HIV Prevention Trials Network

Methodology in Combination Prevention

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NIMH National Institute of Mental Health
NIH National Institutes of Health
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NATIONAL INSTITUTES OF HEALTH
NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Key Scientific Issues

- Effect of the package or the individual components?
  - Are components separable?
  - Synergy/Redundancy of components?
- Short-term vs long-term effects; direct vs indirect effects
- Relationship between coverage and incidence
- Generalizability (across sites, populations)

Methodological Issues

- Outcome measurement
  - Incidence
  - Prevalence
  - Process/surrogate outcomes (e.g. Coverage)
  - Using surveillance data
- Trial Design
  - Individual vs cluster randomization
  - Two arm (all vs none)
  - Factorial
  - Implementation (e.g. stepped wedge)

Outcomes

- HIV incidence
  - Gold standard for measuring intervention effect
  - Cohorts, cross-sectional incidence
  - Expensive, difficult to measure
- HIV prevalence
  - Easier to measure than incidence
  - Lags incidence effect (except, possibly, in teens)
- Process outcomes (e.g. number of MC done, proportion of population tested)
  - Easiest to measure
  - Effects often seen first on process measures
  - May be used for evaluating interventions where relationship with HIV incidence has previously been established
  - Most useful for phase 2 studies, establishing mechanisms in conjunction with HIV incidence outcomes

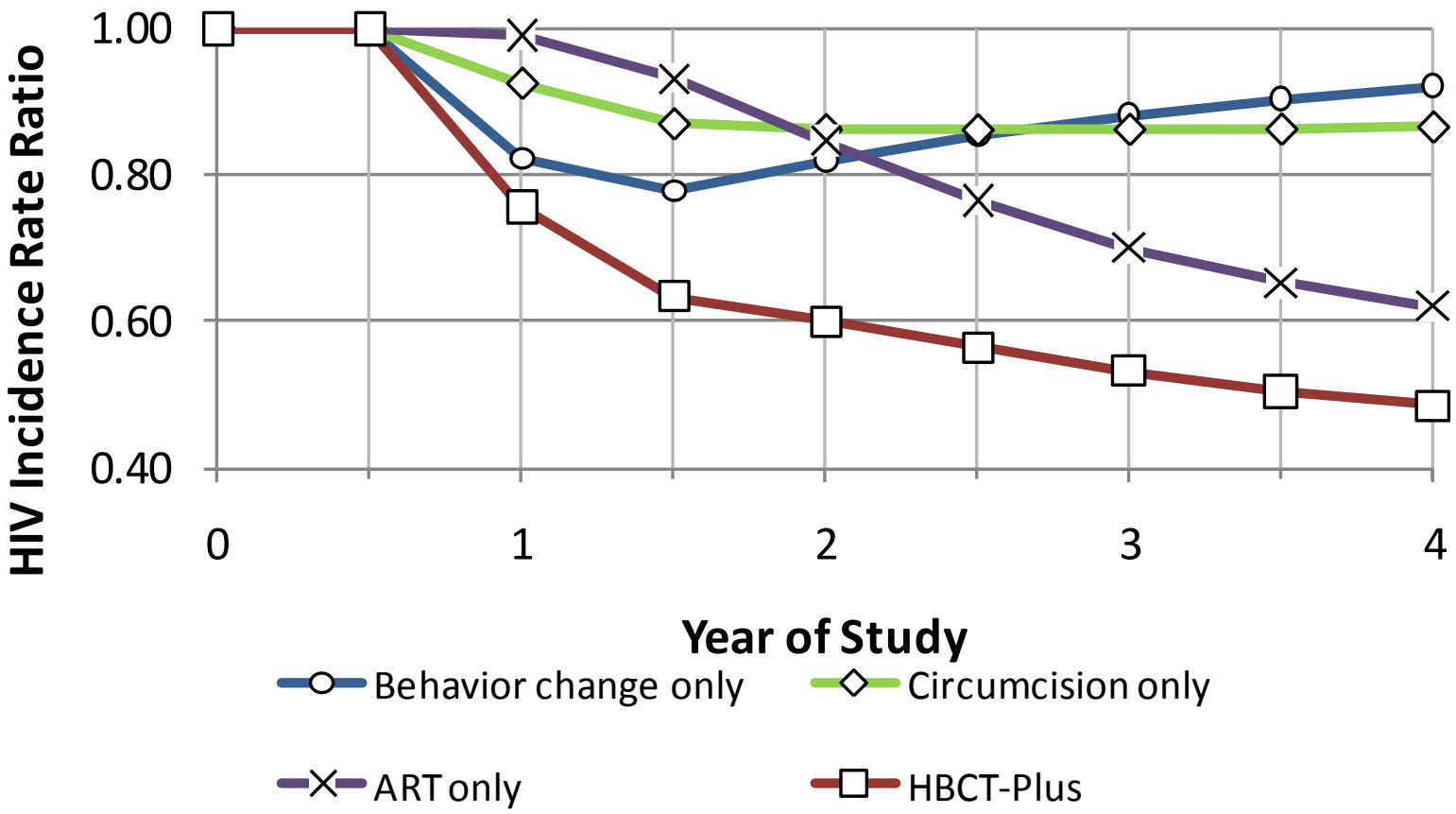
Outcomes

- Using surveillance data (e.g. HPTN 065)
  - Reduces study cost
  - May be lower “quality” compared to research study (more missing, incomplete, errors)
  - (Maybe) only aggregate data available
  - Subject to changes in procedures and policies that are not under the control of the investigator

Level of randomization

- Individual level randomization
  - Appropriate when the intervention is delivered to individuals and outcome measured on same individuals
- Cluster level randomization
  - Appropriate when the intervention is delivered to groups; or when outcome is measured on different individuals from those who received intervention
  - Measures “real world” effect
  - Challenges: contamination/crossover; baseline balance; evolving SOC; testing in control communities; delay in effect

Timing of effects in CRT



Alsallaq and Hallett

Design

- Two-arm trial
  - Assess entire package
  - Components not separable
  - Most components inexpensive or unlikely to have significant effect
- Factorial
  - Interest in effect of individual components or synergy/redundancy
  - Two (or more) components expensive

Factorial Designs

		Intervention A	
		A	no A
Intervention B	B	A,B	no A, B
	no B	A, no B	no A, no B

- Simultaneously addresses questions about marginal effects, incremental effects, combined effect
- Possible for interventions to be applied at different levels i.e. A – community; B – individual

Factorial Designs

- Highly efficient (multiple trials for the price of one) IF individual tx's have independent modes of action
  - Independent:

	RR	RD
Tx A	.8	-.05
Tx B	.7	-.03
Combined	.8*.7 = .56	-.05-.03=-.08

- As modes of action become more dependent, interpretation is more difficult and efficiency gains lost

Two-arm trial

- Compare “All” vs “None”
- Logistically easier, maybe smaller than factorial
- Difficult to determine effects of individual components
  - Variations in coverage across sites form an observational study
  - Detailed measurement of coverage outcomes in space and time are critical

Two-arm trial

- Assessing contribution of individual components
  - Statistical approach - regression
    - Cluster-specific incidence as outcome, component coverages as predictors
    - Need careful consideration of temporal relationships, interactions
    - Minimal assumptions
    - Yields “narrow” predictions
  - Modeling approach
    - Incidence, component coverage, biologic and behavioral parameters as inputs (cluster, subgroup-specific)
    - “Fit” model using trial data to estimate component effects
    - Assumptions about model structure, values of other parameters may be influential
    - “Broader” predictions possible

Stepped Wedge

	Time			
1	**2**	**3**	**4**	**5**
O	X	X	X	X
O	O	X	X	X
O	O	O	X	X
O	O	O	O	X

- Time of crossover is randomized; crossover is unidirectional
- Need to be able to measure outcome on each unit at each time step
- Multiple observations per unit; observations need to be "in sync" to control for time trends (assumed similar across clusters)
- If CRT, then individuals at each time can be same (cohort) or different (cross-sectional)

Stepped Wedge

- Advantages
  - Useful for implementation research
  - Fewer clusters
  - Addresses logistic, social, ethical concerns
  - Can study effect of time on treatment
- Disadvantages
  - Long time to completion (potential for contamination, external events)
  - Intentional confounding of time, treatment
  - Delayed effects reduce power

Conclusions

- Scientific questions should drive design
- Multiple intervention targets, levels, indirect effects and timing of effects all pose key design challenges in combination intervention trials
- Analyses of process outcomes likely will yield valuable insights, but should be calibrated to HIV incidence

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