Developing and Evaluating HIV Infection-control Strategies

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Outline

- Goals of HIV prevention
- Challenges
- Epidemic/Network Modeling
- Studying Local Conditions

Combining Modalities

- Can some combination of prevention modalities reduce the basic reproduction rate to a value below 1 for a defined region community?
- What are the location-specific factors that mediate the impact of combination prevention methods (epidemic/network characteristics, biological and behavioral factors)?
- Estimating these mediators for specific communities needed to scale up results of community-level RCTs.

More than Efficacy

- To understand mediation, large community-level RCTs must provide information about mechanisms by which interventions do or don’t work.
- Studies must be undertaken to increase knowledge of local conditions and to monitor effects of roll-out of interventions.

Individual-level RCTs
Great news, but more is needed.

- HPTN 052: ART for discordant couples—large effects observed, but provides little information on infections transmitted during partnerships formed during acute phase.
- PREP: randomized trials in different at-risk populations have shown modest success, (FEMPrEP did not). Modest individual effects may have large community-level effects if people of “high degree” in sexual network comply.

Challenges

- Learning how to deploy interventions optimally will require epidemic modeling that combines information at individual and population level:
- Proportion of acute and chronically infected patients who can be identified.
- Relationship between VL (other markers) and transmission risk; extent to which benefit of intervention on transmission is mediated through these markers.
- Effect of compliance with interventions, like PrEP, circumcision, and microbicide on transmission, and proportion of those at risk who receive them.
- Surveillance, especially of populations that best reflect current incidence, e.g. ANC clinics.

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.

Local Conditions: Network Features

- **When are egocentric data adequate?**
- **When do we need features that cannot be supplied by egocentric data (e.g. closeness, assortativity)?**
- **How can we best sample a population to estimate these features?**
- **What degree of precision do we require?**

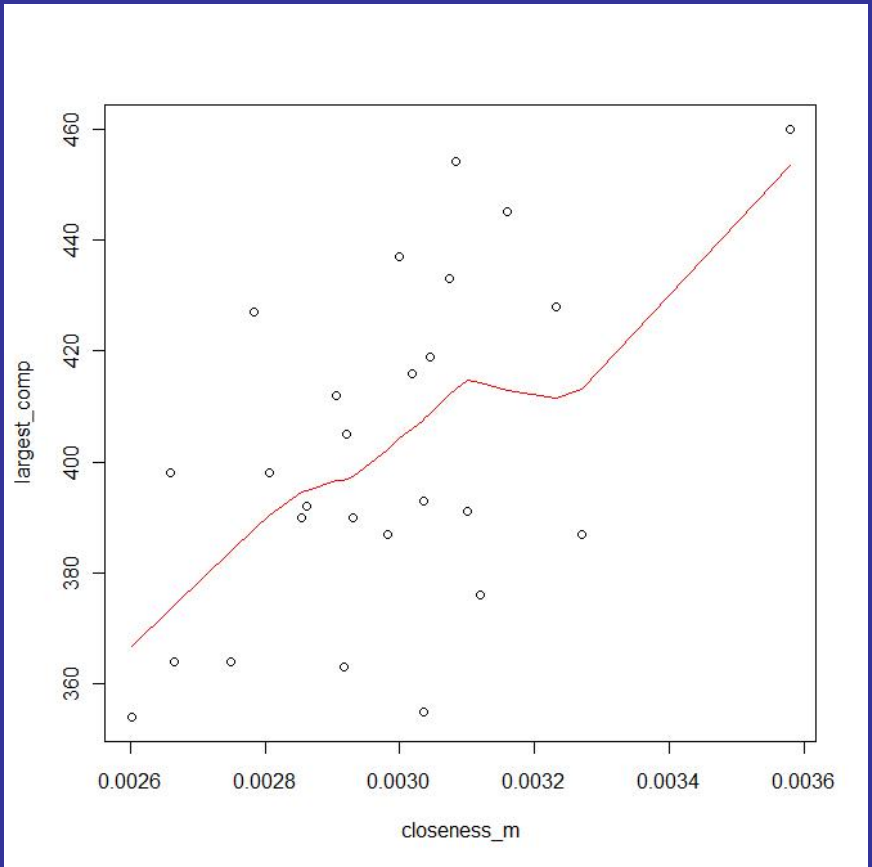
Network Features

- Closeness: Degree to which an individual is near all other individuals in a network (directly or indirectly); inverse of the sum of the shortest distances between each person and everyone else in the network.
- Assortativity: Tendency for people with many partners to choose others who do as well.

Sources of Information

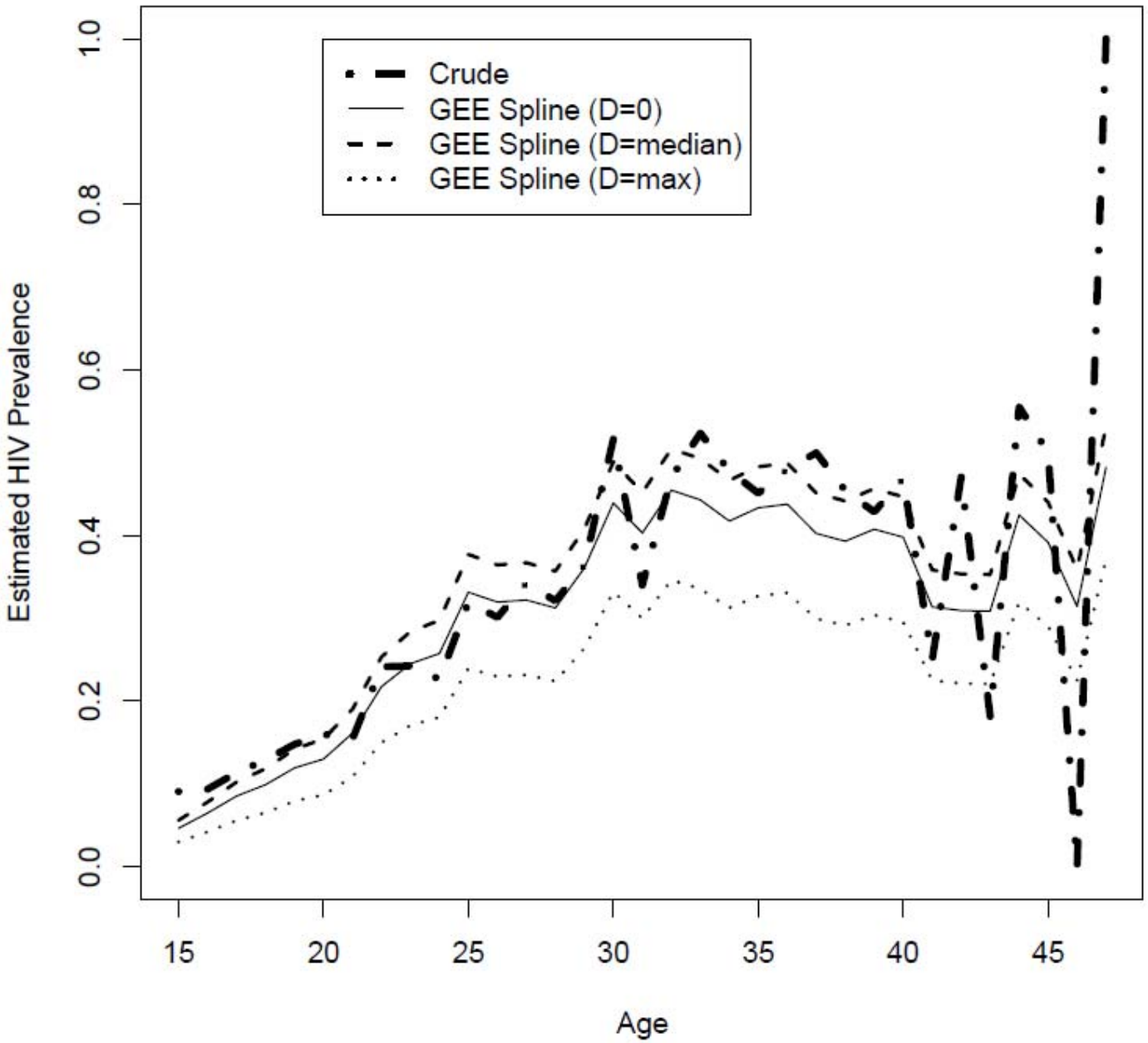
- To investigate sexual partner selection that shapes network features like mixing and concurrency, we might use:
  - Network samples
  - Contract tracing
  - Cell phone/social networking sites
  - Molecular epidemiology to identify chains of transmission and role of acutely infected patients.

Median Closeness vs Largest Component



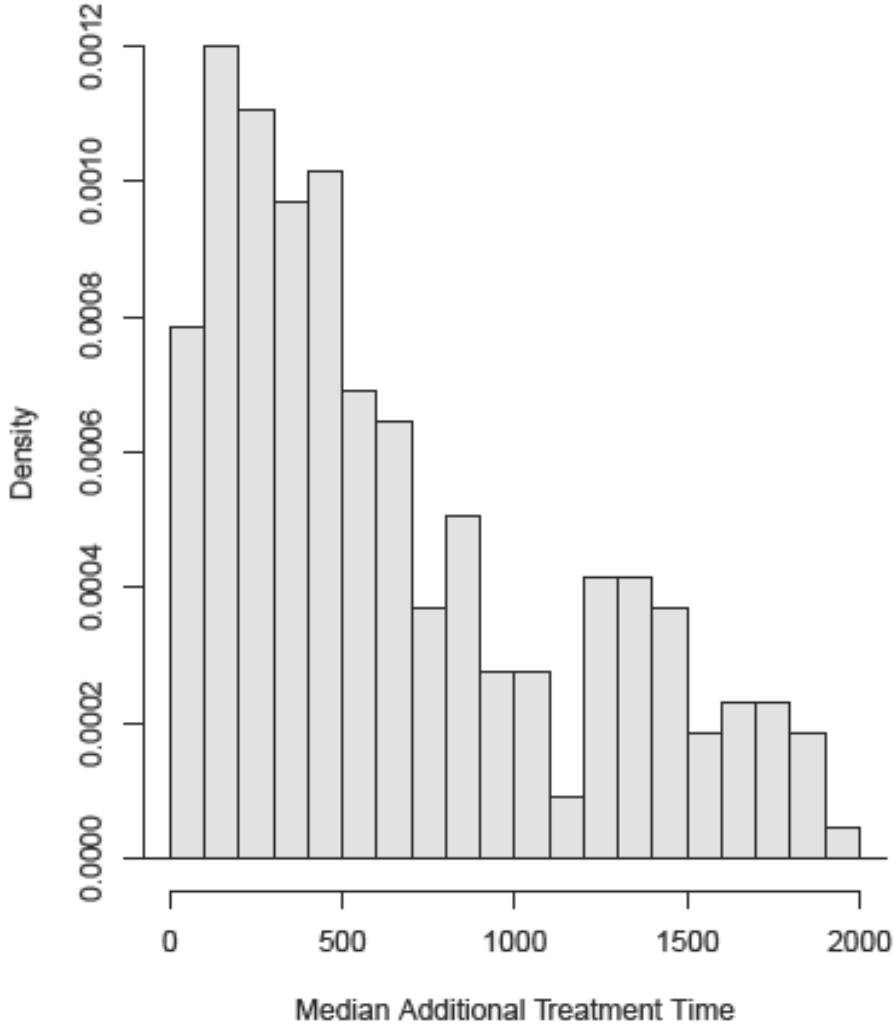
	R-squared
Solely ego centric data (ECD)	0.4975
Closeness w/ ECD	0.8049

Local Conditions: Age-specific HIV prevalence in10 ANC Clinics


Crude
GEE Spline (D=0)
GEE Spline (D=median)
GEE Spline (D=max)
Estimated HIV Prevalence
0.0
0.2
0.4
0.6
0.8
1.0
15
20
25
30
35
40
45
Age

Local Conditions: Cost

- Estimation of additional time on treatment in Mochudi, Botswana for policy of treat all identified HIV + pts.
- Basis for inference is cross-sectional data on CD4 from household survey and long. data from incidence cohort.
- Bayesian methods account for variability that arises from combining data sources as well as uncertainty in prediction
- Metropolis Hastings sampling of inferential targets from posterior distributions using model information from the auxiliary data


Density
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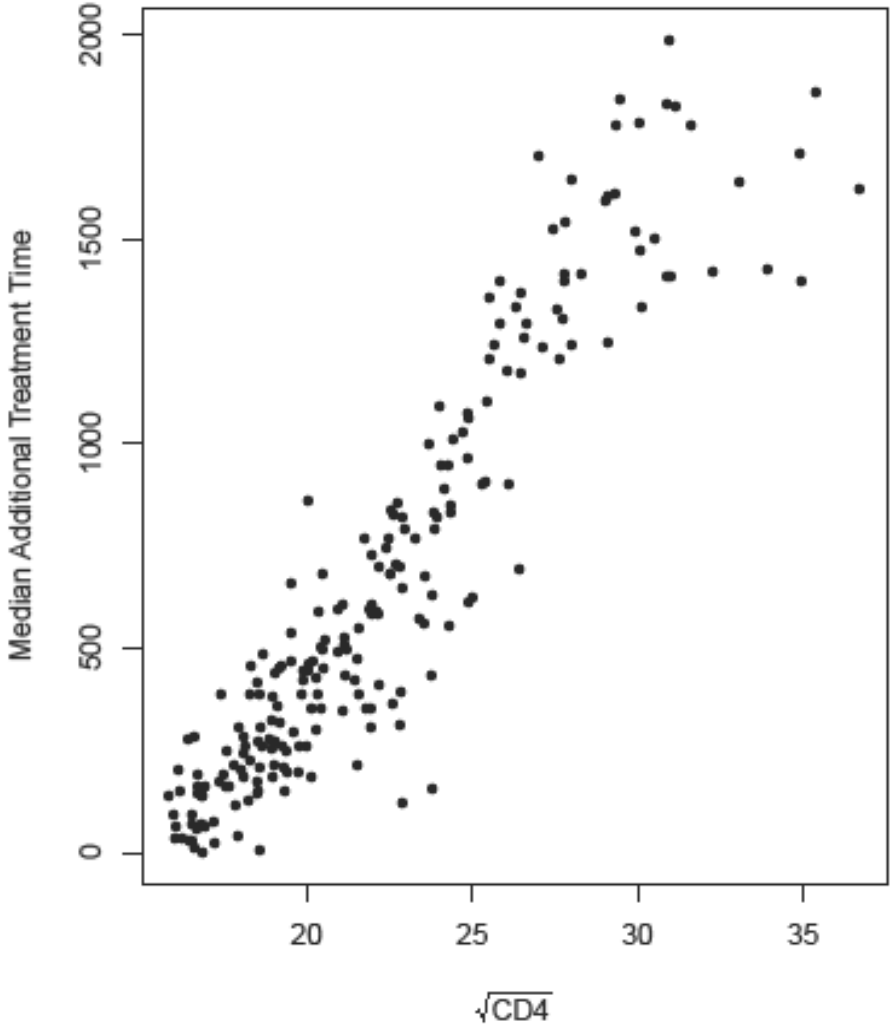
Median Additional Treatment Time


Median Additional Treatment Time
0
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√CD4

Local Conditions: SU as Mediator

- Mayer et al. described 398 HIV+ MSM patients at Fenway Community Health Center showed substance use and VL associated with transmission risk behavior.
- For VL outcome (measured 4 times in 4 categories), SU strongly predicts higher VL categories among treated patients.
- Those with SU more than twice as likely to be viremic.

Conclusions

- Large community-level RCTs must 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.

Powering Studies

- Incidence:
  - Time trend within single community.
    In general, need expected incidence of 100 to have 80% power to observe a reduction of 36%.
  - Comparison between 2 communities is similar.

Study Designs

- Community-level randomized trials provide the greatest power to detect modest effects and would require the fewest assumptions
- Single-site studies would be useful as pilots for the modeling and investigation of uptakes. Some information about efficacy could be developed from: 1) evaluating incidence prior to, as well as during the intervention, and 2) comparison with other similar communities..

Potential Mediators: Network Features

- What features of a sexual network (e.g. degree distribution, concurrency, closeness, assortativity) are

Epidemic Control

- Epidemic models used to assess the conditions under which such control is feasible, and
- Establish the quickest means to achieve it.
- Requires interaction between epidemic and network modelers and statisticians as well as clinical investigators, lab scientists, gov’ts, NGO’s, community representatives, sociologists, to provide needed scientific and epidemiological information

Sampling

- Simulation studies investigated the use of the Horvitz Thomson estimator (inverse probability weighting) to estimate number of triangles in the network.
- Results showed that the mean over simulations estimated the variance well but the variance across simulations was larger than the mean.
- Better sampling methods (RDS) are required.

HIV Prevention Proposal

- Can we identify the conditions under which the epidemic in a village in Botswana could be controlled with existing interventions?
- Can we get sufficient level of compliance with these interventions?

Aim 1

Characterize the HIV epidemic in Mochudi by estimating incidence and prevalence of HIV as well as social, educational, and behavioral risk factors at 3 time points using household survey data

Aim 2

To determine the uptake of the following behavioral interventions:

a. **voluntary counseling and testing (VCT);**
b. **condom use and education for risk reduction with respect to number of partners;**
c. **acceptability of partner notification from contact tracing based on the use of cards distributed by the index case;**
d. **adult male circumcision.**

Aim 3

Explore potential transmission associations within Mochudi by viral genome signature screening and to analyze relationships between viral RNA load and clustering patterns among incident and prevalent cases.

Aim 4

To test uptake, adherence, and feasibility of 3-drug combination antiretroviral treatment (ART) as a mechanism to reduce transmission.

All adults in the acute stage of infection and/or have a high VL in the NES will be tested for uptake of this voluntary intervention.

Aim 5

- **Development of mathematical models to identify control strategies that capitalize on synergies among preventive measures.**
- **Models used to predict (a) most effective combinations of preventive measures and (b) joint thresholds of uptake and effectiveness for individual elements required to interrupt HIV transmission cycle.**
- **Sensitivity analyses to explore how impact of combinations of interventions and coverage thresholds depend on disease dynamics, demography, cultural norms (affecting uptake).**
- **Evaluation of the cost-effectiveness of packages of preventive measures.**

Simulation Studies

- Investigate the plausibility of a reduction of 50% in HIV incidence using our proposed combination interventions using an agent-based epidemic model, in which the epidemic propagates on a realistic sexual network.
- Data on the Likoma Island sexual network in Malawi, developed by Helleringer and Kohler [39].
- Use of an actual sexual network (rather than assume random mixing within compartments) increases the plausibility of our results .

Simulation Study (cont.)

- Parameters: Risk of transmission to a seronegative partner of an infected person, distribution of time to reach the threshold for treatment and to usual time of usual treatment initiation, proportion of individuals receiving testing and circumcision in the control communities, impact of knowledge of seropositivity and of circumcision on risk.
- Targets of 70% testing and 70% circumcision were met.
- Assumptions for control communities: 20% testing and 12.7% circumcision per year.
- On both arms, patients on antiviral therapy if tested when CD4 counts qualify for treatment.

Conclusion

- These simulations demonstrate a reduction in incidence of approximately 50% over a four-year period.

Analytical Goals

1) Investigate uptake of interventions of interest, including acceptance of and adherence to HAART by infection stage, circumcision, VCT/CT.

2) Characterize self-reported behavioral change and participation in interventions.

3) Estimate annual HIV prevalence and incidence and change in HIV incidence over chronologic time

4) Characterize the impact of cofactors on transmission, including VL, behavioral factors genotype on the level of the individual subjects.

Estimate the Following:

5) Proportion of incident cases of HIV infection:
   a) detected through VCT/CT and household survey,
   b) that cluster genetically with incident or prevalent cases
   c) for whom source partners within vs. outside Mochudi can be identified through genetic links and/or through contact tracing.

6) Proportion of transmission pairs linked by viral genotype, for whom confirmation by contact tracing can be established.

7) Impact of cofactors on transmission, including level of VL and behavioral risks.

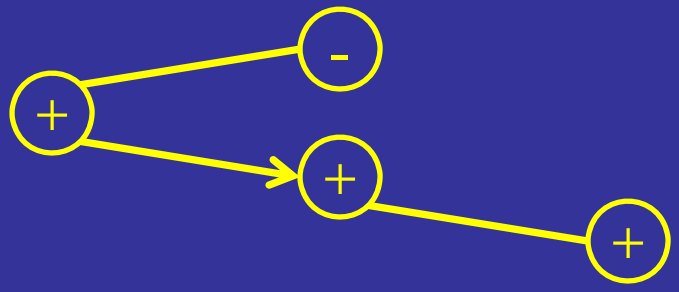
Statistical Issues

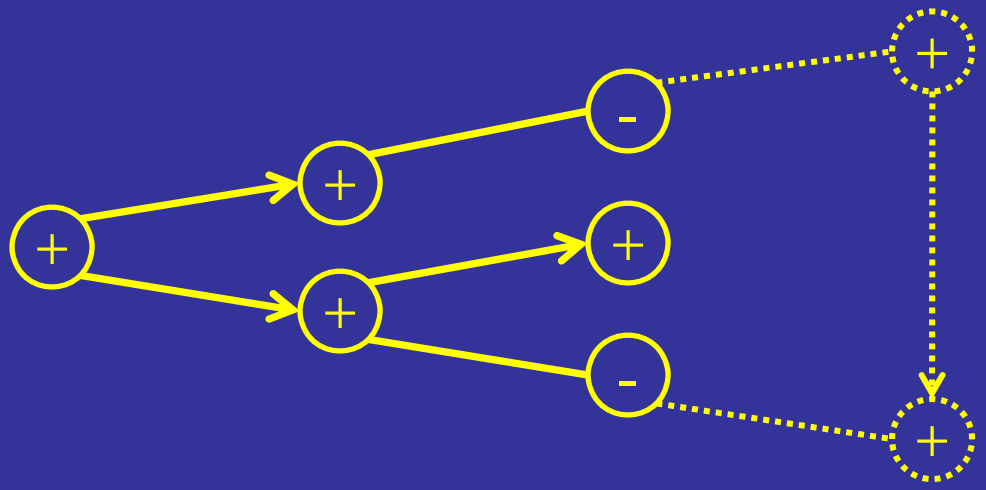
- Estimation of population quantities of interest in the presence of informative censoring and lab error.
- Estimation of risk of transmission per contact and impact of covariates on risk, given correlations arising from chains of transmission, assay censoring, and uncertainty in source partner for transmission
- Modeling sexual networks from data on viral genetic clustering, contact-tracing, and (?) network samples.

Example: Hypotheses about Transmission

1) High viral load cases occur more often in clusters that include one or more incident cases (with and without requiring an epidemiologic link) 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) Viral load increases the risk of transmission after adjustment for behavior and demographic factors.

Transmission Clusters





Testing

- To test 1 and 2, pseudo datasets are created by randomly re-assigning viral load values to genetic sequences-- allows us to calculate the null distribution of the relevant test statistic (e.g. proportion of clusters that include a high viral load case).
- Use similar methods to assess whether patients who cluster together genetically also tend to cluster by place of residence or work.
- These associations may arise either because of an effect of viral load on transmission or because of confounding factors, such as the tendency of subjects with high viral load to have more concurrent partners or more lesions.

Impact of covariates on risk of transmission

A random effects logistic model to accommodates correlation; censoring dealt with by appropriate integration.

Conclusions

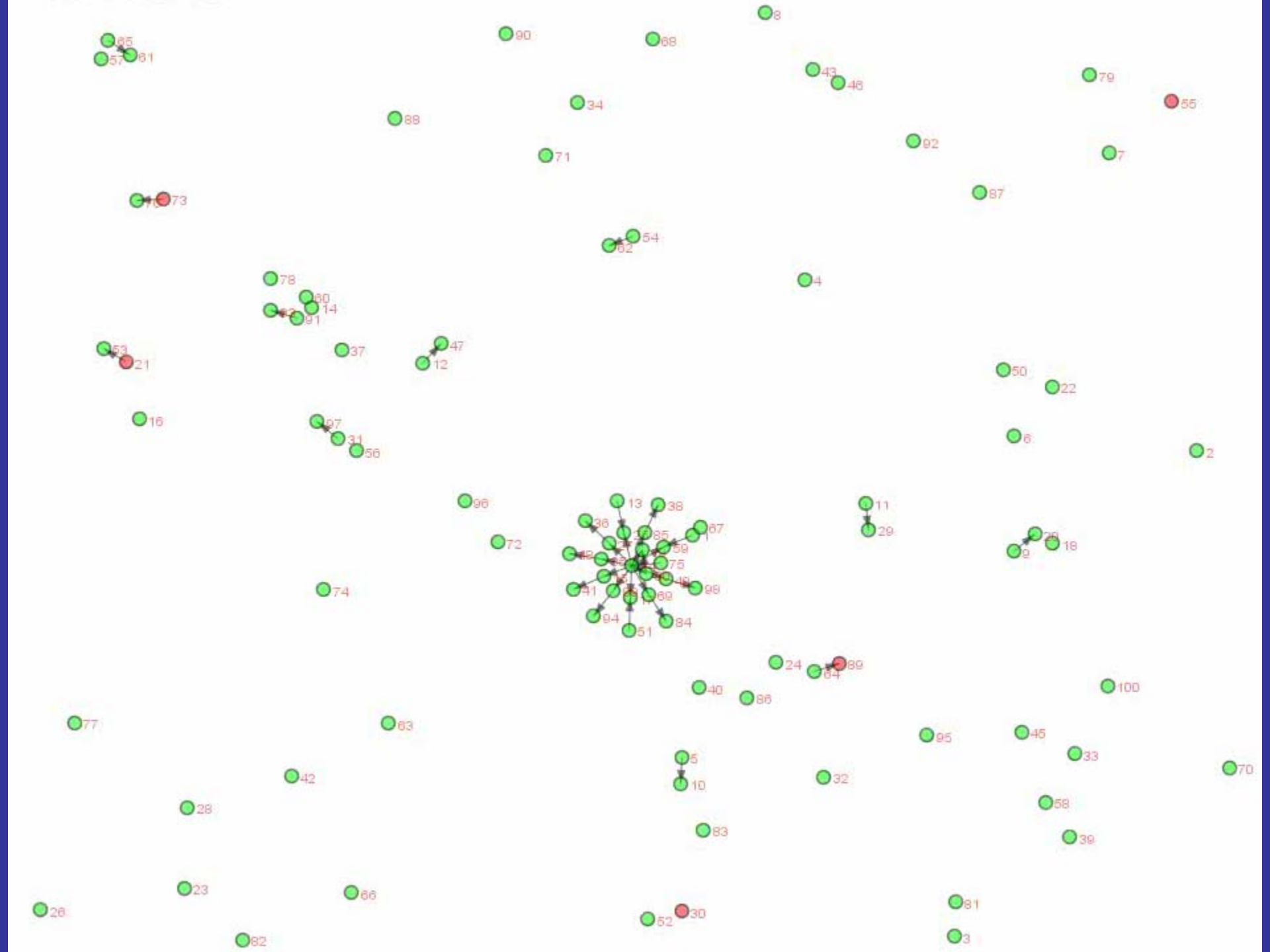
- Community level research essential for determining feasibility of control in different populations
- Collaboration between statisticians, modelers, genetic epidemiologists essential.
- Huge scope for new methods to combine modern lab and data methods with old-fashioned public health practices.
- Study of local conditions must be combined with development of fundamental scientific/statistical principles.

Modeling: an ongoing process

- To allow “mid-course corrections” in prevention programs, models must be updated as knowledge is developed regarding transmission and the population impact of interventions.
- Updating of models will include altering their fundamental structure as well as using the most current estimates of model parameters.

Challenges

- **Necessary information and authority to fund/conduct studies divided over many different organizations. Consider Botswana**:
- Government: Surveillance, Household surveys, National treatment program.
- CDC: Counseling/Testing, PREP, IPT,TB Surveillance.
- HPTN: Discordant couples
- ACTG: Treatment trials
- HBP: Studies of: Acute infection, Treatment, MCT, Natural History, Host/viral genetic effects.
- University of Botswana: Behavioral Research
- Partnerships with Penn, Baylor Universities
- Programs should be reviewed to see if minor changes would help with goal of developing results for models exploring epidemic control.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Workshop on community-level Prevention Research

1) Measuring incidence and prevalence of infection.
   a) pooling of test results
   b) lot quality assurance
   c) cluster sampling--hot spots
   d) methods for making use of detuned assay data

2) Modeling Social Networks
   a) RDS and other proposed methods
   b) thoughts about handling of missing data
   c) practical experience

3) Community randomized trials
   a) design issues: how many communities are required
   b) analysis issues

4) Genetic epidemiology

a) establishing genetic clusters

b) estimating transmission risks and impact of cofactors using data from uncertain clusters

5) Epidemic models

a) using models to suggest study designs for relevant inputs

b) estimating joint levels of effectiveness for epidemic controls--investigating synergy

c) using models to guide roll out of PREP (e.g. regular vs "disco" dosing) and other such interventions

d) modeling impact of co-infections

6) Monitoring and evaluation of public health interventions at population level

a) Successes of contact tracing.

b) behavioral interventions.

Program Evaluation

- Evaluating the impact of intervention strategies requires surveillance of prevalence and incidence of HIV (including resistant strains) to provide real-time population-level results.
- Optimal sampling strategies and laboratory procedures for detecting acute/infection must be devised.

Be bold and mighty forces will come to your aid.

Basil King

Der Worte sind genug gewechselt,
lasst mich auch endlich Taten sehn!

Enough words have been exchanged;
now at last let me see some deeds!

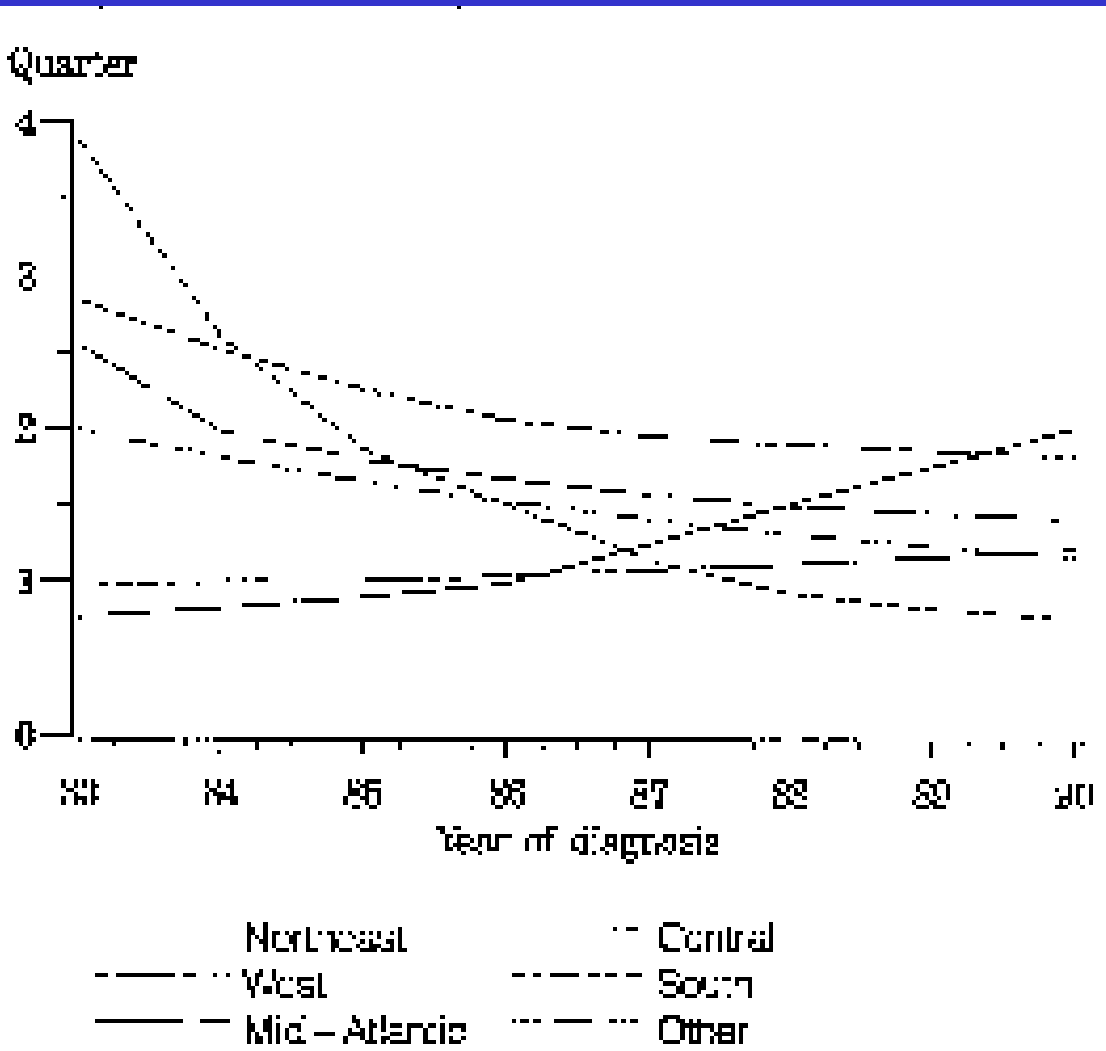
Goethe

Policy: Two Facts

- 1983: Boston Health Dept. officials decline to close gay bath houses despite increasing incidence of GRID

- 2009: Harvard Medical School shuts down for a week after some reported cases of swine flu in a dental student.

Surveillance Data—Reporting Delay



3. Model-based median delays as a function of year of diagnosis for the male IVDU risk group from the multinomial response model.

$$l(\boldsymbol{\beta}) = \prod_{i=1}^{N} \int_{\beta_0=-\infty}^{\infty} \int_{x_{ij}=x_c}^{\infty} \prod_{j=1}^{n_i} \frac{\pi\left(u_{ij}\right)^{y_{ij}}}{\left[1-\pi\left(u_{ij}\right)\right]^{\left(1-y_{ij}\right)}} f\left(\beta_{0i}\right) f\left(u_{ij}\right) du_{ij} d\beta_{0i}$$

where $i = 1,\ldots, N$ denotes unique source partners,
$j = 1,\ldots,n_i$ denotes partner pairs for each source partner,
$y_{ij} = 1$ for transmission, 0 otherwise.

$$\pi(x_{ij}) = \exp(\beta_{0i} + \beta' x_{ij}) \,/\, (1 + \exp(\beta_{0i} + \beta' x_{ij})).$$

Genetic Links

- Determining the proportion of incident cases that cluster genetically with other incident or prevalent cases requires choosing a clustering criteria.
- To estimate the proportion of incident cases for which source partners within Mochudi can be identified through genetic links, we will first determine how many such cases are genetically linked with prevalent potential source partners.
- If more than one case then we will establish links to the incident case in two ways: 1) by contact tracing all of those with incident infection and with high VL, and a sample of those with low VL (including those detected through VCT).
- We will determine how often the genetic link can be confirmed by the link established through contact tracing, both in settings where there was only one eligible source partner genetically linked to the incident case or where there was more than one.

Controlling HIV Infection

- Goal: to assess possibility of controlling the HIV epidemic in some populations from combinations of HIV prevention modalities.
- Control defined as making epidemic unsustainable in a population--some reservoirs of infection may continue to give rise to occasional new cases.
- Interventions include identification and treatment of HIV infection (especially acute, high VL), PrEP, microbicide, circumcision, behavioral interventions, treatment for other infections. vaccine.
- Combine traditional public methods with modern approaches to treatment/prevention, data collection, genetic epidemiology and modeling.

Prevention Study: Single Site, e.g. Mochudi

- Base inference on trends: baseline and follow-up prior to intervention. Then two measurements after intervention.
- Compare trend in study site with national trends.
- Genetic signature clustering used to determine whether infected patients receiving treatment (include acutely infected) no longer gave rise to new infections.

Two (or more) sites

- Use second, control site as a comparator and as a bridge to the national data.
- Control site receives all measurements as the site receiving the intervention.
- This approach also permits comparison of the trends estimated directly from the control site with those estimated from the national sources for this site.
- Can also select a set of control sites from among all sites comparable to the intervention site.

Cluster Randomized Trials

- Community-level randomized trials: optimal way to assess modest impact of treatments.
- Challenge lies in ascertaining incidence.
- Consider combining surveillance data with full enumeration of some neighborhood with high prevalence.
- Allows “bridge” to surveillance data.

Causal methods

- Causal methods have been used to make use of baseline covariates to improve power and adjust for chance imbalance—more relevant when number of randomized units is small.
- These methods have been extended to cluster randomized trials, using both individual-level and cluster-level covariates.
- Improves efficiency by augmenting estimating equations with a function of baseline covariates.
- Covariate adjustment can also be performed for non-randomized setting.

Understanding Local Epidemics

- **Comparing the predicted (from national data) and observed outcomes (from study methodology) for a given control community permits both assessment of the accuracy of prediction and development of approaches to improving it by appropriate adjustment.**
- **Special populations (e.g. women giving birth) can provide basis for adjustment for missing data.**
- **“Borrowing strength” from the national data can help in establishment of epidemic trends.**
- **Best way to accomplish this needs further study.**

Feasibility depends on cost of interventions

Need to assess potential for lower-cost care models, e.g. nurses provide primary care.

Relative contributions of expansion of different modalities must be investigated to identify the most cost-effective approach to epidemic control.