Investigating the Impact of an HIV Combination Prevention Strategy in Botswana

Presented by

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Joint work with

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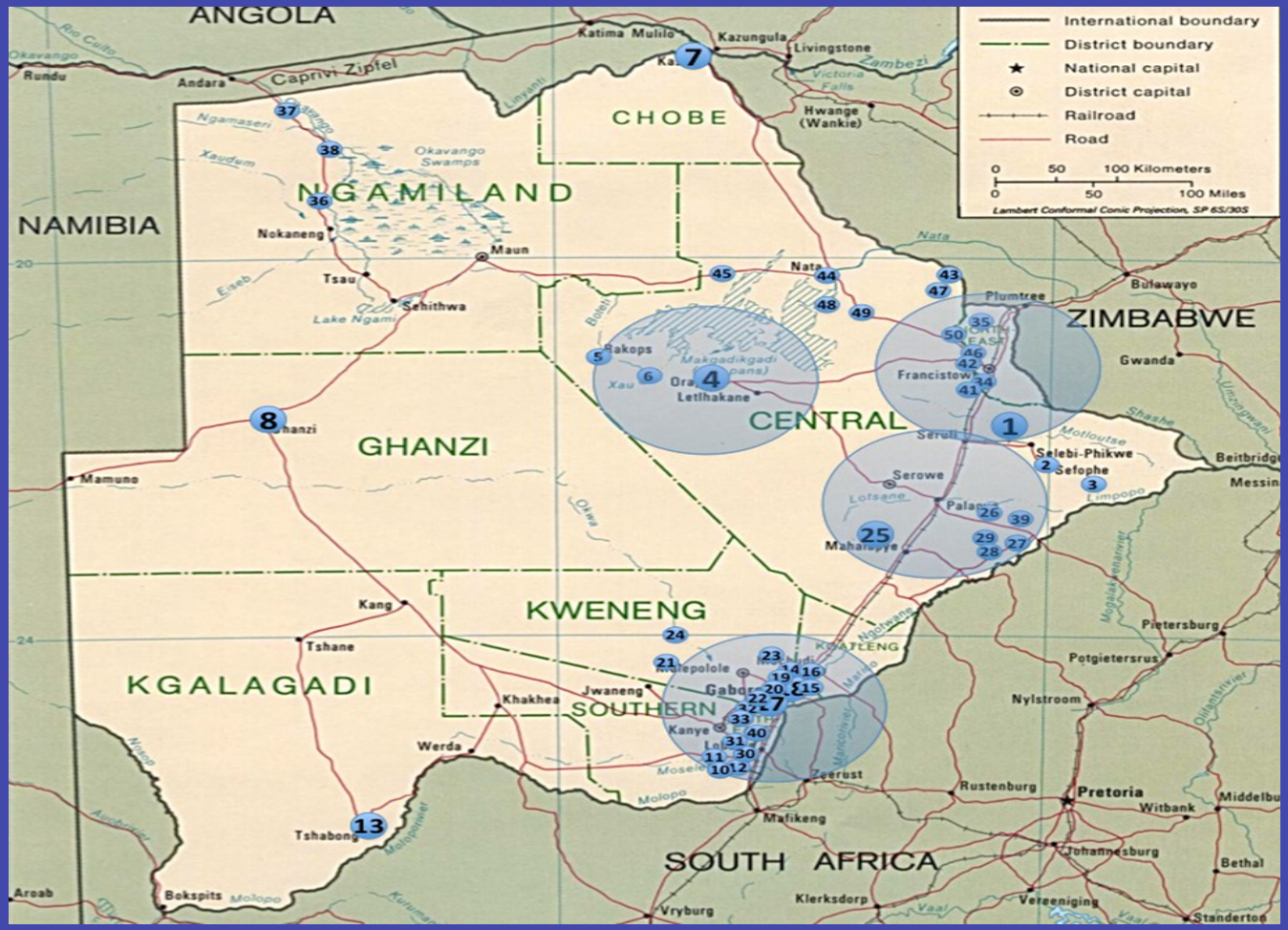
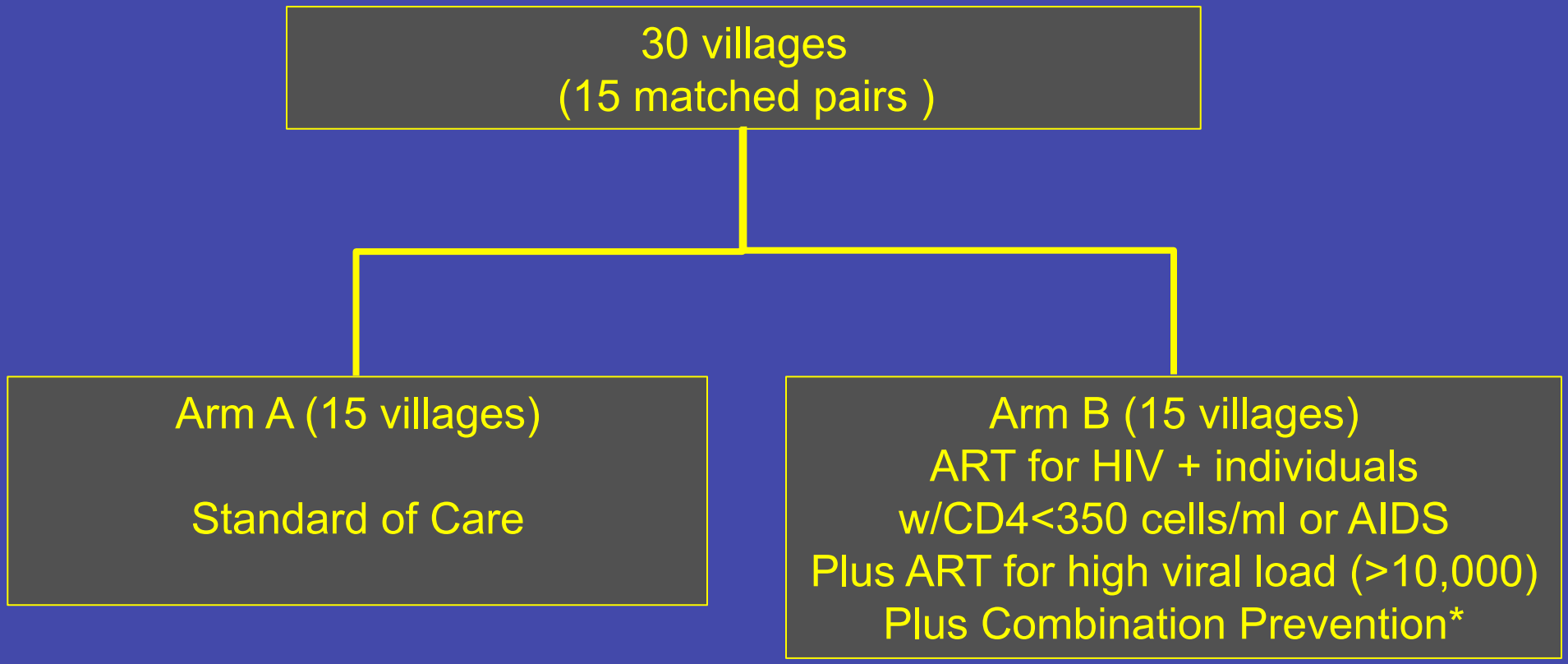
Goal: to evaluate the impact and cost effectiveness of combination HIV prevention interventions on population-level HIV incidence in Botswana



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

Design Overview



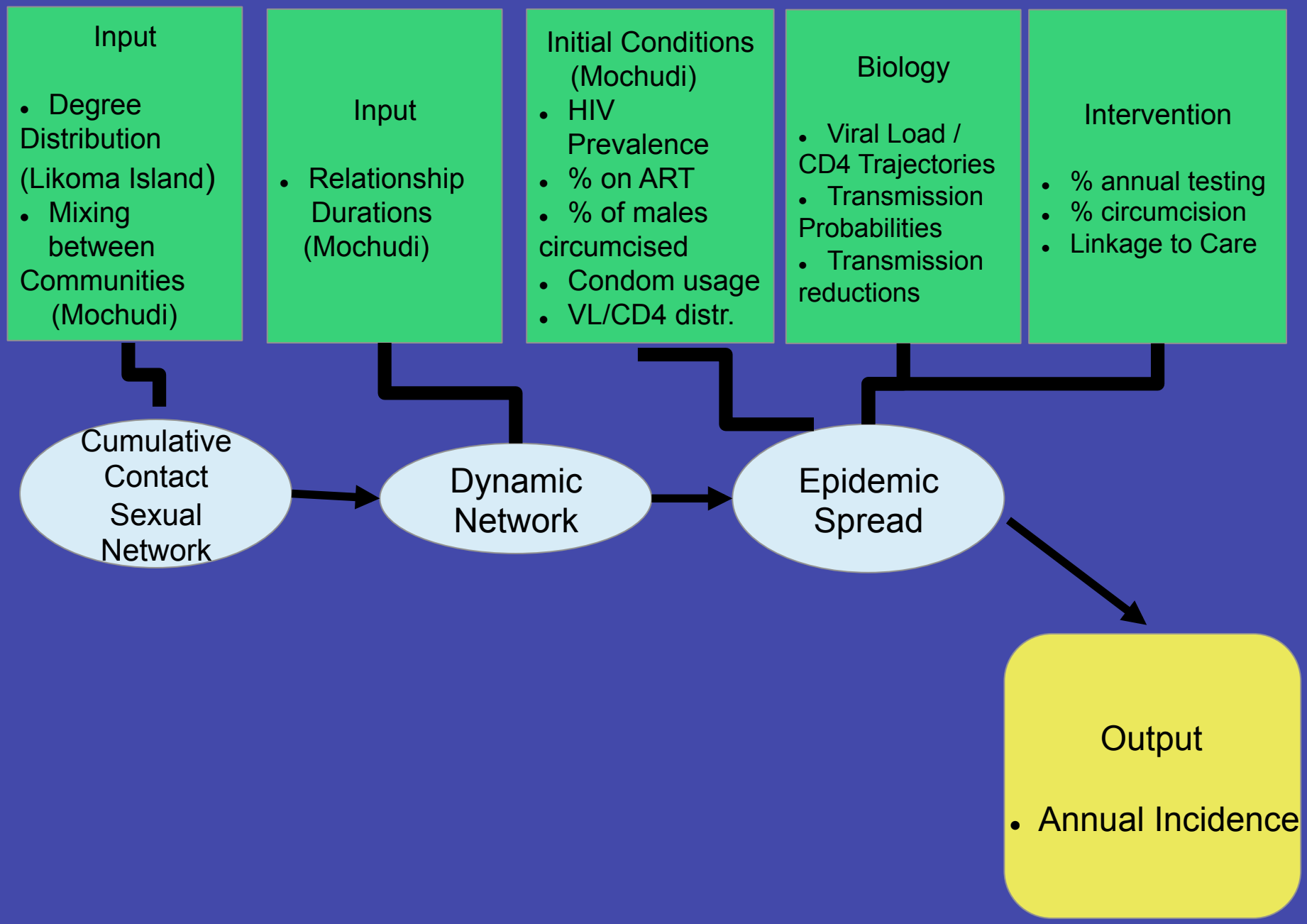
- Combination Prevention includes
  - Enhanced HIV testing and counseling (HTC),
  - Prevention of mother-to-child transmission (PMTCT),
  - Enhanced test-linked care(TLC) in relation to ART
  - Male circumcision (MC)
- Both arms will evaluate HIV incidence, from cohorts (20% of the population) followed 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

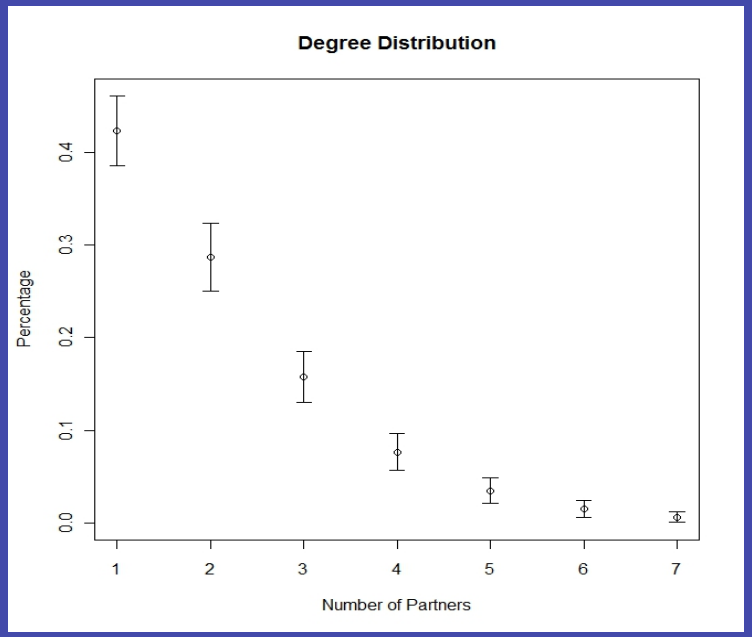
- Community characteristics:
  - Sexual network characteristics (including mixing between communities)
  - Varying coverage level for different prevention modalities
  - Population sizes

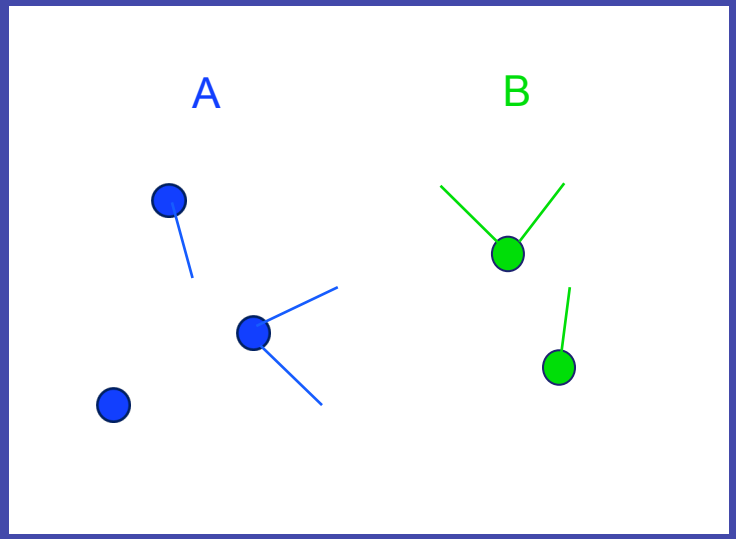
- Individual characteristics:
  - Transmission risk
  - Disease progression
  - Condom use
  - Linkage to care
  - Circumcision status


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

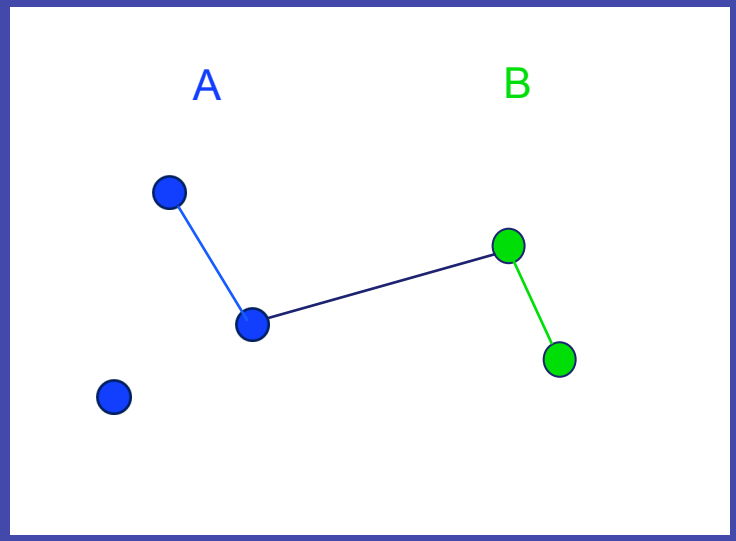
Network Construction

for a pair of communities A and B





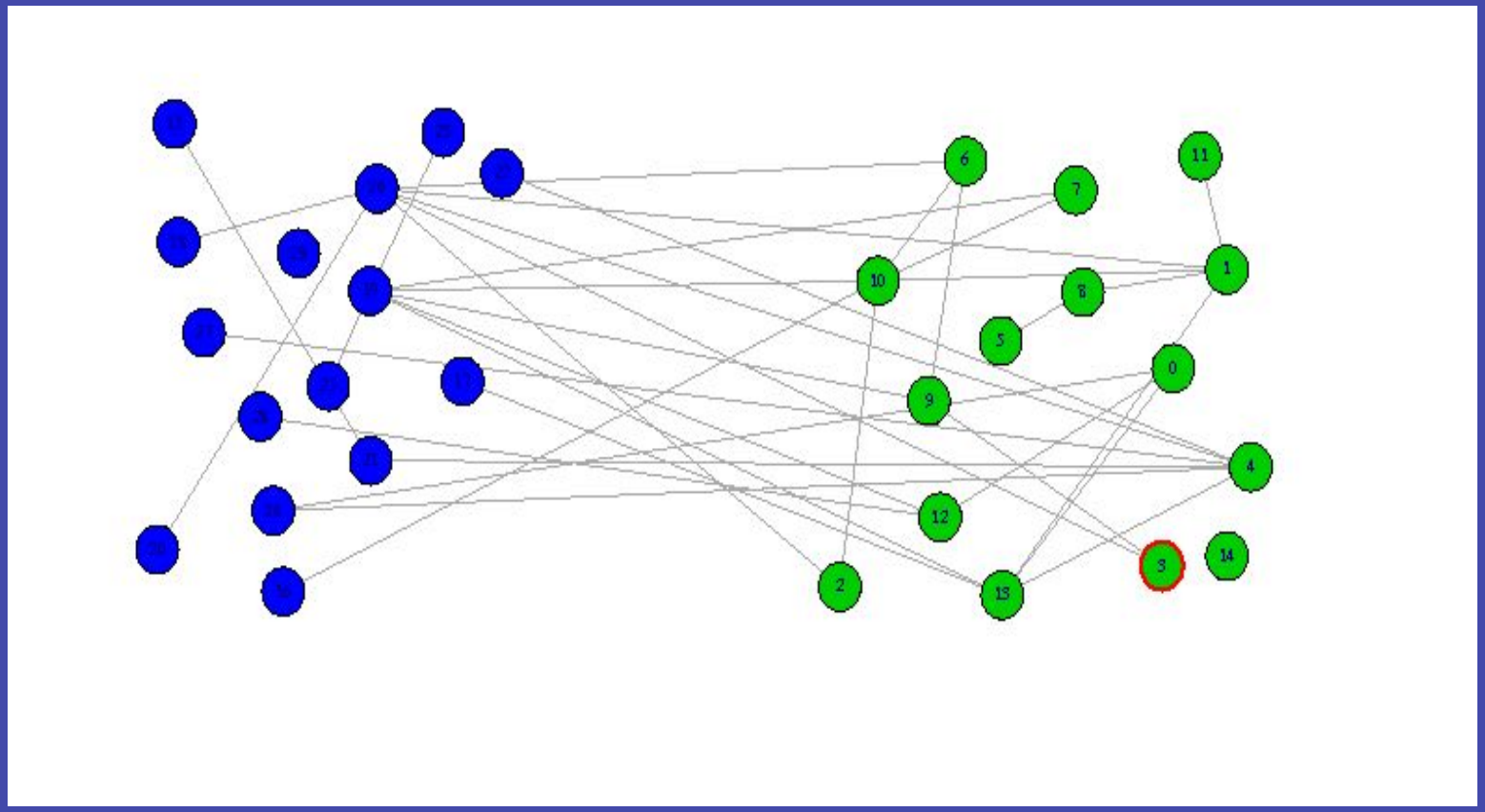
Markov Chain
Monte Carlo



Mixing matrix allowed to vary

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

Network Construction



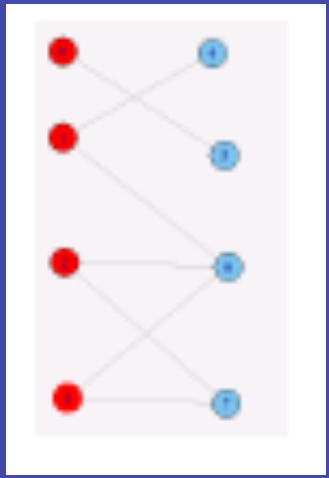
•-Bipartite Graph (Relationship only between genders)

•-Two Arms (Control and Treatment)

•-Control for mixing between the two arms

•-Degree (number of partners) Distribution based on Likoma Island

Degree Mixing Matrix

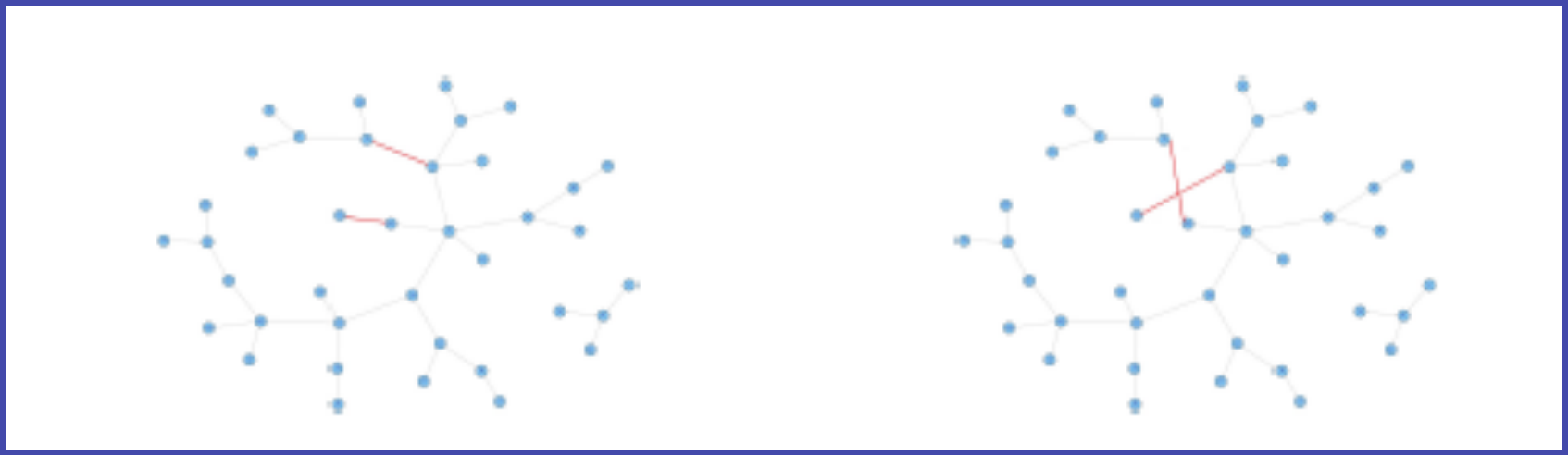


Gender			Male	
	Degree	1	2	3
Female	1	1	0	0
	2	1	2	3

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

Metropolis Hastings Algorithm

Edge switching (or toggling) is used to propose networks



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

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:

$$P(\text{accept}) = P(G = p_{t+1}) / P(G = g_t)$$

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

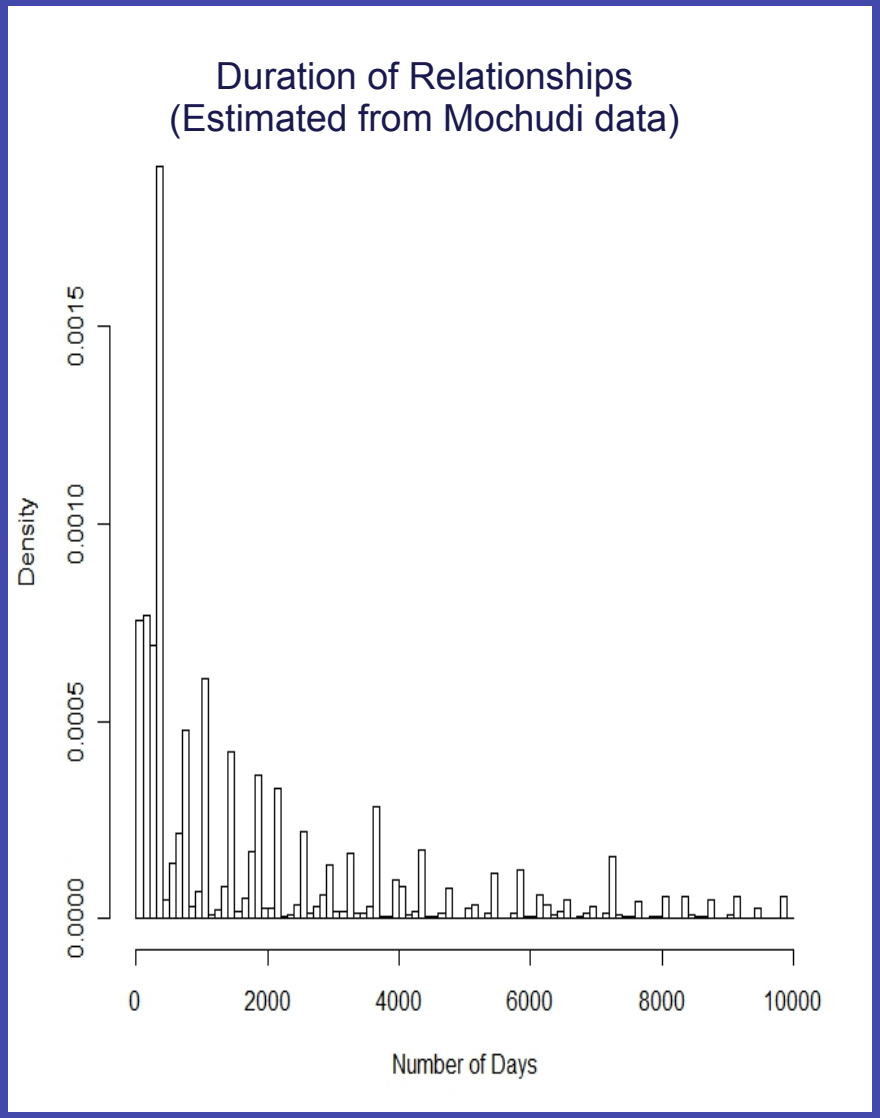
$$= \frac{f\,(C(g), C(p_{t+1}))\, P(C(p_{t+1}))}{f(C(p_{t+1}), C(g))\;\; P(C(g_t))}$$

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(·,·) can be approximated from the degree distributions (egocentric data) or mixing matrices (network level data).

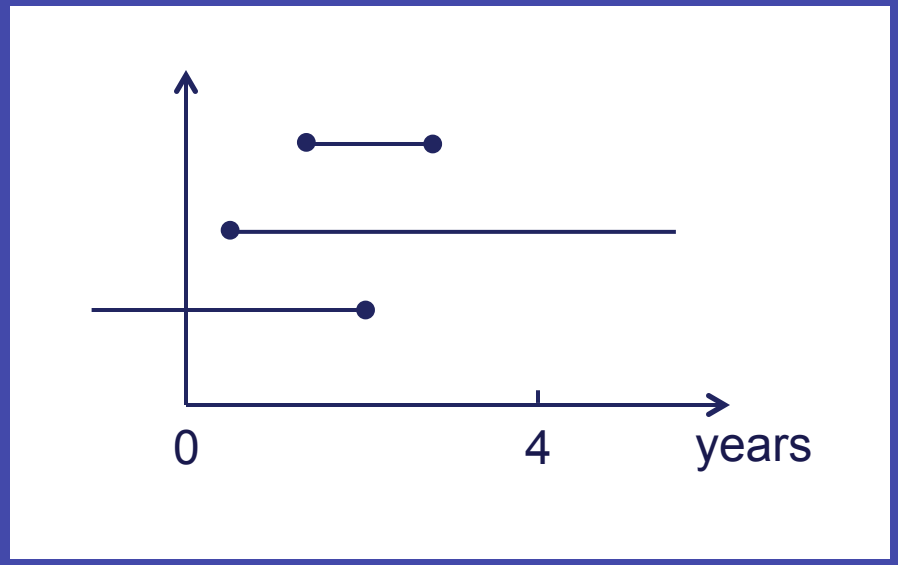
Cumulative sexual contact network

Network Construction

(from cumulative contact network to dynamic network)



Relationship	Duration	Date	Start/End
e1	d1	t1	1
e2	d2	t2	0
.	.	.	.
.	.	.	.
.	.	.	.
e_n	d_n	t_n	1



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%

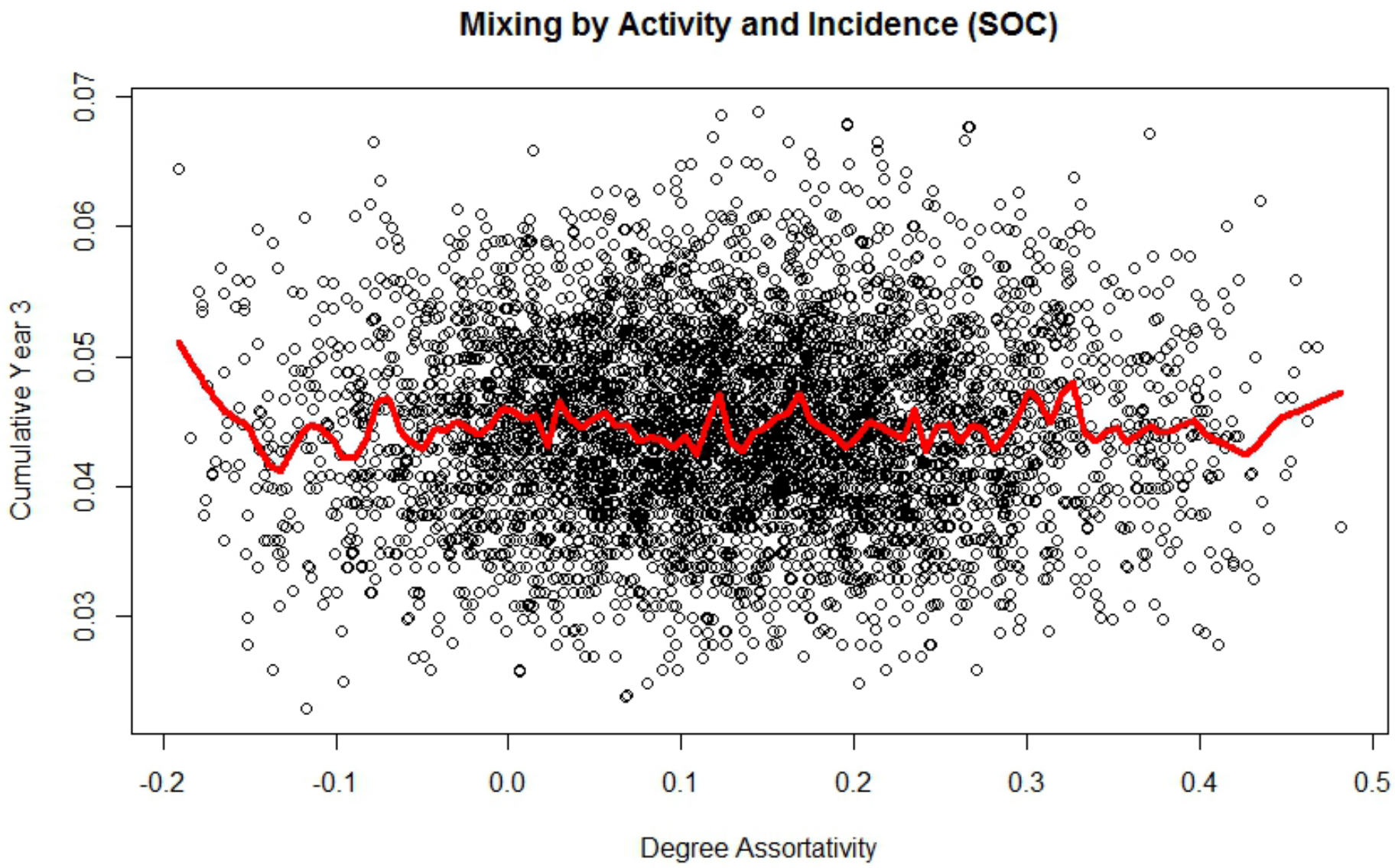
Mixing

- 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:

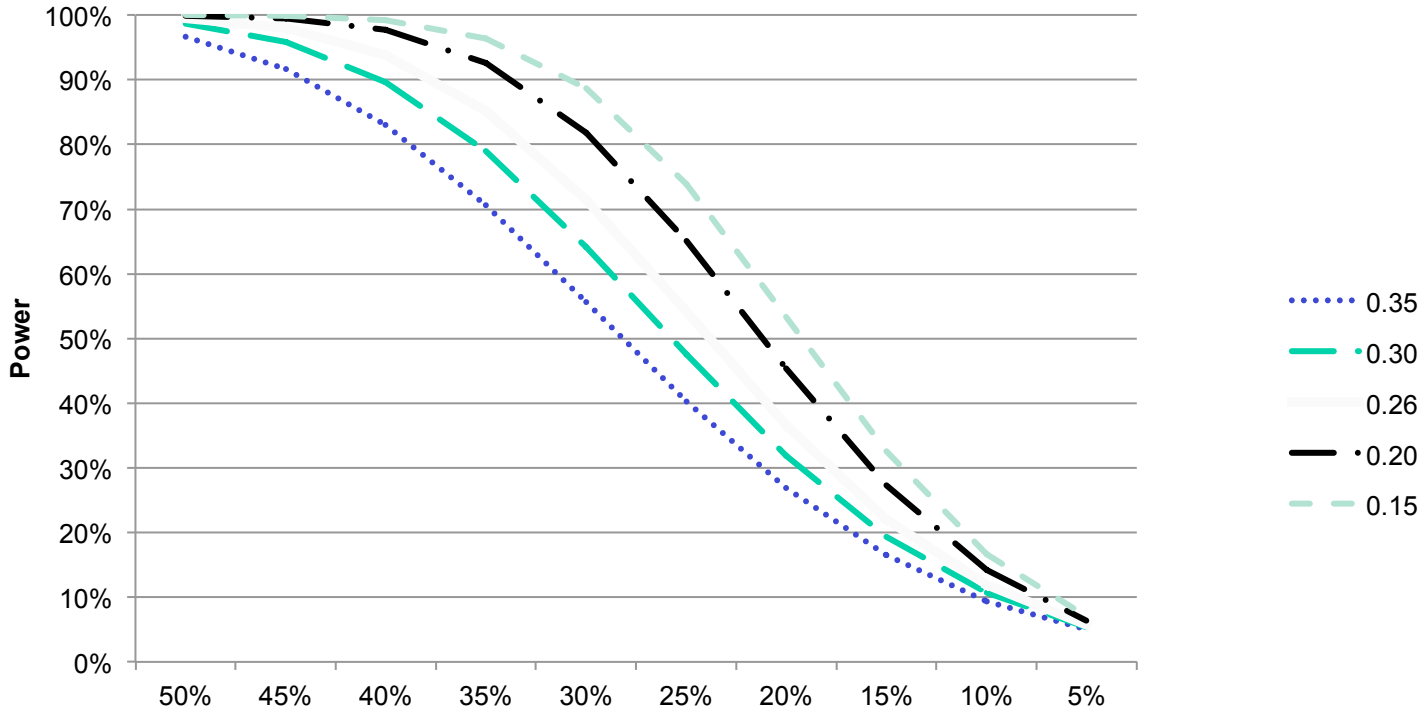
  1) different SOC villages
  2) different INT villages
  3) SOC and non-study villages

Impact of Mixing on Expected Incidence Rates

	INT		SOC
• 10% mixing:	2.7%	vs	5.2%
• 20% mixing:	3.1%	vs	5.2%
• 30% mixing	3.2%	vs	4.3%
• 40% mixing	3.5%	vs	4.6%


Mixing by Activity and Incidence (SOC)
Cumulative Year 3
0.03
0.04
0.05
0.06
0.07
-0.2
-0.1
0.0
0.1
0.2
0.3
0.4
0.5
Degree Assortativity

Sensitive Analysis: Power for Varying Reductions in HIV Incidence in Intervention vs. SOC Arms



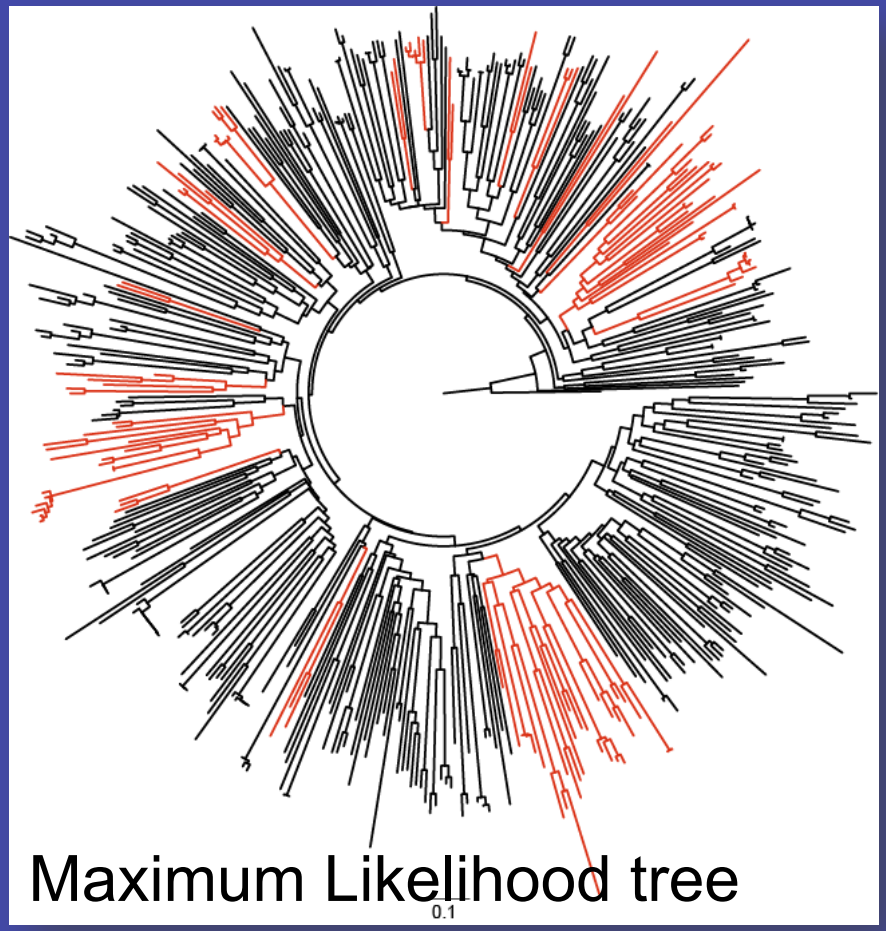
For the planned, assuming a k of 0.26, if the cumulative incidence in the intervention arm is ≥ 35% lower than that in the SOC arm (3.9%), the study will have >80% power.

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

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Stephens AJ, Tchetgen Tchetgen EJ, DeGruttola V. Augmented GEE for improving efficiency and validity of estimation in cluster randomized trials by leveraging cluster- and individual-level covariates. Statistics in Medicine. 2012 May 10. PMCID: PMC3495191