HPTN
HIV Prevention
Trials Network

Trial Designs for Evaluating Integrated HIV Prevention Approaches

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Introduction

- Why integrated approaches?
  - ART-based biomedical intervention prevention approaches, such as TasP and PrEP, have proven efficacious in randomized trial settings
  - Non-biomedical intervention approaches, such as linkage-to-care, risk-reduction counseling, and use of condoms, also are important to help prevent HIV transmission
  - A continuum of HIV care is needed to avoid fragmented health services and unnecessary barriers to accessing services
  - Integrated approaches thus hold greater promise, based on the assumption that elements of an integrated approach may interact with each other synergistically in HIV transmission risk reduction
  - Integrated approaches are expected to improve health outcomes with more holistic, client-centered service delivery

Introduction

- Challenges for assessing integrated approaches
  - Integrated approaches involve multiple preventive intervention elements
  - Different combinations of individual elements of an integrated approach may complicate the evaluation process, and sometimes also cause concerns on perceived study participants' welfare
  - There is a lack of adequate insight about the statistical properties of candidate designs for assessing integrated approaches

Methods

- To provide insight about the relative merits of different trial designs that may be used to assess the effectiveness of an integrated approach
  - Perform Monte-Carlo simulation studies
  - Choose among 5 prevention interventions
  - Compare 4 prototype trial designs

Preventive intervention elements

- ART-based biomedical intervention
  - Treatment-as-Prevention (TasP)
  - PrEP
- Non-biomedical intervention
  - Linkage to Care (LtC)
  - Risk reduction counseling
  - Condom use

Candidate trial designs

- Single-factor design
  - A regimen with a single component is assessed in a controlled, randomized trial.
- Factorial design
  - All possible combinations of multiple components are assessed in a controlled, randomized trial.
- Multi-arm design
  - Multiple single component regimens are assessed in a controlled, randomized trial.
- All-in-one “kitchen-sink” design
  - A regimen with ‘all’ components in the experimental arm is assessed in a controlled, randomized trial.

Designs

Single-factor

$Z = 1$, **hazard rate**: $\lambda_0 e^{\beta}$.
$Z = 0$, **hazard rate**: λ_0.

$coxph(Surv(time, status) \sim Z)$.

Factorial

Multi-arm

All-in-one

Designs

Single-factor

$Z = 1$, **hazard rate**: $\lambda_0 e^{\beta}$.
$Z = 0$, **hazard rate**: λ_0.

$coxph(Surv(time, status) \sim Z)$.

Factorial

	$Z_2 = 1$	$Z_2 = 0$
$Z_1 = 1$	$\lambda_0 e^{\beta_1+\beta_2+\gamma}$	$\lambda_0 e^{\beta_1}$
$Z_1 = 0$	$\lambda_0 e^{\beta_2}$	λ_0

$coxph(Surv(time, status) \sim Z_1 + Z_2)$

Multi-arm

All-in-one

Designs

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$Z_1 = 0$	$\lambda_0 e^{\beta_2}$	λ_0

$coxph(Surv(time, status) \sim Z_1 + Z_2)$

Multi-arm

	$Z_2 = 1$	$Z_2 = 0$
$Z_1 = 1$	$-$	$\lambda_0 e^{\beta_1}$
$Z_1 = 0$	$\lambda_0 e^{\beta_2}$	λ_0

$coxph(Surv(time, status) \sim Z_1 + Z_2)$

All-in-one

Designs

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Factorial

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$Z_1 = 0$	$\lambda_0 e^{\beta_2}$	λ_0

$coxph(Surv(time, status) \sim Z_1 + Z_2)$

Multi-arm

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$Z_1 = 1$	$-$	$\lambda_0 e^{\beta_1}$
$Z_1 = 0$	$\lambda_0 e^{\beta_2}$	λ_0

$coxph(Surv(time, status) \sim Z_1 + Z_2)$

All-in-one

$Z = 1$, **hazard rate**: $\lambda_0 e^{\beta_1+\cdots+\beta_5+\gamma}$.
$Z = 0$, **hazard rate**: λ_0.

$coxph(Surv(time, status) \sim Z)$.

Effectiveness parameters by hazards ratios (1-HR)

Intervention	Effective	Less effective	In-between #1	In-between #2
PrEP	44%	10%	22%	44%
TasP	70%	70%	70%	70%
LtC	10%	0%	10%	0%
Counseling	20%	0%	20%	0%
Use of Condoms	30%	30%	30%	30%

Summary of results

- Sample size: 5000
- Baseline incidence rate: 2%
- Trials simulated: 1000
- About a total of 100, 300, 500 incident HIV infections observed per trial

Without interaction

- One factorial design of sample size 5000 would yield almost identical results that would otherwise need two separate single-factor trials, each of sample size 5000
- Placebo-controlled multi-arm design would yield similar results to factorial design
- All-in-one design would be most impactful

With interaction

- Single-factor design or multi-arm design would not be able to detect an interaction
- All-in-one design would reflect the interaction, but not be able to tell which two would interact, or its magnitude
- Only factorial design would be able to detect an interaction

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