Designing the SEARCH trial: Ph250b in Practice

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*Disclaimer: some simplifications were made to the SEARCH design and analysis for teaching purposes
Outline

1. The SEARCH Trial
2. Two-stage Design & Analysis:
   - Stage 1: best estimate of the 5-year cumulative incidence
   - Stage 2: best estimate of the intervention effect
3. Remaining choices
4. Conclusion
Multinational, multidisciplinary consortium to implement and evaluate bold community health interventions

Directors:
- Dr. Diane Havlir (UCSF)
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Collaborators:
- UCSF, Makerere University, Kenya Medical Research Institute, Infectious Diseases Research Collaboration, UCB, Kenya Ministry of Health, Uganda Ministry of Health, NIH, PEPFAR, WHO, World Bank, Gilead, UNAIDS
Estimate the health, economic and educational impact of a community-based strategy for **early HIV diagnosis with immediate and streamlined ART** (antiretroviral therapy) in rural East Africa.
SEARCH - Rationale

Benefits of early ART

- Preserves the health of HIV+ patients
- Stops transmission between partners
- Stops transmission from mother to child
- Reduces risk of TB, malaria, and maternal/child mortality
- Improves adult employment levels, child nutritional status and school attendance
Benefits of immediate ART

- Current ART strategy allows deterioration of health
- Early universal ART may keep patients in “green zone”
Can a community-based “test-and-treat” strategy stop the HIV epidemic?

- Five-year cluster randomized trial
- 320,000 people
- 32 communities in Uganda and Kenya
The SEARCH Trial

Hypothesis: immediate ART and streamlined care will reduce the 5-year cumulative incidence of HIV and protect and improve health, economic and education outcomes in communities with annual HIV testing campaigns.
Annual **community health campaigns** (CHC) will offer multi-disease prevention and treatment services
- TB, malaria, diabetes, hypertension, HIV, deworming
The SEARCH Trial

- **Arm A**: all individuals testing positive for HIV will be offered immediate ART and streamlined care
  - Enhanced services for initiation, linkage, adherence and retention
  - Optimize the HIV care cascade

- **Arm B**: all individuals testing positive for HIV will be offered ART according to in-country guidelines
The SEARCH Trial

**Stage 1**
Design Analysis

**Stage 2**
Design Analysis

Remaining Choices

Conclusion

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**The SEARCH Trial**

16 villages; n = 10,000 each

**Universal ART** (all CD4 counts)

**Country-guided ART (CD4<350)**

**Control Communities**

**Annual Community Health Campaigns**

HIV Screening/ Diagnosis
Malaria testing & care
HTN and Diabetes testing
Maternal/child health

**Community Health**
- HIV incidence
- HIV population viral load
- AIDS
- Maternal and child health
- TB incidence

**Community Productivity**
- Workforce participation
- Child labor prevalence
- Agricultural output
- Household income
- Educational attainment
- Healthcare utilization

**Outcomes**

**Qualitative Implementation Science**
What is the causal effect of a community-based strategy for immediate treatment and streamlined care on the five-year cumulative incidence of HIV?

Optimal design to answer this question?

Optimal analysis to estimate this effect?
Two-Stage Study Design & Analysis

Our approach to clustered data:

- **Stage 1**: for each community, we want the best measure of HIV incidence
  - Optimal design & analysis?

- **Stage 2**: given these community-level outcomes, we want the best estimate of the intervention effect
  - Optimal design & analysis?
Stage 1: Measuring HIV incidence in each cluster

Serial Cross-sectional:

- At the first CHC, we test attendees for HIV
- At the last CHC, we test attendees for HIV
- Potential advantages?
- Potential problems?
Stage 1: Measuring HIV incidence in each cluster

Serial Cross-sectional:

- Easier & less expensive
- Are attendees of the first CHC representative?
- Are attendees of the last CHC representative?
- What do these cross-sectional measurements capture?
  - Obtain prevalence
  - Want incidence
Stage 1: Measuring HIV incidence in each cluster

Longitudinal Cohort:
- From the first CHC, obtain an HIV- cohort
- Follow this cohort over the five years of the study
- Measure the proportion of seroconversions
- Potential advantages?
- Potential problems?
Stage 1: Measuring HIV incidence in each cluster

Longitudinal Cohort:
- Capture incident cases
- Are attendees of the first CHC representative?
- Are those willing to be followed for five years different?
- What about loss to follow-up?
  - Is it informative?
  - Obtain incidence density
  - Want cumulative incidence
Stage 1: Measuring HIV incidence in each cluster

Why not incidence density?

- Recommended when different observation periods
- Average rate of seroconversion during the person-time of follow-up among the population at risk
  - \(1\text{ person}(1\text{ yr}) = 2\text{ people}(0.5\text{ yr}) = 3\text{ people}(0.3\text{ yr})\)
- Often misinterpreted as a risk or probability
- Requires knowing exact time seroconversion and censoring
  - Intensive follow-up that may itself change behavior
  - Costly
  - Otherwise require assumptions that could lead to biased estimates
Stage 1: Measuring HIV incidence in each cluster

Why cumulative incidence?

- Probability of seroconverting in the 5 study years
- Cumulative risk of HIV infection over the 5 study years
- Interpretable at community-level and individual-level
- Inform policy makers and stake-holders
- How to estimate with informative missingness?
Stage 1: Measuring HIV incidence in each cluster

Efficient Community COhort (ECCO):

1. Baseline census to enumerate community residents
   - Know who is in our study communities
Stage 1: Measuring HIV incidence in each cluster

**Efficient Community COhort (ECCO):**

1. Baseline census to enumerate community residents
   - Know who is in our study communities
2. Annual CHCs
   - Link attendees over years with unique identifiers
   - Know who did not attend
Stage 1: Measuring HIV incidence in each cluster

Efficient Community COhort (ECCO):

1. Baseline census to enumerate community residents
   - Know who is in our study communities

2. Annual CHCs
   - Link attendees over years with unique identifiers
   - Know who did not attend

3. Track a random sample of non-attendees each year
   - Tested for HIV and linked to care
Stage 1: Measuring HIV incidence in each cluster

Efficient Community COhort (ECCO):

1. Baseline census
2. Annual CHCs
3. Track non-attendees
Stage 1: Measuring HIV incidence in each cluster

Efficient Community COhort (ECCO):

- Representative baseline HIV- cohort
  - Know who is in our communities; know who did not attend the first CHC
  - Aim to track 100% of non-attendees after first CHC
Stage 1: Measuring HIV incidence in each cluster

Efficient Community COhort (ECCO):

- Representative baseline HIV- cohort
  - Know who is in our communities; know who did not attend the first CHC
  - Aim to track 100% of non-attendees after first CHC

- Longitudinal individual-level data
  - Link over successive years of the trial
Stage 1: Measuring HIV incidence in each cluster

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- Representative baseline HIV- cohort
  - Know who is in our communities; know who did not attend the first CHC
  - Aim to track 100% of non-attendees after first CHC

- Longitudinal individual-level data
  - Link over successive years of the trial

- Recover from informative missingness
  - HIV status known if attend CHC
  - HIV status known if not attending the CHC, but randomly selected for tracking
Stage 1: Measuring HIV incidence in each cluster

Efficient Community COhort (ECCO):

- Representative baseline HIV-cohort
  - Know who is in our communities; know who did not attend the first CHC
  - Aim to track 100% of non-attendees after first CHC

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- Recover from informative missingness
  - HIV status known if attend CHC
  - HIV status known if not attending the CHC, but randomly selected for tracking

- Achieve (near) universal HIV testing
  - Knowing status is first step
Stage 1: Measuring HIV incidence in each cluster

**Recap** - 3 designs to measure cumulative incidence
- Serial cross-sectional: easy, but prevalence
- Longitudinal cohort: classic, but costly & incidence density
- ECCO: creative & cumulative incidence despite missingness
Stage 1: Estimating HIV incidence in each cluster

Given the ECCO design, we want the best estimate of 5-year HIV cumulative incidence in each community.

- Probability of seroconverting within 5 years
- Not the average rate of seroconversion (ID)
- Not directly observed
  - Final HIV status is unknown for some cohort members
Stage 1: Estimating HIV incidence in each cluster

Naive estimator: observed proportion of seroconversions

- Does not make use of ECCO design
- Biased
  - Missingness likely to informed by HIV status
- Inefficient (lower power)
  - Ignores longitudinal individual-level data
Stage 1: Estimating HIV incidence in each cluster

Inverse-weight by the probability of being observed at the final time-point

- Probability is 1 for subjects attending the last CHC
- Probability is equal to the final tracking proportion for non-attendees
- Unbiased
  - If tracking process is 100% successful
- Inefficient (lower power)
  - Ignores longitudinal individual-level data
Stage 1: Estimating HIV incidence in each cluster

**TMLE**: Targeted minimum loss-based estimation

- **Unbiased**:
  - Under weaker assumptions

- **Maximally efficient**:
  - Uses longitudinal covariate data
  - Individual’s covariates (beyond final CHC attendance) are predictive of final HIV status
  - E.g. prior positive HIV test

- Other nice properties
Stage 1: Estimating HIV incidence in each cluster

**Recap** - Given ECCO, 3 ways to estimate cumulative incidence

- Unadjusted: biased & inefficient
- Inverse weighting: unbiased but inefficient
- TMLE: unbiased & efficient
Stage 1: for each community, we can obtain the best estimate of the 5-year cumulative incidence of HIV
  - Design: ECCO
  - Analysis: TMLE
Two-stage Study Design & Analysis

- **Stage 1**: for each community, we can obtain the best estimate of the 5-year cumulative incidence of HIV
  - Design: ECCO
  - Analysis: TMLE

- **Stage 2**: given these community-level outcomes, we want the best comparison between treatment arms
  - How to assign the intervention?
  - How to estimate the intervention effect?
Stage 2: Measuring the Intervention Effect

Observational study:

- Rollout the intervention to selected communities
- Potential advantages?
- Potential problems?
Stage 2: Measuring the Intervention Effect

Observational study:

- Generalizable
- But confounding is a huge problem
Stage 2: Measuring the Intervention Effect

Randomized trial:
- Assign the intervention randomly to study units
- Potential advantages?
- Potential problems?
Randomized trial:

- No confounding
  - The probability of receiving the intervention is 0.5

Ethics? Logistics? Generalizability?
SEARCH is a cluster randomized trial:

- Communities are randomized
  - Arm A: immediate ART with streamlined care
  - Arm B: ART according to in-country guidelines
- Fundamentally interested in a community-level strategy for community health and well-being
- Individual (patient-level) randomization
  - Not answer our question of interest
  - Logistically impossible
Stage 2: Measuring the Intervention Effect

**Recap** - 2 ways to assign the intervention
- Observational study: fan favorite
- Randomized trial: green light on identifiability
Stage 2: Estimating the Intervention Effect

Within a cluster randomized trial, we want the best estimate of the intervention effect.

- Causal risk difference
- Average treatment effect
- Not causal risk ratio
  - Interpretation on a relative scale?
  - Problematic with rare outcomes
Stage 2: Estimating the Intervention Effect

**Unadjusted estimator:** difference in average outcomes among intervention communities and among control communities

- Outcomes: estimated cumulative incidence from Stage 1
- Easy to understand
- Unbiased
  - Treatment is randomized
- Inefficient (less power)
  - Ignores measured covariate data
Stage 2: Estimating the Intervention Effect

Adjusted estimator (TMLE):

- Unbiased
  - Treatment is randomized
- Maximally efficient (more powerful)
  - No confounding
  - Adjusting for covariates can increase power
Stage 2: Estimating the Intervention Effect

**Recap** - 2 estimators of the intervention effect

- **Unadjusted**: easy, unbiased, but inefficient
- **Adjusted**: unbiased and maximally efficient
Stage 1: Estimate HIV incidence in each community with ECCO and TMLE
- Representative HIV- cohort at baseline
- Recover from informative missingness by tracking a random sample of no-shows
- Use longitudinal data to be maximally unbiased & efficient
SEARCH Trial - Two-stage Design & Analysis

- Stage 1: Estimate HIV incidence in each community with ECCO and TMLE
  - Representative HIV- cohort at baseline
  - Recover from informative missingness by tracking a random sample of no-shows
  - Use longitudinal data to be maximally unbiased & efficient

- Stage 2: Estimate the intervention effect in a randomized trial and with TMLE
  - No confounding
  - Gain power with adjustment
SEARCH Trial - Two-stage Design & Analysis

- **Stage 1**: Estimate HIV incidence in each community with ECCO and TMLE

- **Stage 2**: Estimate the intervention effect in a randomized trial and with TMLE
More on SEARCH

The following slides explore a few more key design/analysis choices.
Pair-Matching

- SEARCH team pair-matched communities on important determinants of the outcome
  - Region
  - Population density
  - Number of trading centers
  - Occupational mix
  - Migration index
Why match in randomized trials?

With only **32 communities**, pair-matched was implemented to

1. Protect study credibility
2. Improve study power
   - No confounding, but still may be imbalance
   - Data sparsity limits our ability to adjust
How to handle death?

Death as right-censoring event

- Want community-level outcome (5-year HIV incidence) that is not a function of mortality patterns
  - Likely to vary over time and across communities
- Will be treated as a competing risk in secondary analysis
How to handle out-migration?

Generate two estimates of cumulative incidence in each community

1. Include those who out-migrate in our measurement cohort
2. Censor at time of out-migration
   - Adjust for multiple hypothesis testing
Conclusion

Intervention

Universal ART (all CD4 counts)
16 villages; n = 10,000 each

Country-guided ART (CD4<350)
16 villages; n = 10,000 each

Annual Community Health Campaigns
HIV Screening/ Diagnosis
Malaria testing & care
HTN and Diabetes testing
Maternal/child health

Community Health
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16 villages; n = 10,000 each

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Outcomes
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WHO
Thank you & Questions

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Happy Halloween!!!