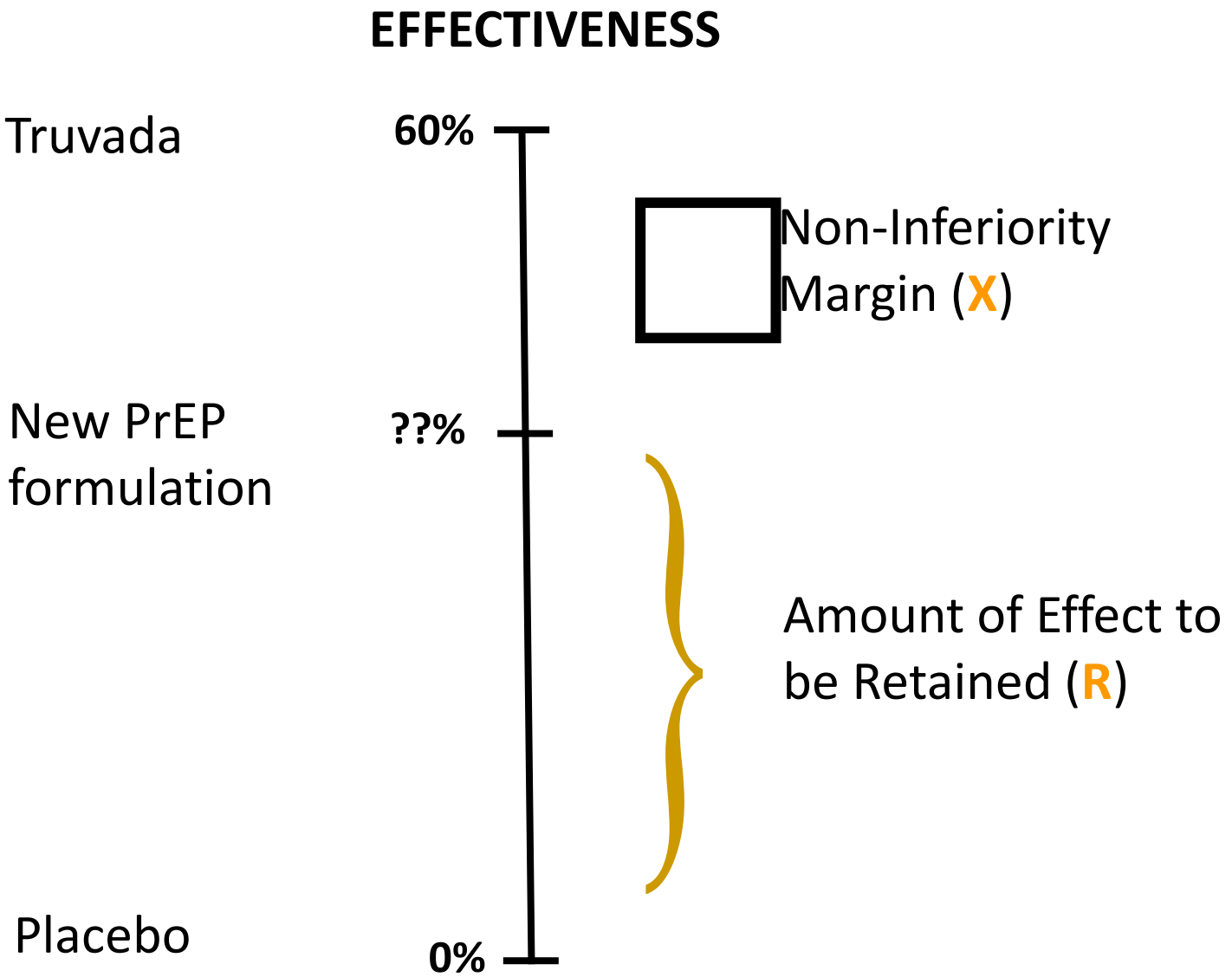
UNION GRADUATE COLLEGE

Studies Using Active Controls (3)

- Problems with superiority trials:
  - We may end up rejecting an effective prevention tool.
- Problems with non-inferiority trials:
  - Determining the margin of allowable inferiority.
  - Sample size.
  - “Biocreep”.
  - Observed effectiveness in the past may no more be valid (constancy assumption)

UNION GRADUATE COLLEGE

Non-Inferiority



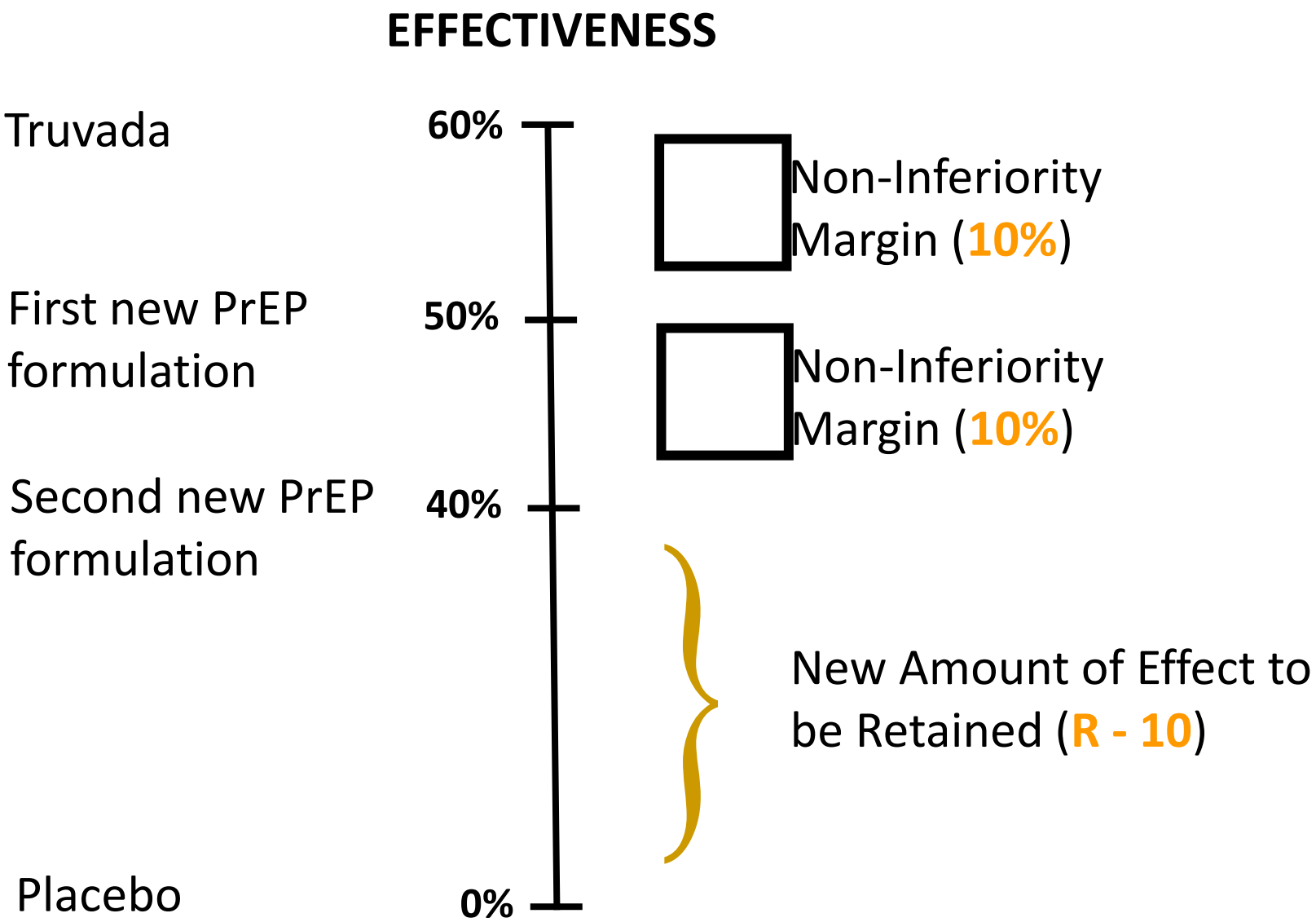
UNION GRADUATE COLLEGE

Non-Inferiority and Sample Size

Active Control Effectiveness	Amount of Effect to be Retained	Number of HIV Endpoints Required	Required Resources
60%	40%	~120	**Average size of current trials (10,000 participants)**
60%	50%	~1200	**~10 times the size of current trials (100,000 participants)**

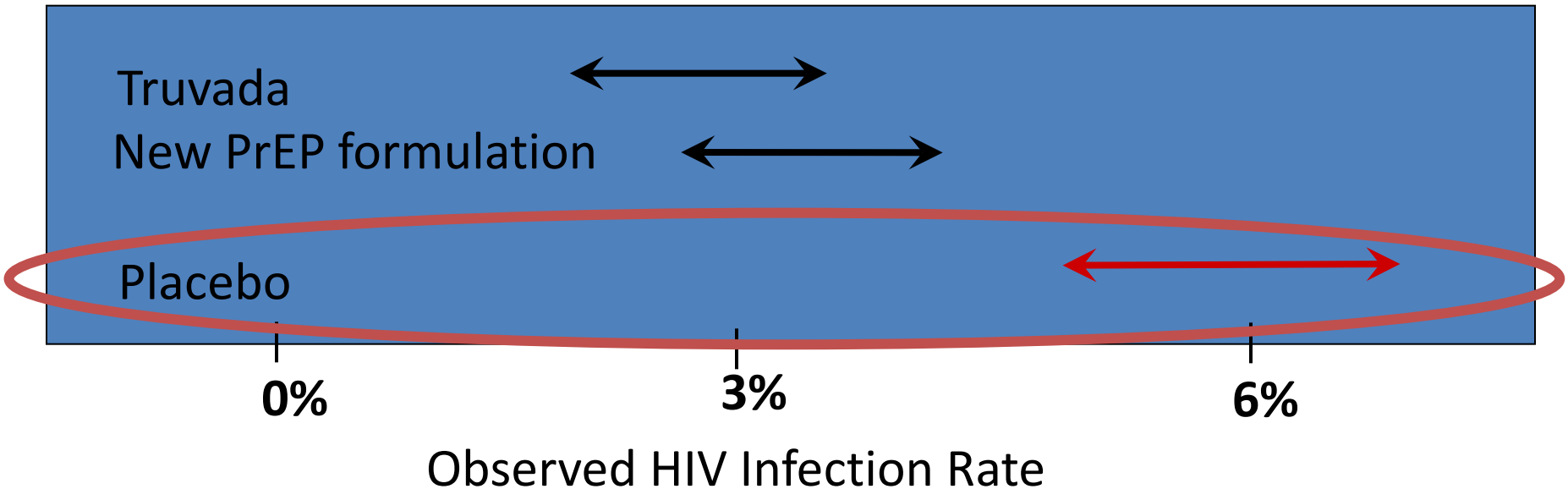
UNION GRADUATE COLLEGE

"Biocreep"



UNION GRADUATE COLLEGE

Consistency Assumption

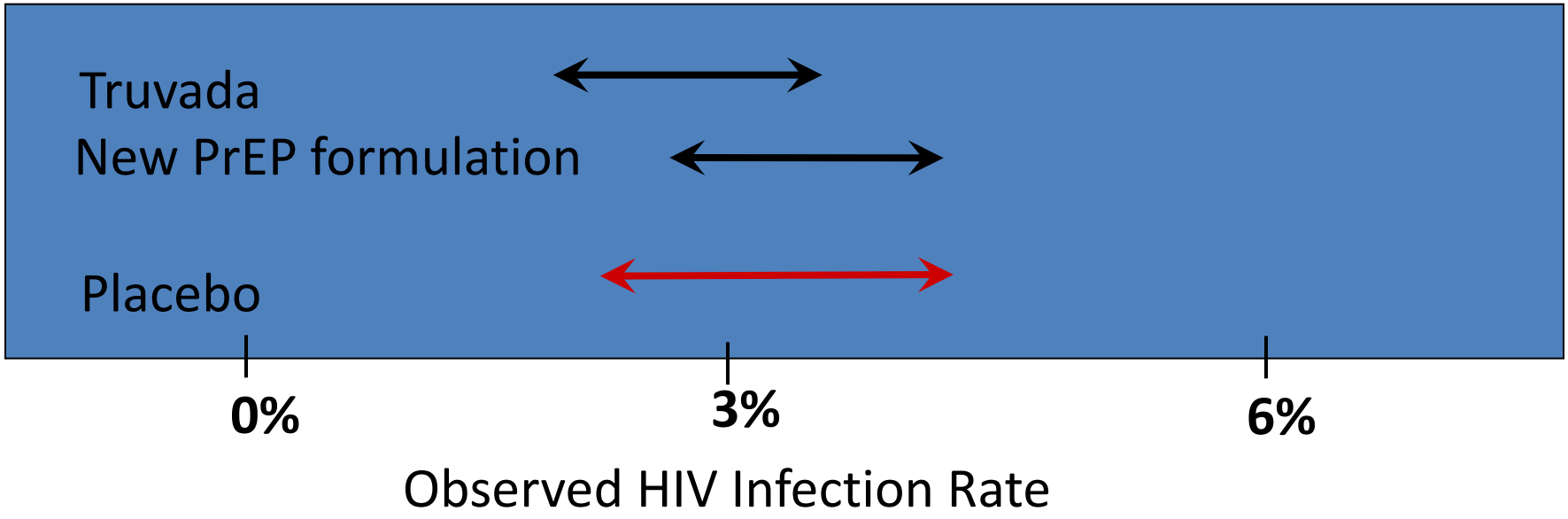


What we assume:

1. New PrEP formulation non-inferior to Truvada.
2. Both are superior to a placebo pill.

UNION GRADUATE COLLEGE

Consistency Assumption (2)



What may be the case:

1. New PrEP formulation non-inferior to Truvada.
2. Both are not superior to a placebo pill.

UNION GRADUATE COLLEGE

Core Research Ethics Principles

- Respect for persons
  - Voluntary informed consent.
  - Protection of vulnerable persons.
- Beneficence
  - Maximize benefits and minimize harms.
  - Some frameworks break this principle into beneficience, non-maleficence and utility.
- Justice
  - Non-exploitation and equitable selection.
  - Individuals and groups that participate in trials should benefit from participation.

UNION GRADUATE COLLEGE

Core Research Ethics Principles

When applied to HIV prevention trials, these three principles require that:

- Participants be informed of the risks and benefits of participation;
- Risks minimized and benefits maximized by providing an appropriate HIV prevention package and other services; and
- Trial participants and communities are not chosen solely for expedience or cost, and are not denied services to which they are normally entitled.

UNION GRADUATE COLLEGE

Beneficence

The principle of beneficence requires that trial participants be treated in an ethical manner

> "not only by respecting their decisions and protecting them from harm, but also by making efforts to ensuring their well-being. Two general rules have been formulated as complementary expressions of beneficent actions: 1) do no harm, and 2) maximize possible benefits and minimize potential harms" (Belmont Report 1979, §B2).

UNION GRADUATE COLLEGE

HIV Prevention Trial Ethics

- All trial participants should have information about proven and established HIV prevention services.
- It is not obligatory, however, to always provide or ensure access to the full range of proven and established prevention tools.
- The prevention package in a trial can vary in the type of services are provided so long as it:

1) Is developed in consultation with the community; and
2) Addresses the specific needs of the community.

UNION GRADUATE COLLEGE

Ethical Issues in Prevention Research

Sean Philpott, PhD, MSBioethics

The Bioethics Program

Union Graduate College-Mt. Sinai School of Medicine