Does Treatment as Prevention really work? An interpretation of HPTN 071 (PopART), BCPP/Ya Tsie, SEARCH, & TasP/ANRS

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What is “treatment as prevention?”

- Quinn et al (NEJM 2000) and Fideli et al (AIDS Res Hum Retrovir 2001) found that lower VL correlated with far lower transmission to sexual partners \( \rightarrow \) HPTN 052 (Cohen et al, NEJM)
- Similar to the concept of PMTCT
- Ecological data from Vancouver on expanding treatment and lower transmission (Montaner et al) and KZN (Tanser et al, Science 2013)
Zambian discordant couples (linked tx only)

No transmissions at <3000 VL/mL

Four large studies of TasP with HIV endpoints

TasP/ANRS
BCPP/Ya Tsie
SEARCH
HPTN 071 (PopART)

REF: Perriat D, et al. Comparative assessment of five trials of universal HIV testing and treatment in sub-Saharan Africa. JIAS 2018 (includes MaxART in Swaziland)
ANRS 12249 TasP

• 80% life-time risk of acquiring HIV
High Coverage of ART Associated with Decline in Risk of HIV Acquisition in Rural KwaZulu-Natal, South Africa

Frank Tanser,¹* Till Bärnighausen,¹,² Erofili Grapsa,¹ Jaffer Zaidi,¹ Marie-Louise Newell¹,³

Tanser F, et al 2013

Adjusted Hazard ratio: incidence

Proportion receiving ART

<10%  10-20%  20-30%  30-40%  40-50% >50%
Effect of population viral load on prospective HIV incidence in a hyperendemic rural African community

Frank Tanser,1,2,3,4* Alain Vandormael,1,2,5 Diego Cuadros,6 Andrew N. Phillips,7 Tulio de Oliveira,3,5,8 Andrew Tomita,1,5,9 Till Bärnighausen,1,4,10,11 Deenan Pillay1,12

Population Prevalence of viremia

Population viral load
Trial procedures

Homestead identification (GPS)

Homestead procedures
1. Household assets questions
2. Individual questionnaire
3. DBS sample, rapid HIV test
4. TasP card

Homestead visit every 6 months
1. Head of household verbal consent
2. Registration of individuals

TasP clinic
- One per cluster (45 min walk max)
- HIV care and treatment according to arm
- Study questionnaires

HIV +
Referral to TasP clinics
Repeat HIV test 6 mths later

HIV -
TasP: 90-90-90 Cascade in Men vs. Women, End of Study

Knowledge HIV+ status
- Males, End of study: 90%
- Females, End of study: 92%
- HIV+ known: 74%
- HIV+ VL<400 in those on ART: 83%
- HIV+ VL<400 in all HIV+: 59%

ART in known HIV+:
- Males, End of study: 55%
- Females, End of study: 59%
- HIV+ known: 39%
- HIV+ VL<400 in those on ART: 71%
- HIV+ VL<400 in all HIV+: 40%

VL<400 in all HIV+:
- Males, End of study: 41%
- Females, End of study: 47%
- HIV+ known: 20%
- HIV+ VL<400 in those on ART: 26%

Iwuji, Larmarange, personal communication
## ANRS 12249 TasP: HIV incidence comparison

<table>
<thead>
<tr>
<th></th>
<th># of HIV+ DBS tests</th>
<th>Person-years</th>
<th>Incidence for 100 PY</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>268</td>
<td>11,787</td>
<td>2.27</td>
<td>2.00-2.55</td>
</tr>
<tr>
<td>Intervention</td>
<td>227</td>
<td>10,646</td>
<td>2.13</td>
<td>1.85-2.41</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>495</td>
<td>22,434</td>
<td>2.21</td>
<td>2.01-2.40</td>
</tr>
</tbody>
</table>

### Adjusted risk ratio*

<table>
<thead>
<tr>
<th></th>
<th>aRR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention vs control</td>
<td>0.95</td>
<td>0.79-1.14</td>
<td>0.58</td>
</tr>
</tbody>
</table>

*Estimated with Poisson regression, adjusted on sex, age, change in national ART guidelines, baseline cluster HIV prevalence and ART coverage.
ANRS 12249 TasP - Estimated cascade of care

UNAIDS target

- Diagnosed: 90.0%
- On treatment: 90.0%
- Virally suppressed: 90.0%

\[\text{Total} = 90.0\% + 90.0\% + 90.0\% = 270.0\% \times 0.9 = 72.9\%\]

TasP trial (1\textsuperscript{st} January 2016)

**Control**
- Diagnosed: 93.4%
- On treatment: 46.0%
- Virally suppressed: 93.6%

\[\text{Total} = 93.4\% + 46.0\% + 93.6\% = 233\% \times 0.9 = 40.2\%\]

**Intervention**
- Diagnosed: 92.3%
- On treatment: 49.2%
- Virally suppressed: 93.4%

\[\text{Total} = 92.3\% + 49.2\% + 93.4\% = 234.9\% \times 0.9 = 42.4\%\]
Botswana Combination Prevention Project (BCPP) / The Ya Tsie Project

• Pair-matched community-randomized trial in 30 communities in Botswana (15 intervention and 15 standard of care)

• **Baseline and annual surveys** conducted in adult 16-64 year old residents of random sample of ~20% of households in all 30 communities, to evaluate:
  – HIV incidence
  – Uptake of components of interventions over time

• Rapid scale-up of interventions in intervention communities following enrollment of HIV incidence cohort at baseline

• Study start in October 2013, interventions ended in March 2018, follow-up completed in June 2018
Study Interventions

• Interventions in the 15 intervention communities:
  – Community mobilization
  – Home-based / mobile HIV testing campaigns, targeted testing
  – Linkage to care support: scheduled appointments, SMS reminder, active tracing
  – Expanded ART at government clinics
    • Universal ART as of June 2016 (with treatment started at first clinic visit)
    • Previously, expanded ART for residents with CD4 351-500, or with CD4 >500 + HIV-1 RNA≥10,000
  – Strengthened male circumcision services

• In the 15 standard of care communities:
  – ART for persons with CD4≤350, WHO III/IV disease or pregnancy until June 2016, when transitioned to universal ART
Participating Communities

- Average community population 6,000
- Total population ~180,800 (9%+ of Botswana population)
HIV Incidence Cohort

- Primary endpoint: cumulative HIV incidence over ~30 months (annualized)
- HIV incidence determined in prospective HIV Incidence Cohort of HIV-negative residents of random sample of ~20% of households from all 30 communities
Enrollment & Retention of HIV Incidence Cohort Participants by Arm

**Standard of Care Arm**
- Enrolled: 4,487
- Re-tested for HIV at least once: 4,290 (96%)
- Deceased: 20 (<1%)
- Ineligible: 2 (<1%)
- Refused retesting: 40 (<1%)
- Absent/moved: 124 (3%)
- Unknown: 11 (<1%)

**Intervention Arm**
- Enrolled: 4,487
- Re-tested for HIV at least once: 4,257 (95%)
- Deceased: 8 (<1%)
- Ineligible: 1 (<1%)
- Refused retesting: 63 (1%)
- Absent/moved: 151 (3%)
- Unknown: 7 (<1%)
## Primary Results: HIV Incidence in the Intervention vs. Standard of Care Arms

57 participants in the intervention arm (annualized HIV incidence: 0.59%) and 90 in the standard of care arm (annualized HIV incidence: 0.92%) acquired HIV.

Results of unadjusted and adjusted analyses of treatment effect

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Inc. Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis (permutation test, pair-specific Cox PHM), unadjusted</td>
<td>0.69</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Analysis to obtain 95% CI (standard pair-stratified Cox PHM), unadjusted</td>
<td>0.65</td>
<td>0.46-0.90</td>
<td>0.01</td>
</tr>
<tr>
<td>Primary analysis, adjusted*</td>
<td>0.62</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Analysis to obtain 95% CI, adjusted*</td>
<td>0.70</td>
<td>0.50-0.99</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Covariates: sex, age, education, marital status, concurrent sex partners, & alcohol w/ last sex

**30% reduction in HIV incidence associated with the intervention**
HIV incidence was quite variable by community (range 0.23 – 1.81)
Proportions of all HIV+ Persons with Undetectable HIV-1 RNA At Study End (from 6 End of Study communities, 3 pairs)

- End of study: additional 18% of HIV+ persons in the intervention arm vs. 7% in SOC arm had VL suppression (p<0.0001)
  - **Intervention arm**: 88% of all HIV+ persons w/ undetectable VL
- Uptake of male circumcision was low in both arms
SEARCH (Sustainable East Africa Research in Community Health)

SEARCH

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.

32 communities, of 10,000 persons each ~320,000 person study.

Uganda East N=10
Uganda West N=10
Kenya N=12
Study Interventions

**INTERVENTION COMMUNITIES**

- Health Fairs: Baseline + Annual *
- 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

**HIV and NCD Diagnosis**

- All (Universal)
- Patient-centered Care**

**ART eligibility**

**Care Delivery**

- Country guidelines adapted over time
- *Multi-disease: HIV, HTN, DM, malaria and other
Follow-up testing for non-participants

**Kwarisiima, JIAS 2017**

Chamie, Lancet HIV 2016
## Study Population

<table>
<thead>
<tr>
<th>Total N=150,395</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region (HIV prevalence)</td>
</tr>
<tr>
<td>Kenya (19%)</td>
</tr>
<tr>
<td>Western Uganda (7%)</td>
</tr>
<tr>
<td>Eastern Uganda (4%)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>15-20 years</td>
</tr>
<tr>
<td>21-49 years</td>
</tr>
<tr>
<td>50+ years</td>
</tr>
<tr>
<td>Hypertension (among ≥30 year olds)</td>
</tr>
<tr>
<td>Stable (≤6 mo. out of community)</td>
</tr>
<tr>
<td>Farmer</td>
</tr>
<tr>
<td>Male Circumcision</td>
</tr>
</tbody>
</table>
Impact of SEARCH on Community Health: Mortality was lower (Also TB and HBP much 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
Among incidence cohort of baseline HIV-negative stable residents; 91% intervention, 91% control alive and not out-migrated by yr 3; of those, 89% intervention and 90% control with HIV status measured at yr 3.
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
Summary

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 yr 3 ann. incidence
- 26% HT control

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

Explanation: SEARCH intervention

*Explanation: Active control

Supported by NIH and PEPFAR
HPTN 071 (PopART) Study:
Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART)
PopART intervention package

- Annual rounds of Home Based Voluntary HIV Testing by Community HIV-care Providers (CHiPs)
- Health promotion, Active Referral and/or Retention in Care support by CHiPs for the following:
  - Voluntary Medical Male Circumcision (VMMC)
  - Prevention of Mother to Child Transmission
  - HIV treatment and care for all PLHIV
  - Promotion of sexual health and TB services
  - Condom provision
- ART irrespective of CD4+ cell count or immune-status provided at the local health centre in Arm A

Original Trial Design
Study Design

Approximately 1 million population

Arm A: Full PopART intervention including immediate ART irrespective of CD4 count

Arm B: PopART intervention except ART initiation according to current national guidelines

Arm C: Standard of care at current service provision levels including ART initiation according to current national guidelines

2,500 random sample from each community (aged 18-44) Population Cohort (N=52,500) Followed up annually for 36 months
Primary Objective

• Measure the impact of the PopART intervention package on new HIV cases
  – Arm A vs Arm C
  – Arm B vs Arm C
COVERAGE and BASELINE
Intervention Activities (3 rounds over 4 yrs)

- **South Africa**
  - 55,515 households visited in the final round of the intervention
  - 78,947 adults consenting to participate in the intervention

- **Zambia**
  - 97,939 households visited in the final round of the intervention
  - 181,418 adults consenting to participate in the intervention
Coverage Estimates for First Two UNAIDS 90-90-90 Targets

Arm A

1st 90 | 2nd 90 | ART Coverage

Start of Round 1 | End of Round 3

Arm B

1st 90 | 2nd 90 | ART Coverage

Start of Round 1 | End of Round 3
Total Number of People in PC

Arm A
12,534 people
28% male
72% female

Arm B
13,213 people
29% male
71% female

Arm C
12,183 people
30% male
70% female
Age of Individuals in the PC

Arm A
- 21% 18-24
- 40% 25-34
- 39% 35-44

Arm B
- 23% 18-24
- 39% 25-34
- 39% 35-44

Arm C
- 22% 18-24
- 38% 25-34
- 40% 35-44
Baseline HIV Prevalence in PC

<table>
<thead>
<tr>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
</tr>
</thead>
<tbody>
<tr>
<td>21% overall</td>
<td>21% overall</td>
<td>22% overall</td>
</tr>
<tr>
<td>12% male</td>
<td>11% male</td>
<td>12% male</td>
</tr>
<tr>
<td>25% female</td>
<td>25% female</td>
<td>27% female</td>
</tr>
</tbody>
</table>
Baseline ART Coverage for People Living with HIV in PC

<table>
<thead>
<tr>
<th>Arm</th>
<th>Percentage on ART</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td>31%</td>
<td>2575</td>
</tr>
<tr>
<td>Arm B</td>
<td>38%</td>
<td>2730</td>
</tr>
<tr>
<td>Arm C</td>
<td>32%</td>
<td>2671</td>
</tr>
</tbody>
</table>
STUDY RESULTS
# Primary analysis: Incidence in

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV Incidence</strong></td>
<td>198/12,990 (1.45%)</td>
<td>157/14,149 (1.06%)</td>
<td>198/12,563 (1.55%)</td>
</tr>
<tr>
<td>(geometric mean of community incidence rates)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adj. Rate Ratio</strong></td>
<td>0.93 (0.74, 1.18)</td>
<td>0.70 (0.55, 0.88)</td>
<td>1</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Incidence compared to Arm C</strong></td>
<td><strong>7% reduction</strong></td>
<td><strong>30% reduction</strong></td>
<td></td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.51</td>
<td>0.006</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age category, sex and baseline community HIV prevalence. Reported numbers include imputation for PC12 and PC24 missed visits.
Subgroup Analyses: New HIV Cases in PC12-PC36

- Men
- Women
- Younger (18-24)
- Older (25+)

Arm A
Arm B
Arm C
Suppression defined as a viral load of less than 400 copies/mL of blood

VIRAL SUPPRESSION IN HIV POSITIVE PC PARTICIPANTS
Primary Analysis: Viral Suppression at PC24

Viral Suppression

- A: 72%
- B: 68%
- C: 63%
Subgroup Analysis: Viral Suppression at PC24

- Men
- Women
- Younger
- Older

Arm A  Arm B  Arm C
COMMUNITY ENGAGEMENT
Communities are not homogenous

Uptake of intervention and choice of community engagement activities were influenced by ‘other things happening’ in a community
• Multiple communities required multiple engagement mechanisms
  – Stakeholder analysis
  – Adult Community Advisory Boards
  – Adolescent Community Advisory Board
  – National CAB (NCAB)
  – Community Partners Platform (CPP)
  – District Implementation Management Teams
  – National Intervention Management Team

Representation mechanisms in PopART
Summary - I

- PopART achieved the first two UNAIDS 90-90 targets (high rates of HIV testing, high rates of linkage to HIV care) in both Arm A and Arm B
- High rates of viral suppression achieved
- PopART intervention package with ART according to local guidelines (Arm B) reduced HIV incidence by 30% in high burden settings
  – shifted to immediate ART midway through the study
Summary - II

• Lack of a significant effect in the full PopART intervention arm (Arm A), where universal treatment was delivered from the beginning of the study, was surprising and not explained by lower rates of viral suppression

• Phylogenetic analysis and qualitative research may throw further light on this surprising finding
Acknowledgements

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- Funded by:
  - The U.S. President's Emergency Plan for AIDS Relief (PEPFAR)
  - The International Initiative for Impact Evaluation (3ie) with support from the Bill & Melinda Gates Foundation
  - NIAID, the National Institute of Mental Health (NIMH), and the National Institute on Drug Abuse (NIDA) all part of the U.S. National Institutes of Health (NIH)
• Community randomization in non-homogeneous environment; Arm A and B differences due to chance?
  – Their combined difference with Arm C approximately a 20% reduction in incidence

• Community randomization imbalance post-randomization?
  – e.g., 38% of Arm B participants living with HIV were already on ART at baseline vs. 31-32% in the other arms
• Immediate implementation of the full intervention in Arm A too much, too fast?
• “Last unreached 25%” responsible for a disproportionate number of transmissions?
• Time to deploy the interventions, short time to evaluate
  – 3-year study duration not long enough to fully observe the effect of the intervention?

Figure 1: Viral suppression, HIV incidence rates and overall effectiveness in HIV prevention: Results from community-based cluster-randomized control trials of universal test-and-treat strategies

<table>
<thead>
<tr>
<th>Location</th>
<th>Viral Load Suppression (%)</th>
<th>Effectiveness</th>
<th>HIV Incidence Intervention vs Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana (Ya Tsie)</td>
<td>+5%*</td>
<td>31%</td>
<td>0.59 vs 0.92</td>
</tr>
<tr>
<td>South Africa, Zambia (PopART – B)</td>
<td>+8%*</td>
<td>30%</td>
<td>1.06 vs 1.55</td>
</tr>
<tr>
<td>South Africa, Zambia (PopART – A)</td>
<td>+12%*</td>
<td>7%</td>
<td>1.45 vs 1.55</td>
</tr>
<tr>
<td>Kenya, Uganda (SEARCH)</td>
<td>+11%*</td>
<td>6%</td>
<td>0.25 vs 0.27</td>
</tr>
<tr>
<td>South Africa (TasP)</td>
<td>+2%**†</td>
<td>-1%</td>
<td>2.11 vs 2.27</td>
</tr>
</tbody>
</table>

*Difference in viral suppression (≤400 copies/mL) between the intervention and control groups at the end of the trial. **The dot is the viral suppression % at baseline and the arrow is the viral suppression % at the end of the trial. †Viral suppression at baseline in the TasP trial was estimated from baseline ART coverage assuming 90% of the patients on ART were virally suppressed. *The dot is the point estimate of effectiveness in reducing HIV incidence and the lines on either side represent the 95% confidence interval. †p=0.006 (the other 4 estimates of effectiveness were not statistically significant, i.e. p>0.05). **HIV incidence is per 100 person-years.

ACKNOWLEDGEMENTS

• Slides generously shared: Max Essex; Sarah Fidler & Richard Hayes; Diane Havlir; Deenan Pillay & Frank Tanser, Susan Allen

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