SEARCH (Sustainable East Africa Research in Community Health)

Thank you NIH and PEPFAR for supporting SEARCH
We are grateful for all who work on SEARCH, our multilateral partners, and the communities we serve.

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http://www.searchendaids.com
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SEARCH Hypothesis: HIV “test and treat” with universal ART using a multi-disease, patient-centered care model would reduce new HIV infections and improve community health compared to a country guideline approach.

Study Design: Pair-matched, community randomized study of 32 rural communities.

Study Population: Age ≥ 15 years
- Comprehensive baseline census with biometric identifier.
Study Interventions

**INTERVENTION COMMUNITIES**
- Health Fairs: Baseline + Annual *
- All (Universal)
- Patient-centered Care**
  - “Chronic care” model: HIV and HTN/DM
  - Rapid ART start and VL counseling
  - Welcoming environment, flexible clinic hours
  - Mobile phone triage and reminders

**“CONTROL” COMMUNITIES**
- Health Fairs: Baseline only
- Country guidelines adapted over time
- Country standard-of-care for HIV and HTN/DM

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**HIV and NCD Diagnosis**

**ART eligibility**

**Care Delivery**

*Multi-disease: HIV, HTN, DM, malaria and other*

**Follow-up testing for non-participants**

**Kwarisiima, JIAS 2017**

**Chamie, Lancet HIV 2016**
<table>
<thead>
<tr>
<th>Category</th>
<th>Study Endpoint</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV cascade</td>
<td>HIV testing coverage</td>
<td>Confirmed rapid antibody testing</td>
</tr>
<tr>
<td>HIV cascade</td>
<td>ART start</td>
<td>Ministry of Health record</td>
</tr>
<tr>
<td>HIV cascade</td>
<td>Viral suppression</td>
<td>Plasma HIV RNA at health fair measured with Roche assay, Viral Suppression &lt;500 c/mL</td>
</tr>
<tr>
<td>Community Health</td>
<td>Mortality</td>
<td>Key informant interviews at Year 3; classified as due to illness, childbirth, suicide or accident</td>
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<tr>
<td>Community Health</td>
<td>Tuberculosis</td>
<td>TB Registry at health dispensaries</td>
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<tr>
<td>Community Health</td>
<td>Hypertension control</td>
<td>Blood pressure &lt; 140/90 mmHg</td>
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<tr>
<td>Community Health</td>
<td>Diabetes control</td>
<td>Blood glucose &lt;11 mmol/L at the health fairs</td>
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<tr>
<td>HIV</td>
<td>*Cumulative 3 year HIV incidence</td>
<td>Rapid HIV antibody testing with Geenius and Western Blot confirmation at Year 3 health fairs among 117, 114 persons HIV-negative at baseline</td>
</tr>
<tr>
<td>HIV</td>
<td>Annual HIV incidence</td>
<td>Confirmed rapid HIV antibody testing at annual health fairs in the intervention arm</td>
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*primary study endpoint
Statistical Methods

• Randomization: pair matched on region, population density, number of trading centers, occupation mix and migration

• Powered to detect 25-40% reduction in 3 year cumulative HIV incidence

• Comparison of outcomes between arms using community-level analysis
  1. Calculate community-level outcomes
  2. Compare between arms
     • Targeted maximum likelihood estimation (TMLE) and pre-specified adjustment to improve precision
  3. Two-sided hypothesis testing, 5% significance level, pair as the independent unit

• Pre-specified sensitivity analyses to look at robustness of findings

Rapid Uptake of National ART Guidelines in Control clinics

**Kenya – Baseline to Year 3**

**2013**
- ART for all
- ART CD4 <350 (WHO 2010)

**2017**
- ART for all
- ART CD4 <500 + (WHO 2013)
- Early implementation of expanded ART eligibility

Intervention Clinics

Control Clinics
Results: SEARCH Adult Open Cohort

Baseline Enumerated
355,848 persons

Baseline Age < 15 years
174,502 age <15 years
12 missing age

Baseline Age > 15 years
181,334

Non-resident
30,685

Died by start of CHC
254

Baseline Residents
150,395

Died
2,633

Out-migrated
13,822

Turned 15 years old
26,858

In-migrated
25,556

Year 3 Residents
186,354

Enter cohort
Leave cohort
# Study Population

<table>
<thead>
<tr>
<th>Total</th>
<th>N=150,395</th>
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<tbody>
<tr>
<td><strong>Region (HIV prevalence)</strong></td>
<td></td>
</tr>
<tr>
<td>Kenya (19%)</td>
<td>53,872</td>
</tr>
<tr>
<td>Western Uganda (7%)</td>
<td>47,328</td>
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<tr>
<td>Eastern Uganda (4%)</td>
<td>49,195</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>67,981 (45.2%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>15-20 years</td>
<td>36,655 (24%)</td>
</tr>
<tr>
<td>21-49 years</td>
<td>84,022 (56%)</td>
</tr>
<tr>
<td>50+ years</td>
<td>29,718 (20%)</td>
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<tr>
<td><strong>Hypertension (among ≥30 year olds)</strong></td>
<td>22,599 (20%)</td>
</tr>
<tr>
<td><strong>Stable (≤6 mo. out of community)</strong></td>
<td>143,870 (96%)</td>
</tr>
<tr>
<td><strong>Farmer</strong></td>
<td>76,695 (51%)</td>
</tr>
<tr>
<td><strong>Male Circumcision</strong></td>
<td>20,597 (34%)</td>
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</table>
Among all residents ≥ 15 years, including in-migrants and aged-in; Pre-baseline: self-report at time of testing; Baseline-Year 2: Testing status based on documented HIV test (SEARCH or Ministry record).

Control Pre-BL: 65,074, N= BL: N=70,577; Intervention: Pre-BL: N= 72,978 ,BL N=79,818, Y1 N=89,994, Y2 N=93,008
Among baseline HIV+ residents not on ART at baseline (N=5,952, 44% of baseline HIV+); Community-level estimates of probability of initiating ART by 6, 12, and 24 months based on Kaplan-Meier, censoring at death or outmigration.

- More rapid ART start in the intervention vs. control arm
- More rapid ART in intervention arm at all CD4+ strata, including CD4<350: 80% intervention vs. 45% control at 1 year (p<0.001)
Viral suppression among all HIV-infected persons over time

- Year 3 suppression 11% higher (p<0.001) in intervention vs. control
- Year 3 suppression ~10% higher in intervention vs. control in: women, men, youth
- Year 3 suppression in intervention: women (81%), men (74%), youth (55%)

2020 UNAIDS population viral suppression 73% target

RR: 1.15 (95%CI: 1.11, 1.20) p<0.001

Among all residents including in-migrants and aged-in, excluding out-migrants and deaths; adjusted for missing HIV serostatus and plasma HIV RNA measures; numerator for each suppression estimate using 4,192–6,800 RNA measures
Impact of SEARCH on Community Health: Mortality was lower

- Mortality among HIV-infected persons was 21% lower in the intervention vs. control arm (p=0.02)
- Mortality rate among all persons 11% lower in intervention arm
  - RR 0.89 (95%CI 0.79, 1.02)

Death due to illness among baseline HIV+ stable residents (N=13,066) and all baseline stable residents (N=171,431); community-level estimates of risk by 2.7 years using Kaplan-Meier censored at outmigration or death due to other cause.
Impact of SEARCH on Community Health: Tuberculosis was lower

- HIV-TB or death among HIV+ 20% lower in the intervention vs. control arm (p=0.004)
- 59% lower TB incidence rate in year 3 among baseline HIV+ in intervention vs. control arm (p=0.02)

HIV-TB/death from illness among baseline HIV+/unknown (N=26,096); TB incidence among HIV+ (N=13,430) stable residents; estimates of HIV-TB/death risk by 2.75 years using Kaplan-Meier censored at outmigration or death from other cause
Impact of SEARCH on Community Health: Hypertension control was higher

- Population-level HTN control at year 3 was 26% higher in intervention vs. control arm (p<0.001)
- HTN-HIV dual control higher in intervention vs. control (p=0.002)
- Similar findings for combined HTN/DM

Among baseline stable residents aged ≥30 years, N=59,218 with HTN measured at FUY3; adjusted for missing measures of HTN control; *also adjusted for unknown HTN status.
Among incidence cohort of baseline HIV-negative stable residents; 91% intervention, 91% control alive and not out-migrated by year 3; of those, 89% intervention and 90% control with HIV status measured at year 3.

No difference in 3 year cumulative HIV incidence between arms.

**Impact of SEARCH on Cumulative HIV Incidence**

- **All Region**
  - Control: 0.8%
  - Intervention: 0.8%
  - RR: 1.01 (95% CI: 0.62, 1.65) p=0.95

- **Kenya**
  - Control: 1.1%
  - Intervention: 1.1%
  - RR: 0.95 (95% CI: 0.77, 1.17) p=0.60

- **Western Uganda**
  - Control: 0.9%
  - Intervention: 0.8%
  - RR: 1.02 (95% CI: 0.66, 1.56) p=0.91

- **Eastern Uganda**
  - Control: 0.3%
  - Intervention: 0.4%
  - RR: 0.69 (95% CI: 0.23, 2.03) p=0.39

**No difference detected**

- **N=49,590**
- **360 seroconversions**

- **N=45,493**
- **344 seroconversions**

**Region**

- **Intervention**
- **Control**
Why no difference?

1. Active control:
   - 90% persons aware HIV status after baseline fairs in both arms
     - Greater health-seeking behaviors in the control after baseline
   - We implemented new guidelines; ART eligibility was “near universal” within one year
   - Mathematical model predicted 10% reduction in HIV incidence (0-19%) which we may not have detected*

2. New Infections from:
   - Outside the community
   - Acute infection outbreaks
   - Small subset of unsuppressed

*Jewell, IAC, 2018
In SEARCH study, did our annual measured HIV incidence decline over time? Yes

- 32% decline in annual HIV incidence from year 1 to year 3
- 45% decline in Kenya
- 49% decline in men; 19% decline in women

Intervention arm - incidence rate calculated in 3 annual incidence cohorts of HIV-negative adult residents (inclusive of immigrants and aging-in) with repeat HIV test one year later (Year 1 N= 52,468; Year 2 N=55,526; Year 3 N=57,858); Change over time using Poisson GEE adjusted for age, sex, mobility, w/ exchangeable covariance matrix
What annual HIV incidence would we predict in the absence of SEARCH – a true control?

- Model: SEARCH reduced incidence 40%
- Model:
  - No SEARCH: 0.7%
  - SEARCH: 0.3%
- Measured:
  - SEARCH: 0.4%

Individual-based network model (EMOD-HIV) of annual HIV incidence (blinded to all incidence results) in SEARCH communities under various scenarios.
A community health approach with a patient-centered, multi-disease model rapidly increased population-level HIV suppression from 42% to 79% (intervention) compared to control (68%) at 3 years.

**Improved Community Health**
- 21% HIV mortality
- 59% HIV/TB year 3 annual incidence
- 26% HT control

**Reduced HIV incidence**
- 32% Annual HIV incidence within arm
- Cumulative HIV incidence between arms*

*Explanation: Active control

**Hypothesis**: Community health approach with patient-centered, multi-disease model would reduce HIV and improve community health compared to SOC with baseline HIV testing

**Study Design**: 32 community RCT: N=150,395 persons > 15 years rural Uganda/Kenya

**Intervention**: Baseline + annual health fair, Universal ART, Streamlined care for HIV/NCD

**Control**: Baseline health fair; ART by 2010, 2013, 2015 WHO guidelines
Conclusions

• SEARCH multi-disease, patient-centered approach is one model that can be adapted in rural Africa to accelerate reductions in mortality, TB and new HIV infections synergistically with improved NCD control-- in line with Sustainable Development Goals.

• To achieve HIV elimination at <0.1% incidence, we need to: increase viral suppression among youth, understand HIV transmission dynamics, and integrate new treatment and prevention (VAMC, PreP, vaginal ring, etc) interventions efficiently and effectively in a multi-disease and financed approach.
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