Investigating the Impact of an HIV Combination Prevention Strategy in Botswana

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Joint work with
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Goal: to evaluate the impact and cost effectiveness of combination HIV prevention interventions on population-level HIV incidence in Botswana.

Map of 50 Botswana communities with population sizes ranging from 3,000 to 15,000 (provided by Hermann Bussmann and colleagues).
Design Overview

30 villages
(15 matched pairs)

Arm A (15 villages)
Standard of Care

Arm B (15 villages)
ART for HIV + individuals w/CD4<350 cells/ml or AIDS
Plus ART for high viral load (>10,000)
Plus Combination Prevention*

- Combination Prevention includes
  - Enhanced HIV testing and counseling (HTC),
  - Prevention of mother-to-child transmission (PMTCT),
  - Enhanced test-linked care (TLC) in relation to ART
  - Male circumcision (MC)

- Both arms will evaluate HIV incidence, from cohorts (20% of the population) followed longitudinally for 3 years.
Simulation studies
Model intervention impact on HIV spread over 4 years

- Generate sexual networks then propagate disease spread on these networks

- Community characteristics:
  - Sexual network characteristics (including mixing between communities)
  - Varying coverage level for different prevention modalities
  - Population sizes

- Individual characteristics:
  - Transmission risk
  - Disease progression
  - Condom use
  - Linkage to care
  - Circumcision status
Input
- Degree Distribution (Likoma Island)
- Mixing between Communities (Mochudi)

Input
- Relationship Durations (Mochudi)

Initial Conditions (Mochudi)
- HIV Prevalence
- % on ART
- % of males circumcised
- Condom usage
- VL/CD4 distr.

Biology
- Viral Load / CD4 Trajectories
- Transmission Probabilities
- Transmission reductions

Intervention
- % annual testing
- % circumcision
- Linkage to Care

Cumulative Contact Sexual Network

Dynamic Network

Epidemic Spread

Output
- Annual Incidence
Network Construction
for a pair of communities A and B

Mixing matrix allowed to vary

A | 40% | 10%
B | 10% | 40%

Markov Chain Monte Carlo
Network Construction

- Bipartite Graph (Relationship only between genders)
- Two Arms (Control and Treatment)
- Control for mixing between the two arms
- Degree (number of partners) Distribution based on Likoma Island
Degree Mixing Matrix

Assortative: monogamous couples; partners who each of whom has many others
Dissassortative: married people with sex worker partners

<table>
<thead>
<tr>
<th>Gender</th>
<th>Degree</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
Metropolis Hastings Algorithm

Edge switching (or toggling) is used to propose networks

Target: \( P(G=g) \) is proportional to \( \frac{1}{\text{(# in } C(g)) \cdot P(C(g))} \)

where \( C(g) \) is the congruency class, i.e. all networks share a given feature
MH will accept a proposal network, \( p_{t+1} \), with probability:

\[
P(\text{accept}) = \frac{P(G= p_{t+1})}{P(G=g_t)}
\]

\[
= \frac{\text{# of graphs in } C(g_t) \cdot \frac{P(C(p_{t+1}))}{P(C(g_t))}}{\text{# of graphs in } C(p_{t+1}) \cdot \frac{P(C(p_{t+1}))}{P(C(g_t))}}
\]

\[
= \frac{f(C(g), C(p_{t+1})) \cdot P(C(p_{t+1}))}{f(C(p_{t+1}), C(g)) \cdot P(C(g_t))}
\]

where \( f(C(a), C(b)) \) is the average number of elements in \( C(a) \) that are valid proposals from an element in \( C(b) \). The value of \( f(\cdot, \cdot) \) can be approximated from the degree distributions (egocentric data) or mixing matrices (network level data).
Cumulative sexual contact network
Network Construction
(from cumulative contact network to dynamic network)

Duration of Relationships
(Estimated from Mochudi data)

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Duration</th>
<th>Date</th>
<th>Start/End</th>
</tr>
</thead>
<tbody>
<tr>
<td>e1</td>
<td>d1</td>
<td>t1</td>
<td>1</td>
</tr>
<tr>
<td>e2</td>
<td>d2</td>
<td>t2</td>
<td>0</td>
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<td>.</td>
</tr>
<tr>
<td>e_n</td>
<td>d_n</td>
<td>t_n</td>
<td>1</td>
</tr>
</tbody>
</table>

Duration of Relationships

Graph showing the density of relationships over the number of days.

Graph showing the duration of relationships over years.
Initiation Conditions

- HIV Prevalence, 24.8%
- Condom use: 40%
- % of males circumcised: 12.7%
- VL/CD4 distribution: based on data from Mochudi
- % on ART among eligible subjects (CD4<350): 60.9%
Epidemic Spread

• Disease progression of HIV infected subjects
  • Duration of high VL after infection: Incidence cohort
  • Rate of CD4 decline: Incidence cohort/Mochudi

• Transmission risk
  • Depending on VL category: Quinn et al. (2000)
  • Reduction in transmission risk
    • From knowledge of serostatus: 30%
    • From condo use: 85%
  • Reduction in acquisition risk from circumcision: 60%
Mixing

• In Mochudi about 30% of partners of villagers were reported to living outside of the village

• Partnerships do not attenuate treatment effects if partners are from:
  1) different SOC villages
  2) different INT villages
  3) SOC and non-study villages
Impact of Mixing on Expected Incidence Rates

<table>
<thead>
<tr>
<th></th>
<th>INT</th>
<th>SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>2.7%</td>
<td>5.2%</td>
</tr>
<tr>
<td>20%</td>
<td>3.1%</td>
<td>5.2%</td>
</tr>
<tr>
<td>30%</td>
<td>3.2%</td>
<td>4.3%</td>
</tr>
<tr>
<td>40%</td>
<td>3.5%</td>
<td>4.6%</td>
</tr>
</tbody>
</table>
Mixing by Activity and Incidence (SOC)
For the planned, assuming a $k$ of 0.26, if the cumulative incidence in the intervention arm is $\geq 35\%$ lower than that in the SOC arm (3.9%), the study will have $>80\%$ power.
DSMB review

• Reviews DSMB 0-4 take place at baseline and the ends of yrs 1, 2, 3 and 4.
• DSMB 1-2 evaluate intervention rollout and safety.
• DSMB 3 can recommend stopping for efficacy or futility, or extending the study by 1 year if:
  - poor intervention coverage, or
  - low incidence in the SOC arm.
• Conditional power assessed by simulation studies.
Phylogenetic analysis

- Analyze DNA or amino acid sequences to gain information about evolutionary relationships.

- Can use properties of phylogenetic trees to create test statistics to determine whether certain demographics are more likely to be clustered.

- Common algorithms for tree construction:
  - maximum likelihood
  - neighbor joining
  - maximum parsimony

Maximum Likelihood tree
Conclusions

• Network models can help in designing and monitoring studies of HIV prevention in Africa and in investigating the attenuation resulting from mixing across communities.

• Mixing by degree does not appear to impact the efficacy of interventions.
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References
