

# HIV Prevention Trials – Design Issues and the US Epidemic

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# Challenges in HIV Prevention Research

- Cluster/Community randomized trials
- Multicomponent interventions
- Surrogate endpoints
- Prevention for positives

# Cluster Randomized Trials

- Randomization at group level; outcome measured on individuals within the group
- Clusters may be large (cities, schools) ... or small (IDU networks, families)
- Why?
  - Individual randomization not feasible (e.g. structural intervention)
  - potential contamination
  - want to measure community effect (phase IV trial)
- Usually, less efficient than individually randomized trial

# Cluster Randomized Trials

- A common error: two communities, flip a coin, one gets intervention; other gets control
- Underlying differences between communities confounded with treatment effect
- “Change from baseline” doesn’t (completely) solve the problem
- Key: Effective sample size is number of clusters, not number of individuals measured (though both are important)

# Key Considerations

- What is the unit of randomization?
- How/to whom is the intervention delivered?
- How/on whom is the outcome measured?
- Examples
  - PREVEN
  - HPTN037
  - Mwanza HIV prevention trial

# Multifactor Interventions

- “Packages” of interventions are often site or culture-specific
- Two-arm vs multiarm (factorial) design
  - What’s the question?
  - What will change public health practice?
- Factorial designs
  - The promise: two (3, 4?) trials for the price of one
  - The reality: only if individual tx’s have independent modes of action
- Packages which include both prevention for positives and prevention for negatives may have different levels of randomization for different components

# Multilevel Factorial Design

## Trial for “Women at Risk”

- Goal: Reduce HIV incidence in women with interventions aimed at both the women and their partners
- Intervention for HIV+ men - randomized at the community level
- Intervention for HIV- women - randomized at the individual level within communities
- Allows one to estimate ...
  - the direct effect of the female intervention for preventing infection in HIV- women
  - the indirect effect of the male intervention for preventing infection in HIV- women
  - the total effect of both interventions

# Multilevel Factorial Design

## Potential ISIS trial

		Community-level	
		Intervention	Control
Individual-level	Intervention	WI-CI	WI-CC
	Control	WC-CI	WC-CC

# Surrogate Endpoints

- Some things we all know that we forget ...
  - association is not causation
  - behavioral endpoints are self-reported
  - observational studies are subject to confounding
  - there are some things we don't know we don't know
- If you want to know if an intervention can reduce risk of HIV infection, you need to measure HIV infection (almost always\*)
- There are many examples where we have been fooled by relying on surrogate endpoints and/or observational studies (CASS, WHI, EXPLORE)

# Prevention in Positives

- Transmission endpoint
  - Harder to measure than acquisition
  - Unit of intervention and unit of analysis differ
- Designs
  - Surrogate endpoint e.g. viral load, STI acquisition, self-reported behavior
  - Partner studies
  - Community Randomized Trials

# Prevention in Positives

- Surrogate endpoint e.g. viral load, STI acquisition, self-reported behavior
  - Useful for phase II or pilot work
  - Intervention specific
  - Identification of appropriate behavioral surrogates difficult
  - Modeling of some behavioral endpoints (e.g. numbers of acts) difficult
  - Consider the endpoint “expected number of transmissions”

$$\sum_{i \in \text{partners}} 1 - (1 - \lambda(X))^{n_i}$$

# Prevention in Positives

- HIV discordant partner studies
  - Stability of partnership critical → dissolution of partnerships lead to loss of power; identification of new partners after randomization could lead to bias
  - Issues of representativeness
  - Distinguishing “linked” vs “unlinked” transmissions challenging
  - Inherent complications when intervention is delivered to one partner and outcome is measured in the other

# Prevention in Positives

- Community Randomized Trials
  - Best “real world” evidence for effectiveness
  - Some designs allow estimation of direct, indirect and total treatment effect
  - Potential dilution of effect relative to direct measurement of partners
  - Time to observe the full effect of the intervention may be long
  - Data needed for powering trials is “scarce”

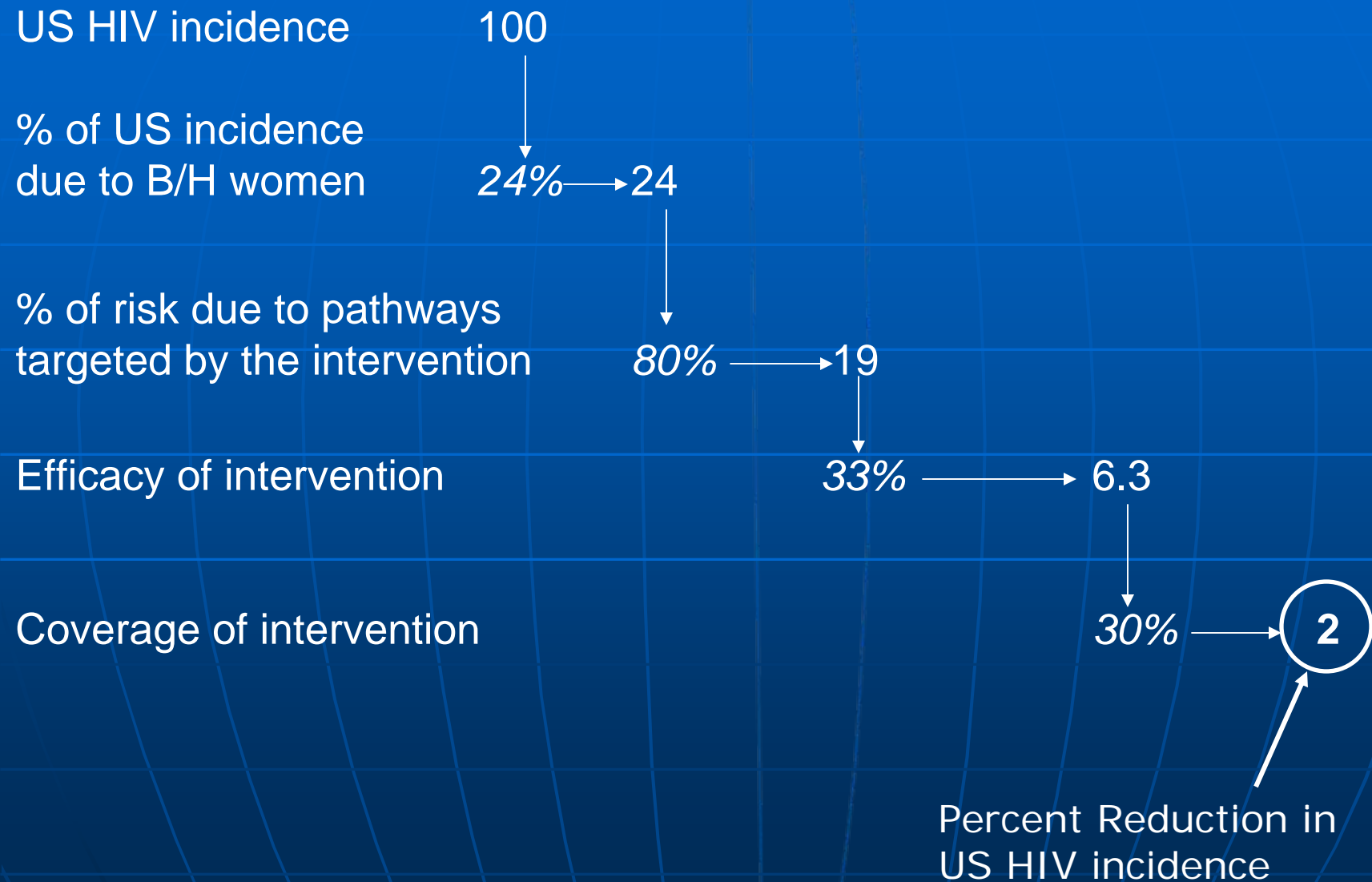
# US HIV Epidemic

	% total infections by Gender		% total infections by Gender and Risk		% total infections by Gender, Risk and Race.
Men	70%	MSM	49%	White Black Hispanic Other	22% 18% 8% 1%
		IDU	10%	White Black Hispanic Other	2% 4% 4% 0%
		MSM+ IDU	3%		3%
		Heterosexual	8%	White Black Hispanic Other	1% 5% 2% 0%
		Other	0%		0%
Women	30%	Heterosexual	23%	White Black Hispanic Other	4% 15% 4% 0%
		IDU	7%	White Black Hispanic Other	2% 3% 2% 0%
		Other	0%		0%
<b>Total</b>	<b>100%</b>		<b>100%</b>		<b>100%</b>

# Criteria influencing impact of HIV prevention intervention

- What's the intervention?
- Percent of HIV risk addressed
  - Size of the risk group
  - Attributable risk of intervention pathway
  - Potential reduction in secondary transmissions
- Plausible reduction in relative risk
- Feasible level of coverage of target population

# HIV intervention impact - example



# Conclusions

- Community randomized trials, prevention in positives, use of surrogate endpoints and evaluating multicomponent interventions present unique design challenges
- Realistic assessment of intervention impact requires knowledge of attributable risk of the intervention pathway, effect of the intervention, and potential uptake/coverage.



# Stepped Wedge Designs

Time				
<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>
O	X	X	X	X
O	O	X	X	X
O	O	O	X	X
O	O	O	O	X

- Everyone gets the intervention; time of implementation is randomized
- Measure outcome on each unit at each time step (repeated cross-sectional samples or cohorts)
- Intervention must be fully effective and measurable in the time step when it is introduced; delayed intervention effectiveness reduces power.

# Advantages/Disadvantages of the Stepped Wedge Design

- Efficiency: Units act as their own control, so fewer units may be needed
- Study the effect of time on intervention effectiveness (i.e. seasonality, time since introduction of intervention)
- An ethical approach to rolling out and evaluating interventions previously shown to be efficacious in an individually randomized trial or in a different setting; logistical or financial constraints preclude introducing the intervention everywhere at once.

# Measuring Incidence

## ■ Cohort

- Classic approach to measuring incidence

But ...

- Participants in a cohort may not reflect true community incidence
- Loss to followup a problem
- Large infrastructure needed; expensive
- In some cases (e.g. intervention to increase HIV testing), a cohort effectively provides an intervention in the “control” communities

# Measuring Incidence

- Cross-sectional surveys based on e.g. BED, avidity, etc.
  - Able to distinguish “recent” (within a window) infections
  - False positives (i.e. falsely called recent) have been an issue esp. with non-clade B virus
  - No issues of retention but ascertainment strategy important
  - Extremely important area of ongoing research