

Cluster-randomized trials of combination prevention interventions

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Combining Modalities

- Can some combination of prevention modalities control the HIV epidemic (make it unsustainable without infections arising from outside the community) for a defined region or community?
- What are the location-specific factors that mediate the impact of combination prevention methods (epidemic/network characteristics, biological and behavioral factors)?
- Can estimation of mediators and their effects for specific communities help scale up results of community-level RCTs?

Sources of Information

- Community Randomized Trials
- Ongoing HIV Surveillance
 - As interventions get rolled out, useful to evaluate impact in real time
 - Need information about roll-out, health outcomes, and incidence
 - Methods for combining across datasets in other settings may be useful.

What trials are there?

- 3 OGAC funded studies:
 - **HPTN 071- PopART** (OGAC,NIH,NIAID,Gates)
 - **Iringa** JHU
 - **BCPP** (OGAC,CDC, Havard)
- **TasP** (ANRS)
- **HPTN 065 TLC-Plus**: A Study to Evaluate the Feasibility of an Enhanced Test, Link to Care, Plus Treat Approach for HIV Prevention in the United States

PEPFAR-Sponsored Combination Prevention Cluster-Randomized Trials in Africa

Study	LSTMH/PopART Hayes/Ayles NIH – HPTN	BHP/BCPP Essex/DeGruttola CDC	Iringa, JHU Celentano/Kerrigan USAID
Sites	Zambia/S Africa	Botswana	Tanzania
Trial Arms	<ol style="list-style-type: none"> SOC Test and ARV for all positives, plus combination prevention package* Test-linked ARV for all CD4 <350, plus combination prevention package* 	<ol style="list-style-type: none"> SOC Test and ARV for all viral load above 10,000, plus combination prevention package* 	<ol style="list-style-type: none"> SOC Test-linked ARV for all CD4 <350, plus combination prevention package*
Efficacy evaluation	24 villages (60,000)	30 villages (20,000)	24 clusters (12,000)

*Combined prevention package: highest possible HTC, MC, treatment for CD4 <350, PMTCT.

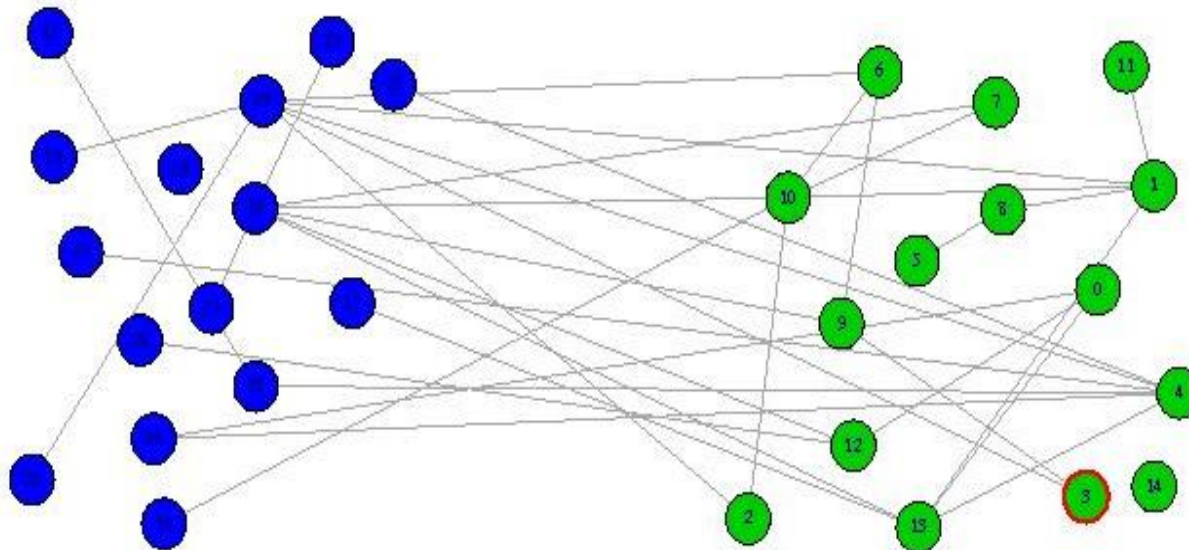
KwaZulu Natal, S Africa (2 arms) – TasP trial

- Arm 1. Expanded testing, male circumcision, immediate ART, IEC, STI treatment etc.
- Arm 2. As above but ART at CD4<350
- 32 clusters (16 vs 16)
- 1,250/cluster, total 40,000, 24m follow-up (total population)
- Funding currently available for initial feasibility study in 4 of the 32 clusters

BCPP Design Overview

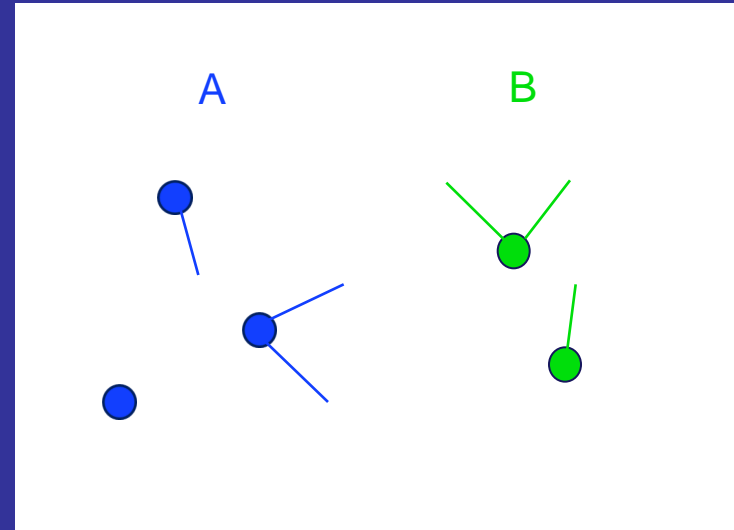
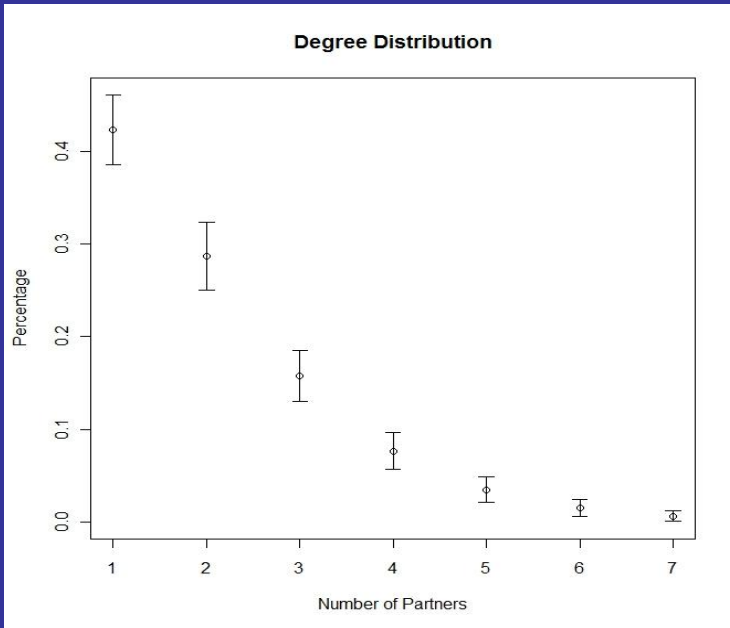
- Two-arm Study
 - Arm A: control communities - standard of care
 - Arm B: treat for all subjects with viral load higher than 10,000 copies/ml, plus combination prevention package including highest possible coverage for:
 - HTC
 - Male circumcision
 - Rapid linkage to care after detection of HIV
 - PMTCT
- Both arms will evaluate HIV incidence from cohorts (20% of the population) followed longitudinally over the 4-year period.

Network Construction

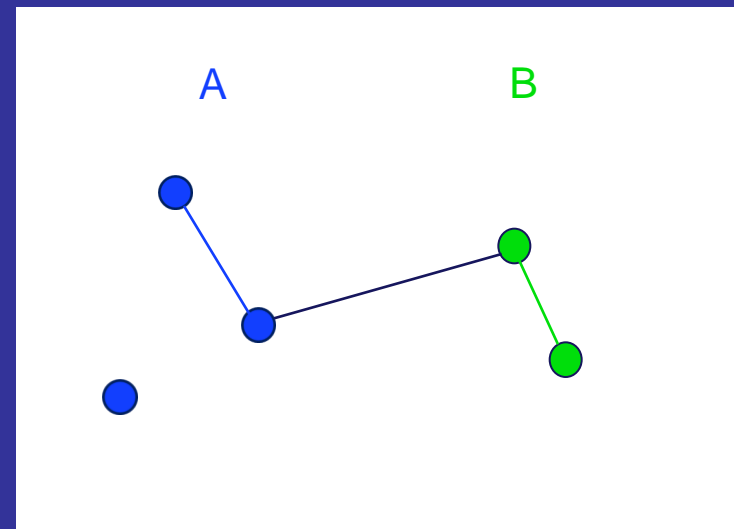


- Bipartite Graph (Relationship only between genders)
- Two Arms (Control and Treatment)
- Control for mixing between the two arms
- Degree (number of partners) Distribution based on Likoma Island

Network Construction for a pair of communities A and B



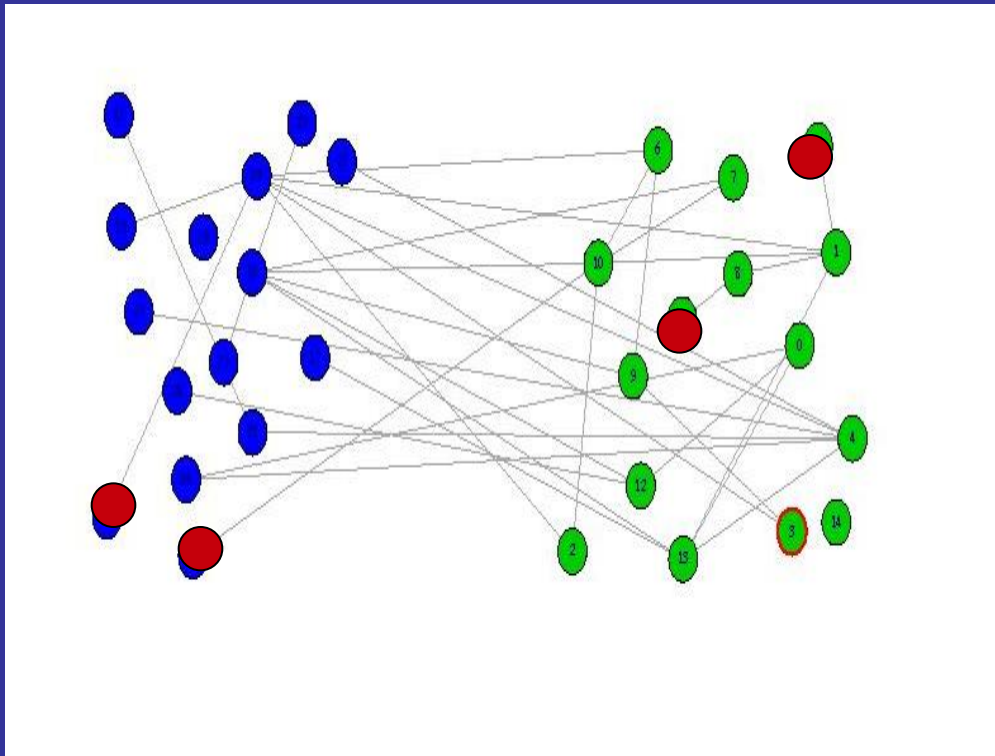
Markov Chain
Monte Carlo



Mixing matrix allowed
to vary

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

Simulation: Initial Conditions



- Selection Initial HIV+ Nodes
- From HIV+ nodes, select those on treatment (CDC)
- % in each CD4 category (CDC)
- % who are High Viral Load (Mochudi)

Power

- From simulation, we expect cumulative proportion infected to be 5.1% in SOC and 2.5% in intervention arms.
- This leads to 99% power to detect effects.

Mediation: Network Features

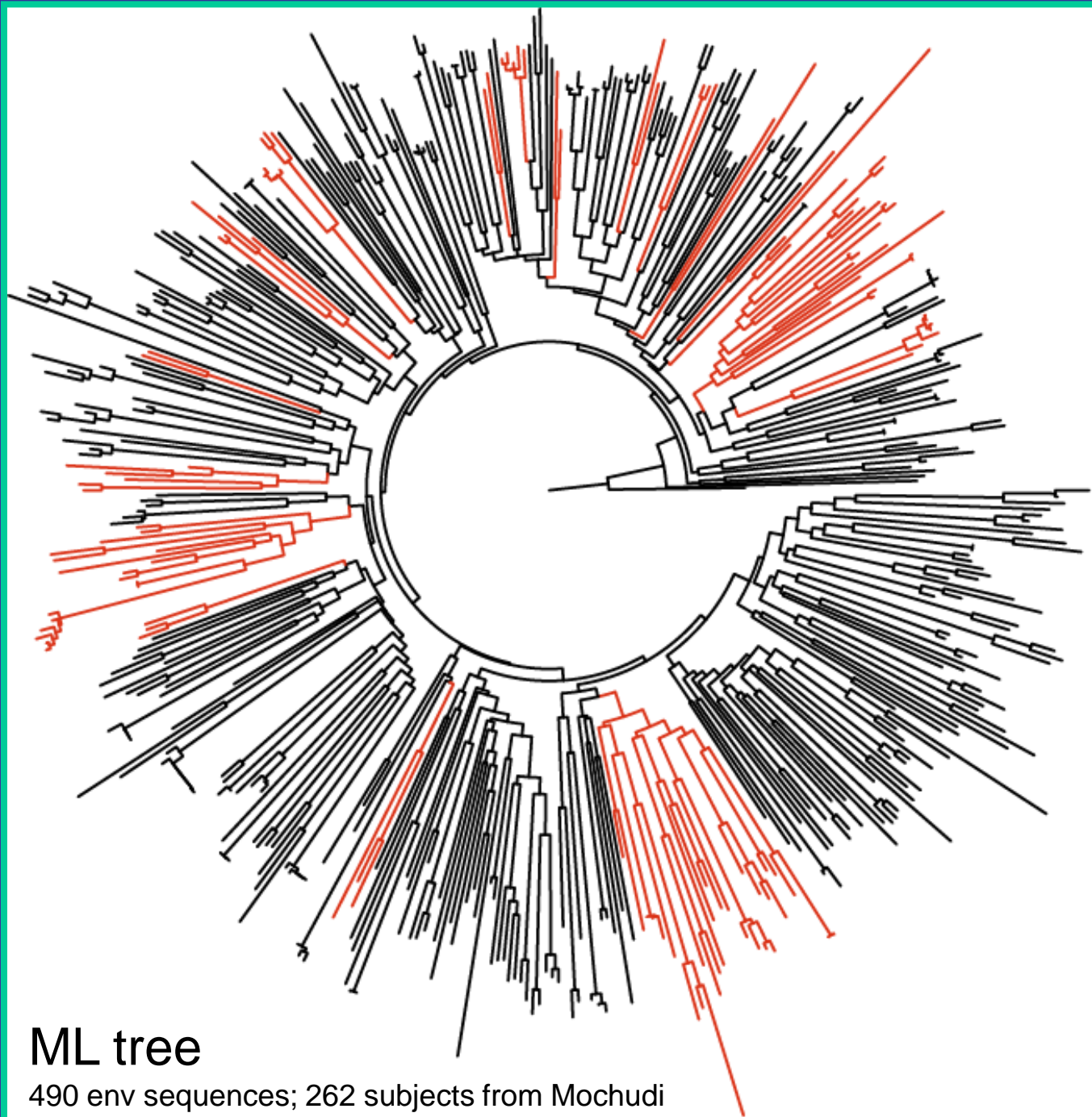
- Assortativity: Tendency for people with many partners to choose others who do as well.
- Mixing matrices may also take into account spatial issues

Sources of Information

- To investigate sexual partner selection that shapes network features like mixing and concurrency, we might use:
 - - Egocentric data
 - Network samples
 - Contact tracing
 - Cell phone/social networking sites
 - Molecular epidemiology to identify chains of transmission and role of acutely infected patients

Phylogenetic Analyses

- Does not provide unambiguous transmission chains.
- But still may be informative about the impact of an intervention (learn about mechanism).
- If intervention works, recipients should be less likely to propagate their HIV (and have partners who do) and therefore tend to be less highly clustered than those who do



ML tree

490 env sequences; 262 subjects from Mochudi
18 clusters with $aLRT \geq 0.98$

0.1

Phylogenetic analyses may be useful to investigate:

- Drivers of the epidemic (based on biology, behavior, network features).
- Indications of where/in whom interventions are working or failing.
- Sexual mixing across clusters.
- Development/spread of resistant virus

Challenges

- Uncertainty in clustering
- Need for high levels of participation (for certain uses).
- Need to adjust for informative non-participation.

Can we estimate effect had all communities received intervention?

- Interest lies in what magnitude of treatment effect would have been had intervention been rolled out throughout Botswana so that mixing across communities would not attenuate effects
- Goal is to accomplish something similar to HPTN 052 when only linked cases were included in preliminary analyses.
- But methods development is needed in this case because of likely presence of missing data.

Conclusions

- Large community-level RCTs can provide information about mediation as well as overall efficacy.
- Single-site studies needed to measure mediators in specific populations.
- Real-time information from surveillance more important than ever as intervention packages rolled out.
- Information should be fed into increasingly realistic epidemic models to establish when and where we are on-track for epidemic control.

Conclusions

- To accommodate uncertainty in degree of uptake, mixing across communities, and dropout rates, network models are useful in design of cluster randomized trials of infectious disease prevention.
- Phylogenetic analyses may aid in providing early indications of success or failure of investigations.
- Novel methods based on developments of collections of networks allow for incorporation of uncertainty in network features on analyses.

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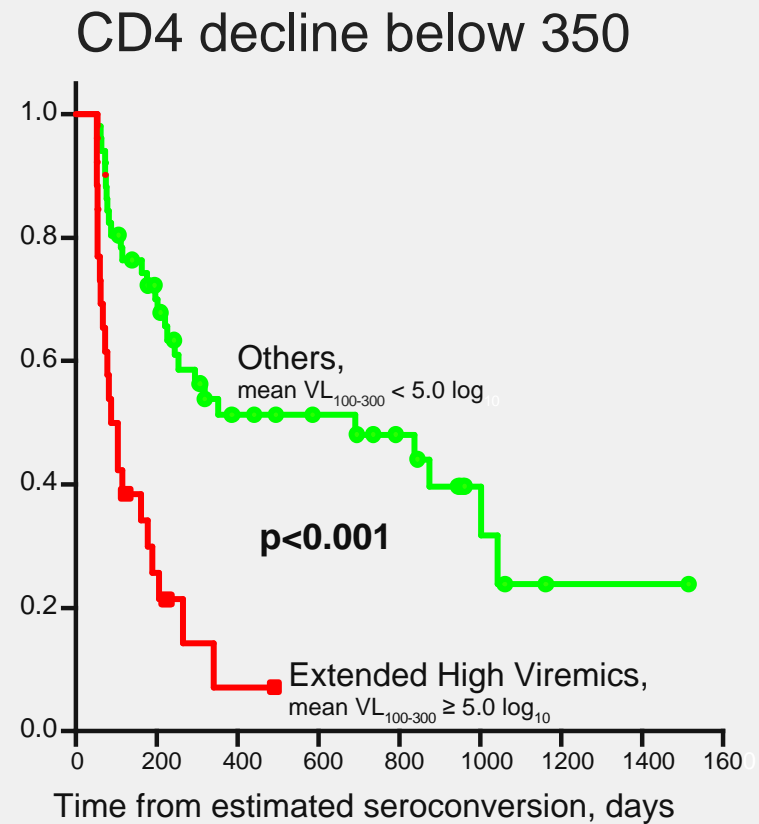
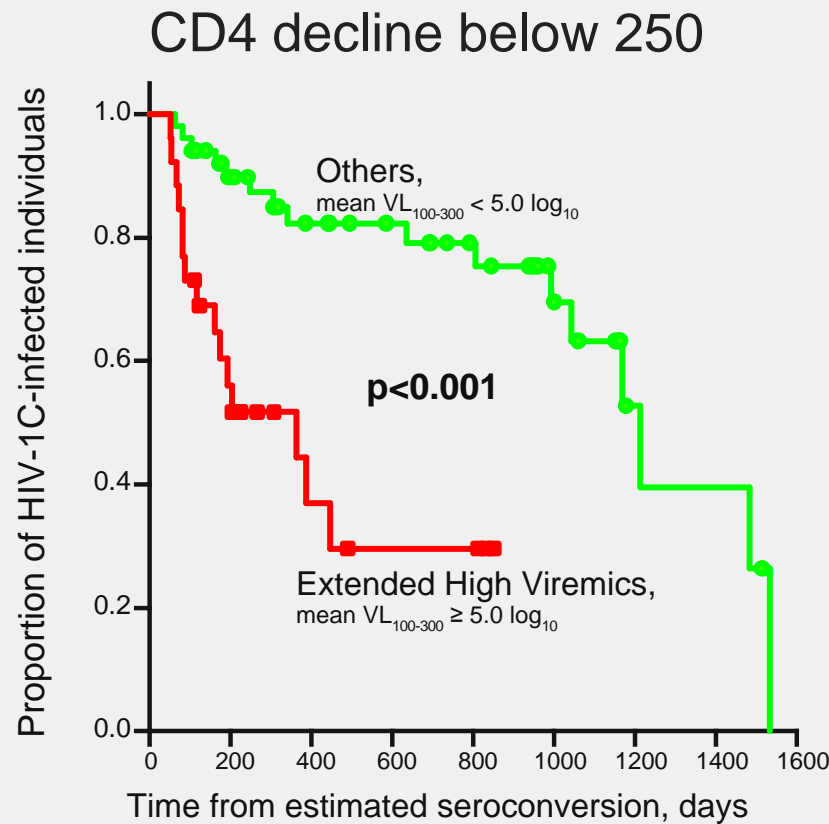
Sponsored by:

United States Centers for Disease Control and Prevention (U01GH000447)

Pharmaceutical Support Provided by:

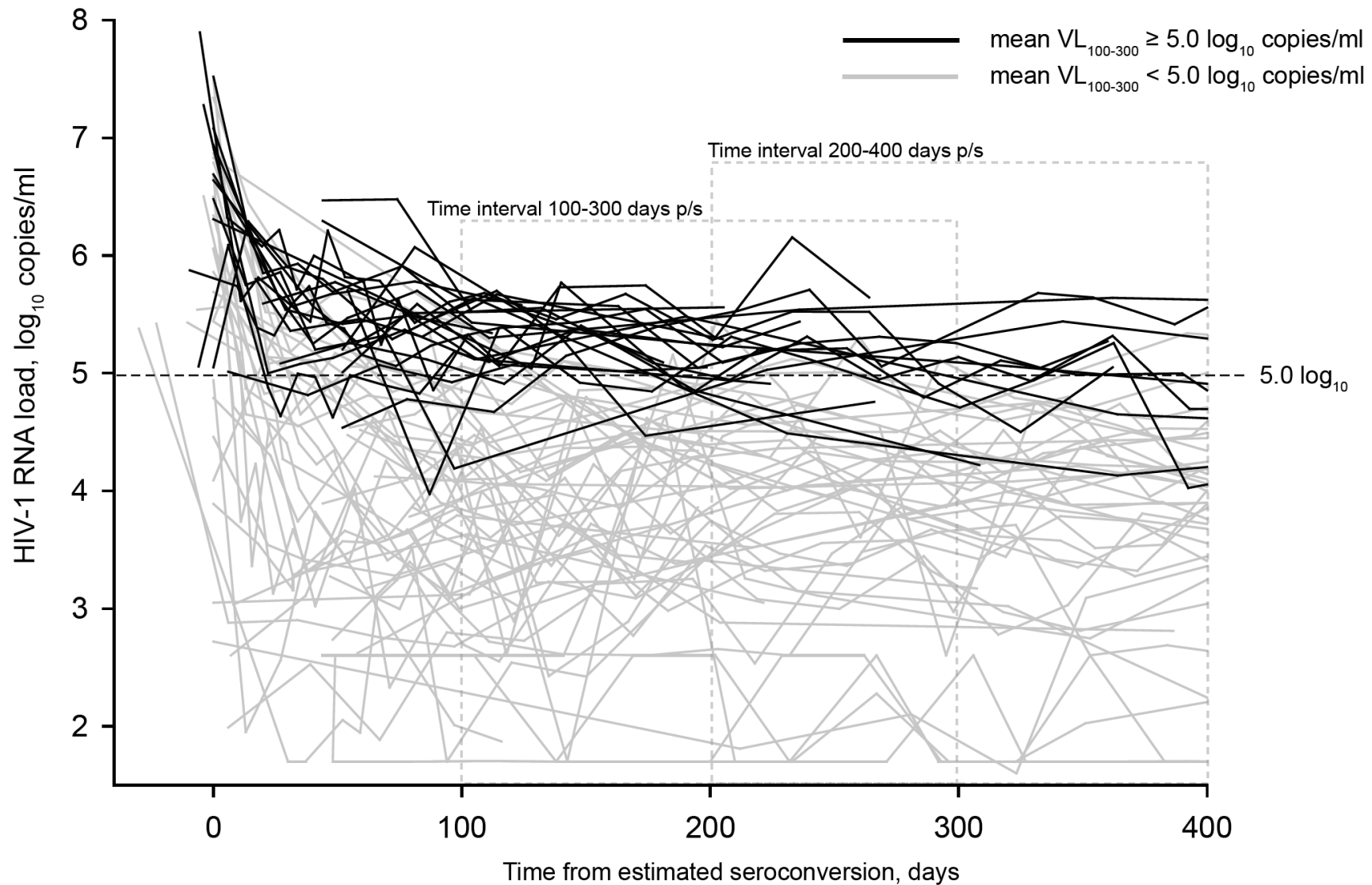
United States President's Emergency Plan for AIDS Relief (PEPFAR)

Decline of CD4+ T cells



Others:	51	39	30	26	21	12	4	3	51	31	19	16	12	5	1	1
Ext. High Vireemics:	26	13	5	3	3	0	0	0	26	6	1	1	1	1	1	1

Viral RNA Dynamics in Primary HIV-1 Subtype C Infection (n=75, pre-HAART data)



Modeling Impact of Interventions

- Testing
 - Percentage of individuals in the control and treatment arms selected to be tested annually
- Male Circumcision
 - Percentage of males in the control and treatment arms who are circumcised during the study (circumcisions occur uniformly over time).
- Treatment
 - At time of test the eligible HIV+ individual put on treatment immediately or after a time interval (distributed as $N(30,5)$), with probabilities that vary in control and treatment communities.
- Condom Use
 - Percentage of individuals who regularly use condoms

Simulation studies to assess power

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

Simulation Study of HIV spread over 4 years

Parameters: Source of Info.

Number of partners: Likoma Island

Duration of Partnerships: Mochudi

Distribution of VL at baseline: Mochudi

Distribution of CD4 at baseline: CDC

Percent on treatment: CDC

Duration of high VL after infection: Incidence Cohort (more on next slide)

Rate of CD4 decline: Incidence Cohort

Trans. risk to HIV- partner by VL of HIV+ partner: Quinn et al.

Reduction in trans.risk from knowledge of serostatus: 30%

Reduction in acquisition risk from circumcision: 60%

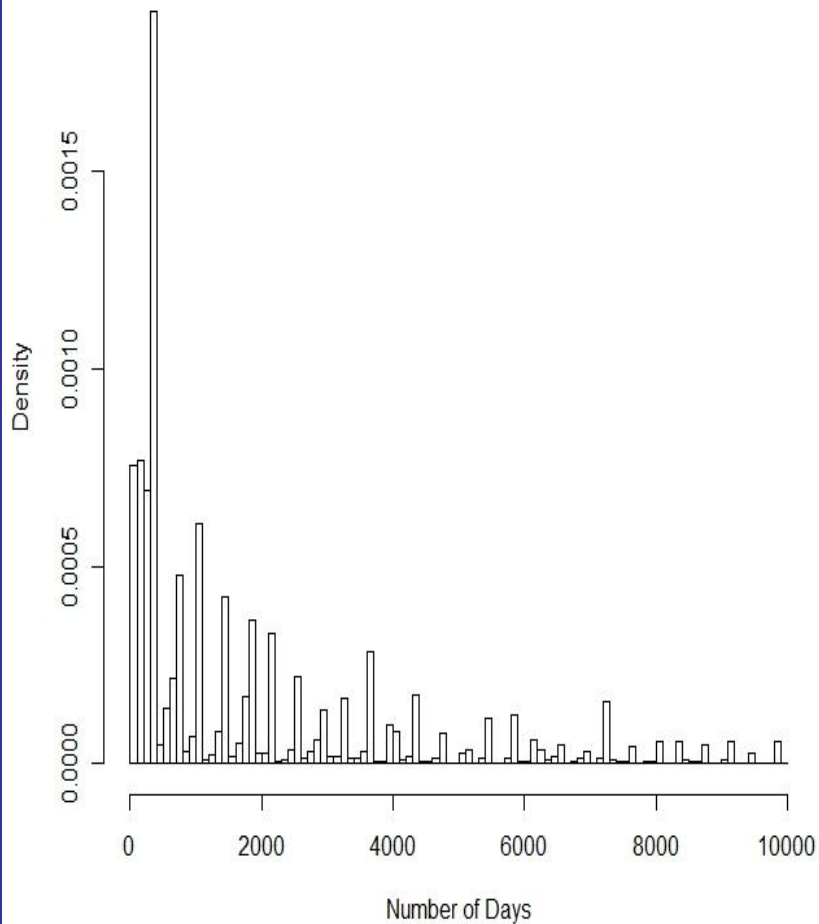
Reduction in trans. Risk: 85% among 40% of users

Hypotheses about Transmission

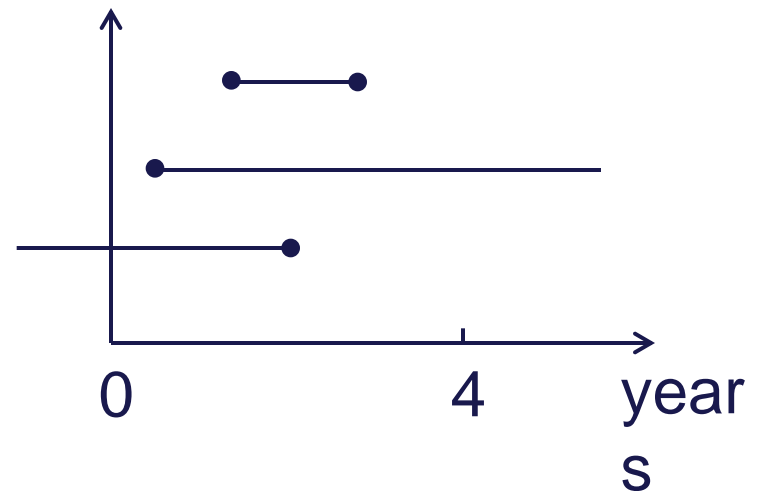
- 1) High viral load cases occur more often in clusters that include one or more incident cases than would be expected by chance.
- 2) High viral load cases occur more often in clusters (regardless of presence of an incident case, and with and without an epidemiologic link) more often than would be expected by chance.
- 3) Subjects in intervention communities occur less often in clusters than do subjects in SOC communities.

Network Construction

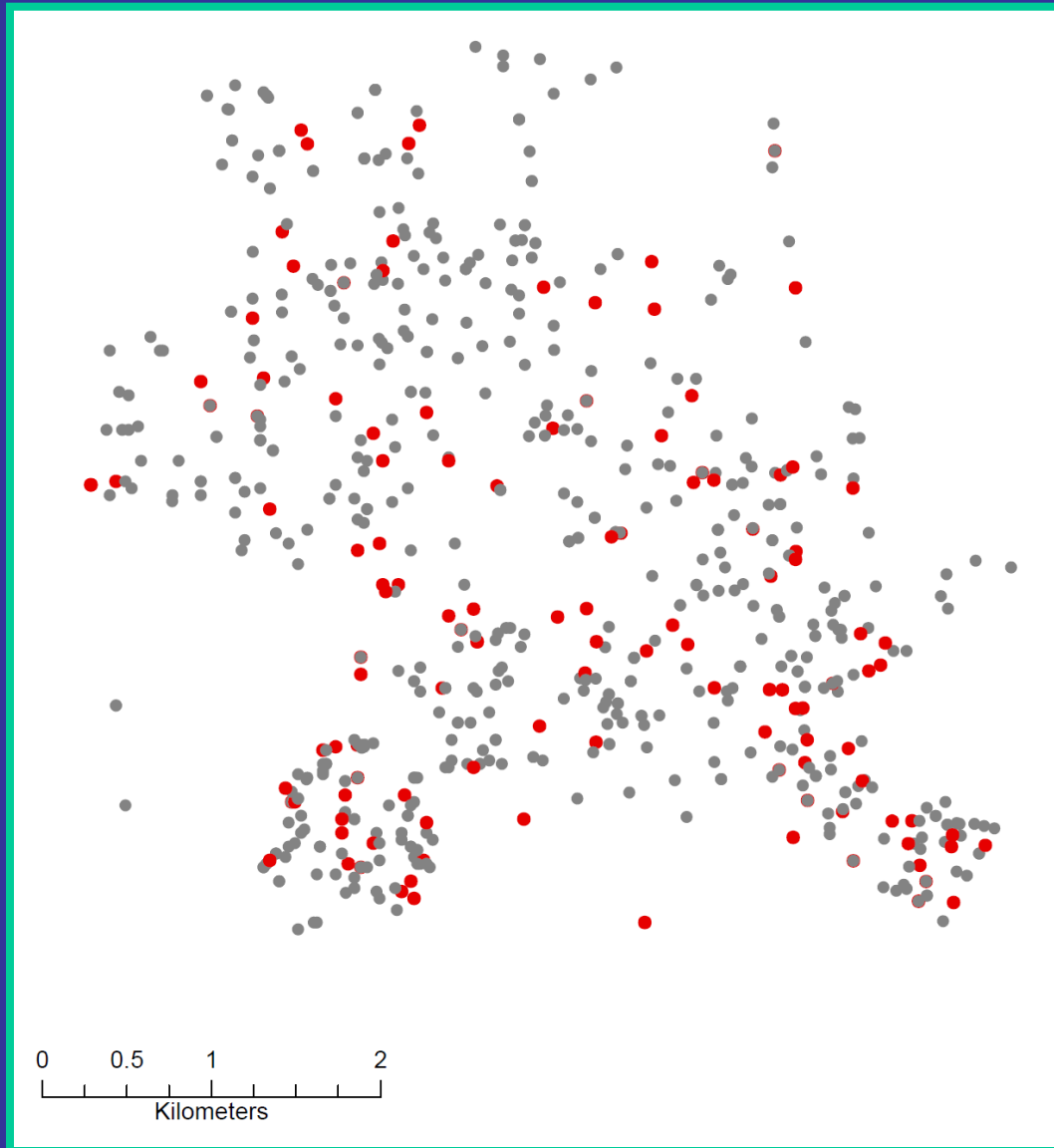
Duration of Relationships
(Estimated from Mochudi data)



Relationship	Duration	Date	Start/End
e1	d1	t1	1
e2	d2	t2	0
.	.	.	.
.	.	.	.
.	.	.	.
e _n	d _n	t _n	1

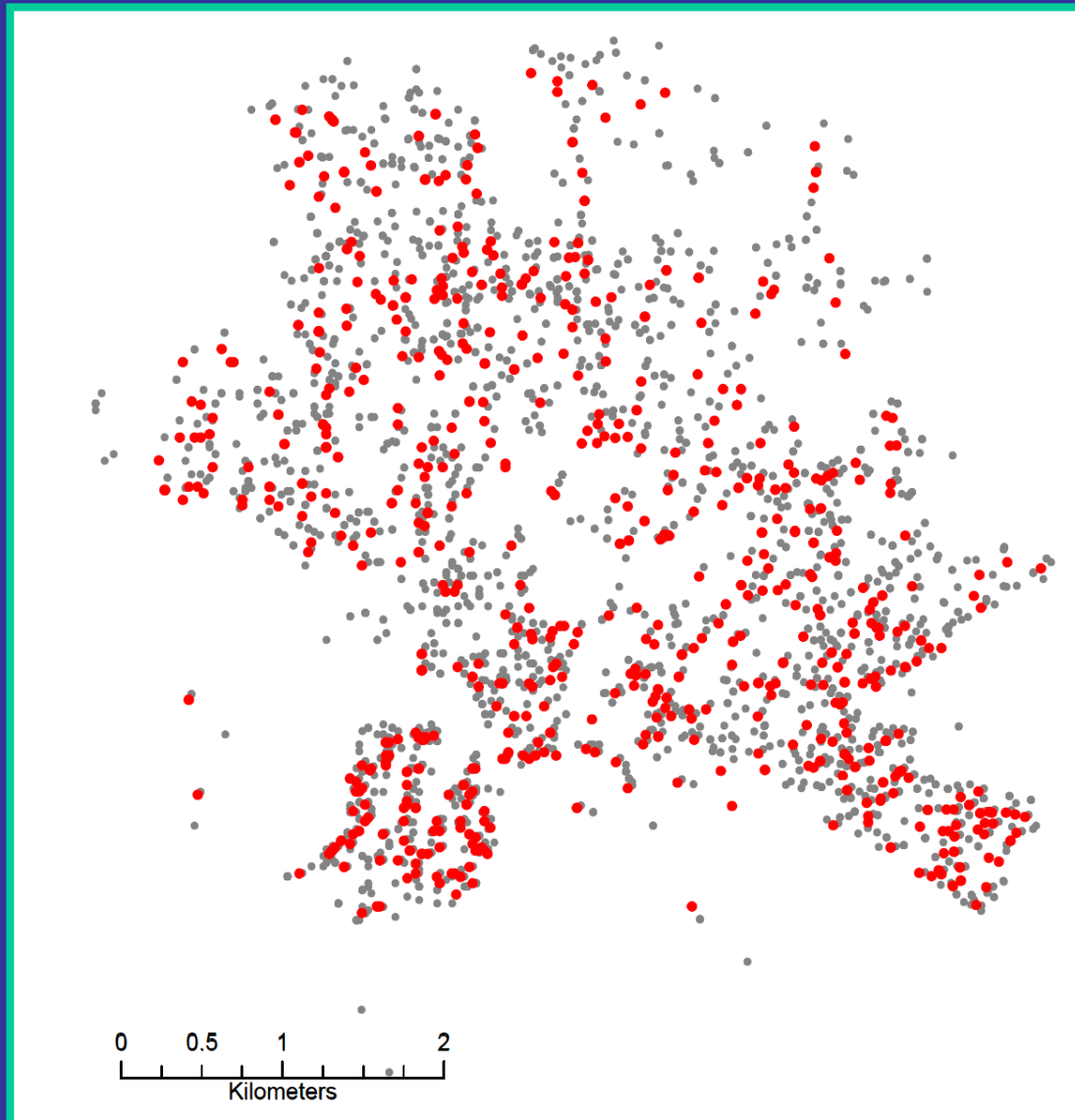


Distribution of HIV-Positive Individuals by Max Viral Load



- $< 50,000$ copies/mL
- $\geq 50,000$ copies/mL

Distribution of HIV-Negative and HIV-Positive Individuals in Mochudi



- HIV-
- HIV+

Goals of network/epidemic modeling

- Determine combinations of interventions (including breadth of coverage) likely to achieve reductions in HIV incidence of different levels (needed for study design).
- Assess the uncertainty in these determinations, (e.g. in proportion of population that must receive PREP or of acute cases that must identified and treated) in order to bring about control.
- Identify community characteristics (including network features) that mediate the impact of prevention interventions.
- Determine gaps in knowledge that most contribute to uncertainty and most efficient way to design studies to fill these gaps.

Goals of epidemic modeling

- Determine combinations of interventions (including breadth of coverage) needed for control of HIV within a population,
- Assess the uncertainty in these determinations, (e.g. in proportion of population that must receive PREP or of acute cases that must identified and treated) in order to bring about control.
- Identify community characteristics (including network features) that mediate the impact of prevention interventions.
- Determine gaps in knowledge that most contribute to uncertainty and most efficient way to design studies to fill these gaps.