Spillover Infections Drive Transmission in HIV Prevention Trials: BCPP/Ya Tsie study

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Lerato E. Magosi[1,2], Eric Tchetgen Tchetgen[3], Vlad Novitsky[4,5], Molly Pretorius Holme[4], Janet Moore[6], Pam Bachanas[6], Refeletswe Lebelonyane[7], Christophe Fraser[8], **Sikhulile Moyo**[5], Kathleen E. Hurwitz[9], Tendani Gaolathe[5], Ravi Goyal[10], Joseph Makhema[5], Shahin Lockman[4,5,11], Max Essex[4,5], Victor De Gruttola[9], & Marc Lipsitch[1] for the Botswana Combination Prevention Project (BCPP / Ya Tsie Trial)

[1]Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Harvard University, Boston, USA, [2]Wellcome Sanger Institute, Cambridge, United Kingdom, [3]Department of Statistics, The Wharton School, University of Pennsylvania, Philadelphia, USA, [4]Harvard T.H. Chan School of Public Health AIDS Initiative, Department of Immunology and Infectious Disease, Harvard T.H. Chan School of Public Health, Harvard University, Boston, USA, [5]Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, [6]Division of Global HIV/AIDS and TB, Centers for Disease Control and Prevention, Atlanta, USA, [7]Ministry of Health, Republic of Botswana, Gaborone, Botswana, [8]Oxford Big Data Institute, Li Ka Shing Center for Health Information and Discovery, Nuffield Department of Medicine, Old Road Campus, University of Oxford, Oxford, UK, [9]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Harvard University, Boston, USA, [10]Division of Infectious Diseases and Global Public Health, University of California San Diego, La Jolla CA, USA, [11]Brigham and Women's Hospital, Division of Infectious Diseases, Boston, USA

BACKGROUND

Motivation:

- Several community-randomized trials to evaluate whether universal HIV testing and treatment could reduce HIV incidence in general populations showed mixed results[1]
- Namely, the BCPP or Ya Tsie trial in Botswana, the PopART trial in South Africa and Zambia, the Search trial in Kenya and Uganda, and the TasP trial in South Africa[1,2]

Goal:

- To aid interpretation of these complex trials where the intervention is administered on one group (people with HIV) and the outcome (incidence) is measured on a different group (seroconverters)
- our goal was to estimate the relative contribution of different sources of infection in the Botswana trial

Hypotheses:

- Our hypotheses were that the size of effect observed in universal test-and-treat trials was reduced by "spillover effects" from sexual contact between intervention and control communities, and with communities outside the trial



- If dilution of intervention effect by "spillover effects" was large then impact of universal test-and-treat interventions at the national level would be larger than that in the trials.

METHODS

1. Deep-sequenced HIV viral whole genomes from 5,114 participants in Botswana trial[3]
2. Inferred directed opposite-sex transmission pairs between trial communities using deep-sequence phylogenetics
3. Modeled the risk of transmission between trial communities using the inferred directed opposite-sex pairs i.e. Negative-binomial model: expected probability of viral linkage

Accounting for spillover infections shows the effect of HIV Treatment-as-Prevention (TasP) in general populations is considerably larger than initially reported.

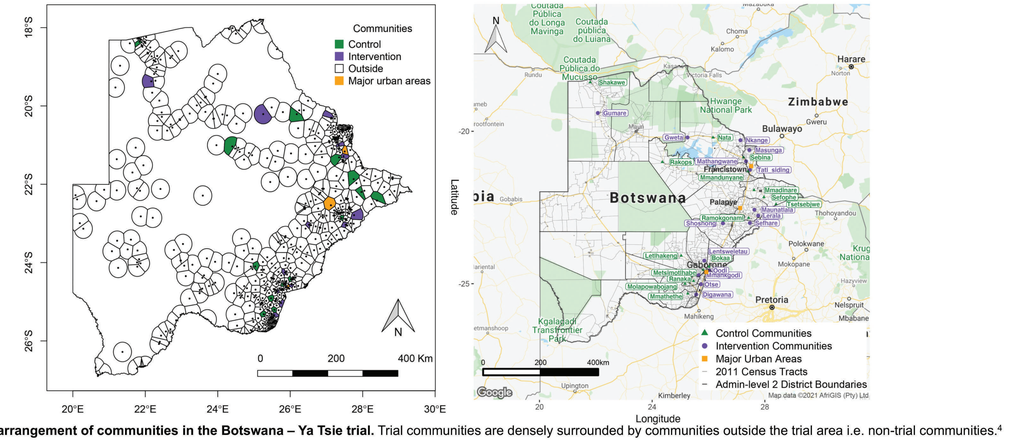


Figure 1. Spatial arrangement of communities in the Botswana – Ya Tsie trial. Trial communities are densely surrounded by communities outside the trial area i.e. non-trial communities.[4]

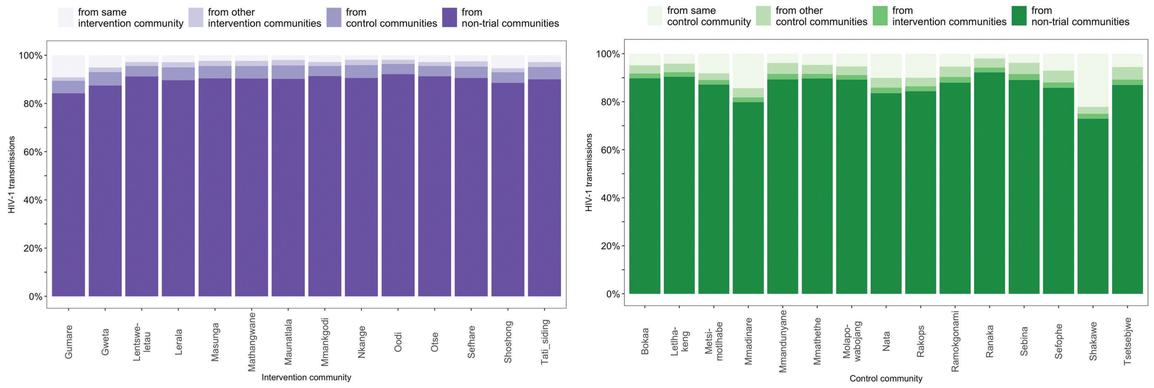


Figure 2. Estimated HIV-1 transmissions into trial communities from different sources of infection. Fewer transmissions occurred to control communities from intervention community sources than the reverse compatible with a benefit of treatment-as-prevention. [4]

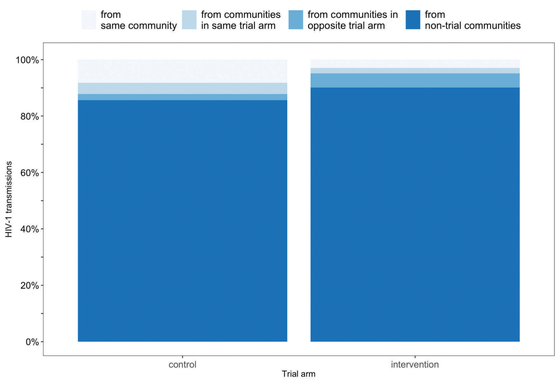


Figure 3. Mean estimates of HIV-1 transmissions into trial communities from different sources of infection. On average 90% [95% CI: 81 - 93] of transmissions to intervention communities and 86% [74 – 90] of transmissions to control communities originated from individuals in non-trial communities. [4]

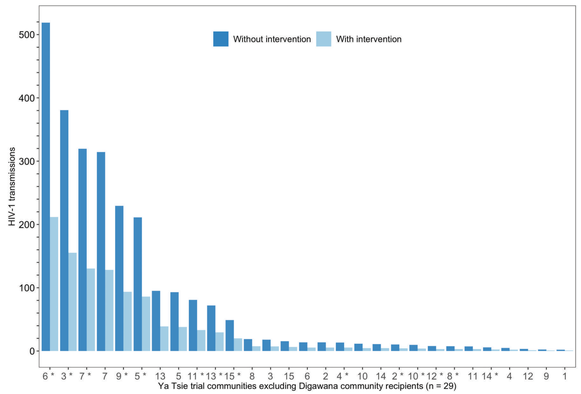


Figure 4. Counterfactual estimates of HIV-1 transmissions into trial communities showing the impact of a nationwide intervention. Transmissions to trial communities could have been reduced by 59% [3 - 87] if the intervention had been applied nationally. Intervention communities are denoted by an asterisk.[4]

4. Used model and census data to predict risk of transmission to trial communities from communities nationally
5. Estimate proportions of transmissions to trial communities from sources of infection in: same community, same trial arm, opposite-trial arm and non-trial communities
6. Estimated what the impact of the intervention would have been if applied nationally

RESULTS

- Most transmissions to trial communities occurred from non-trial communities substantially reducing the impact of the intervention (Figures 1-3).



- A national application of the intervention would have reduced transmissions to trial communities by 59% [3 - 87] compared to the observed 30% reduction (Figure 4).



CONCLUSIONS

- This work *transforms* our thinking about the effectiveness of TasP for HIV prevention in general populations to a highly effective intervention when applied nationwide to maximize the capture of sources of transmission.
- Put simply, when most infections originate from sources outside a community then a targeted intervention to that community and a few of its neighboring communities is similar to installing a fence full of holes, with limited gains, which explains why the TasP trials showed mixed results.
- A provision of TasP to all communities nationwide "fixes the holes" averting considerably more transmissions.

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lm22@sanger.ac.uk / lmagosi@hsph.harvard.edu