Toward Evaluation of Disseminated Effects of HIV Prevention Interventions Among Networks of People who Inject Drugs

Ashley Buchanan, DrPH, MS

Assistant Professor, Biostatistics
College of Pharmacy
University of Rhode Island

University of Washington Biostatistics Seminar 2019

Outline

Definition

Implementation Science

Translation and scale-up of research evidence into practice (Madon et al., 2007; Padian et al., 2011)

- Natural clustering by social network or community
- Biological and social influence in networks
- Understanding this influence can inform public health practice and policy

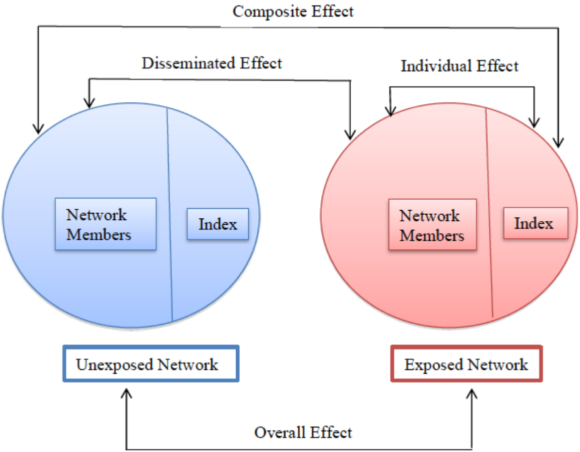
Causal Inference

- A Potential Outcome (i.e., Counterfactual)
  - $Y(0)$: Response that would have been seen if (possibly contrary to fact) the participant were not exposed
  - $Y(1)$: Response that would have been seen if (possibly contrary to fact) the participant were exposed
- Assumptions: Consistency, No Interference, Positivity, Exchangeability (Cole and Frangakis, 2009; Rubin, 1980)
- *With associations, we can predict the future. With causation, we can change the future.*

Two-stage Randomized Design

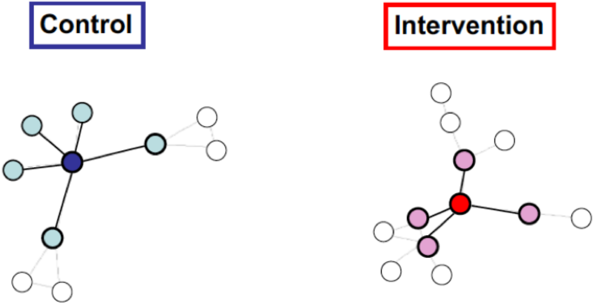
- One approach to conduct causal inference with interference or dissemination is to use **two-stage randomized design** (Halloran and Struchiner (1991), Hudgens and Halloran (2008)).
- In this design, networks/communities are randomly assigned to an allocation strategy of exposure (or coverage of exposure) at the first stage, then, in the second stage, individuals in a community are randomly exposed according to the coverage assigned in the first stage.
- **Coverage** of exposure is defined as the proportion of subjects who are exposed in a certain community.

Cluster-Randomized Trial



Adapted from Halloran and Struchiner (1991, 1995).

Network-Based Study



Adapted from Benjamin-Chung, et al. (2017).

- Connections: Shared HIV risk (injection or sexual)
- Index shaded blue or red nodes
- Nearest neighbors outlined nodes

Study Motivation

- Injection drug use increases HIV risk through sharing equipment (e.g. syringes, needles, etc.) and often correlates with risky sexual behaviors
- PWIDs are not only at high risk of HIV infection, but also face unique barriers along the HIV treatment cascade (Ghosh et al., 2017)

Primary Motivation

PWIDs are embedded in HIV/AIDS risk network and such network structure can support and sustain **positive behavioral change** via interventions that leverage network structure.

Motivating Example

The Social Factors and HIV Risk Study (SFHR)

- Sociometric network study conducted between 1991 and 1993 in Bushwick, Brooklyn, New York among *street-recruited injection drug users*
- Investigated how HIV/AIDS infection spread through shared sexual and injection risk behaviors.
- 767 participants along with 3,162 dyadic relationships (i.e. a connection b/w two people).
- Connections were shared **risk behaviors** (i.e. inject drug together and/or having sexual intercourse) within 30 days before the interview.

▸ full network

Goal of the Study

- To assess attitudes toward HIV/AIDS risk among PWIDs and their effect on health-seeking behaviors.
- Used **causal inference methods** under the presence of *dissemination or spillover effects* in an observational study.
- Exposures were (1) **health beliefs** and (2) **blame attributes** of each participants.
- Outcomes were (1) **receipt of study-based HIV testing result** and (2) **a recent medical visit** within the past year.

SFHR PWIDs Network for Analysis

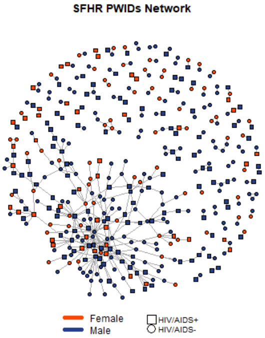
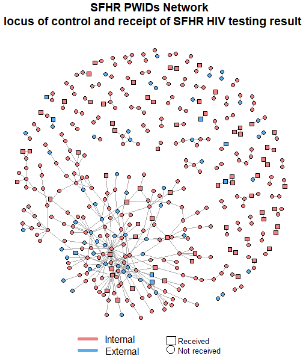


Figure 1: SFHR PWIDs Network for Analysis. There are 402 vertices and 403 edges.

A network (or graph) G is defined as a collection of vertices (or nodes) (V) and edges (or links)(E), $G = (V, E)$. Here, G is the SFHR PWIDs network.

SFHR PWIDs Network for Analysis



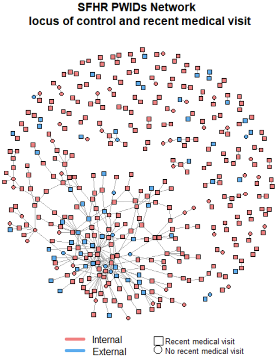


Figure 2: The Social Factors and HIV Risk Study PWIDs' network for the analysis. Locus of control and receipt of HIV testing result (Left) and recent medical encounter (Right).

Data Pre-processing

Table 1: Questions about Health Beliefs in SFHR (5-point Likert Scale)

Questions related to belief (BLF)
Q1. It is my own behavior which determines whether I get AIDS or not.
Q2. No matter what I do, if I'm going to get AIDS, I will get AIDS.
Q3. I'm in control of whether or not I get AIDS.
Q6. Getting AIDS is largely a matter of bad luck.
Q7. No matter what I do, I'm likely to get AIDS.
Q8. If I take the right actions, I can avoid getting AIDS.
Q10. No matter what I do, I'm unlikely to get AIDS.

Questions related to blame (BLM)
Q4. My family have a lot to do with whether I get AIDS.
Q5. If I get AIDS, I'm not to blame.
Q9. If I get AIDS, it is because of the society we live in.

Causal Parameters

$$\textit{Direct effect}: \quad \overline{DE}(\alpha) = \overline{Y}(a=0;\alpha) - \overline{Y}(a=1;\alpha)$$

$$\textit{Indirect effect}: \quad \overline{IE}(\alpha,\alpha') = \overline{Y}(a=0;\alpha) - \overline{Y}(a=0;\alpha')$$

$$\textit{Total effect}: \quad \overline{TE}(\alpha,\alpha') = \overline{Y}(a=0;\alpha) - \overline{Y}(a=1;\alpha')$$

$$\textit{Overall effect}: \quad \overline{OE}(\alpha,\alpha') = \overline{Y}(\alpha) - \overline{Y}(\alpha')$$

coverage: $\alpha < \alpha'$

Causal Inference with Observational Study Data

- **Inverse probability weighting (IPW)** method to adjust for confounding in an observational study (Tchetgen and VanderWeele, 2012)

APPROACH

1. Split the SFHR network into smaller subnetworks/ communities of PWIDs.
2. Calculate group-level propensity score (i.e., probability of having specific attitude toward HIV/AIDS risk) for each subnetwork based on individual-level covariates of sex, race, education, age and their pairwise interactions.
3. Use the inverse of propensity scores as weights to compute IPW estimators of potential outcomes.

Assumptions

(1) **Partial interference**: Allow interference within a subnetwork/community, but not between subnetworks.

(2) **Stratified interference**: Individual's potential outcome is dependent only on own exposure and the proportion of exposed in the community.

(3) **Bernoulli individual group allocation strategy**: The distribution of exposure selection mechanism A is assumed to be a Bernoulli distribution and used to define the potential outcomes Y^a.

(4) **No homophily**: Assume there is no latent variables related to health-seeking behavior with which an individual has a tie with another individual who has the similar characteristics.

(5) **Well-defined interventions**: Locus of control is a well defined exposure and there is no other version of locus of control in the study.

(6) **Positivity**: Probability of exposure is positive given each level of covariates.

(7) **Conditional exchangeability**: Assume that conditioning on a set of covariates is sufficient to control confounding.

Community Detection

- **Community**: A set of vertices densely connected, with only sparser tie to vertices that belong to other groups or communities.
- **Hierarchical clustering**: Common methods for community detection where the closest or most similar vertices are combined to form communities with *a measure of similarity* or *connection strength* between vertices based on the network structure.
- As the measure of similarity, we use **modularity** (Kolaczyk, 2009; Newman, 2006)

Modularity

Modularity is defined as following:

- Assume there are $C = \{C_1, C_2, \cdots, C_K\}$ candidate of K communities in an observed network G.
- We also define $f_{ij} = f_{ij}(C)$ as the fraction of edges in the original network that connect vertices in cluster i with vertices in cluster j, $i \neq j$.
- Given this,

$$mod(C) = \sum_{k=1}^{K} [f_{kk}(C) - f_{kk}^*]^2, \quad (1)$$

where f_{kk} is the fraction of edges which connect vertices within the same cluster k in G, and f_{kk}^* is the expected value of f_{kk} under some model of random edge assignment.

IPW estimation: Group-Level Propensity Score

Group-level propensity score can be calculated by adjusting for individual-level covariates among those in the community.

$$f_{A_i|X_i}(A_i|X_i;\theta_x,\theta_s) = \int \prod_{j=1}^{n_i} h_{ij}(b_i;\theta_x)^{A_{ij}} \{1 - h_{ij}(b_i;\theta_x)\}^{1-A_{ij}} f_b(b_i;\theta_s) db_i$$

where
$h_{ij}(b_i;\theta_x) = Pr(a_{ij} = 1|X_{ij}, b_i, \theta_x) = logit^{-1}(X_{ij}\theta_x + b_i)$ is a propensity score for jth individual in community i and $f_b(\cdot;\theta_s)$ is the density of community specific random effect and assume $b_i \sim N(0,\theta_s)$.

IPW estimation: IPW estimator

IPW estimator for group-level potential outcome:

$$\hat{Y}_i^{ipw}(a, \alpha) = \frac{\sum_{j=1}^{n_i} \pi_i(A_{i,-j}; \alpha) I(A_{ij} = a) Y_{ij}}{n_i f_{A_i|X_i}(A_i|X_i; \hat{\theta})} \tag{2}$$

Marginal potential outcome:

$$\hat{Y}_i^{ipw}(\alpha) = \frac{\sum_{j=1}^{n_i} \pi_i(A_i; \alpha) Y_{ij}}{n_i f_{A_i|X_i}(A_i|X_i; \hat{\theta})} \tag{3}$$

Population-level IPW estimators

$$\widehat{DE}(\alpha) = \hat{Y}^{ipw}(a = 0; \alpha) - \hat{Y}^{ipw}(a = 1; \alpha)$$

$$\widehat{IE}(\alpha, \alpha') = \hat{Y}^{ipw}(a = 0; \alpha) - \hat{Y}^{ipw}(a = 0; \alpha')$$

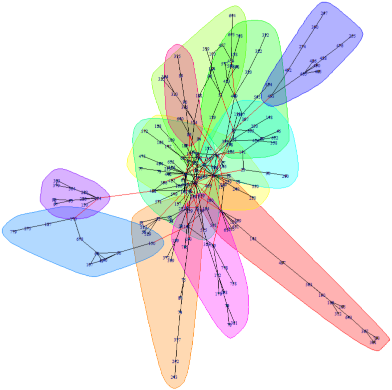
$$\widehat{TE}(\alpha, \alpha') = \hat{Y}^{ipw}(a = 0; \alpha) - \hat{Y}^{ipw}(a = 1; \alpha')$$

$$\widehat{OE}(\alpha, \alpha') = \hat{Y}^{ipw}(\alpha) - \hat{Y}^{ipw}(\alpha')$$

coverage: $\alpha < \alpha'$

Modularity-based Community Detection

85 connected components and one of them forms the giant component that include 199 participants. In total, **96 communities** in the SFHR network for analysis.



Descriptive Statistics (1)

Table 2: The Relationship between Locus of Control and Health-Seeking Behaviors

	Odds Ratio (95% CI)		
	Giant	Not Giant	Total
Received Not received	1.94 (0.55, 6.85)	1.64 (0.59, 4.57)	1.87 (0.85, 4.11)
Recent medical visit No recent medical visit	1.32 (0.49, 3.56)	0.88 (0.28, 2.72)	1.07 (0.51, 2.24)

Descriptive Statistics (2)

Table 3: The Relationship between Blame and Health-Seeking Behaviors

	Odds Ratio (95% CI)		
	Giant	Not Giant	Total
Received Not received	1.35 (0.56, 3.29)	1.00 (0.52, 1.98)	1.15 (0.68, 1.96)
Recent medical visit No recent medical visit	1.09 (0.47, 2.55)	0.89 (0.39, 1.99)	0.96 (0.54, 1.74)

Observed Distribution of Locus and Blame Coverages

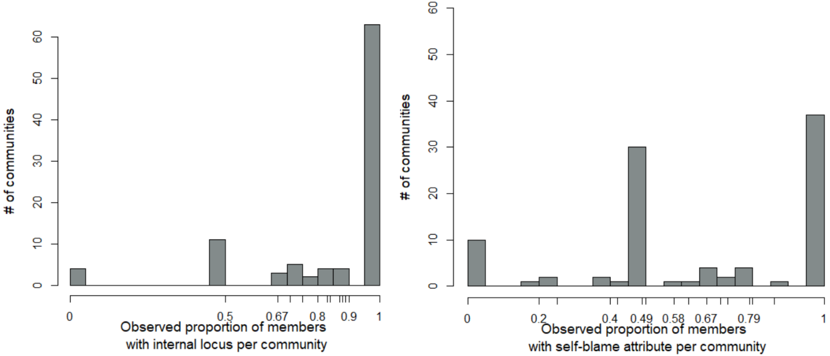


Figure 3: Observed coverages of subjects with internal locus (left) and subjects with self-blame (right).

Causal Inference: IPW estimation - Model 1

Table 4: Estimated risk differences (RDs) with 95% CIs of **locus of control** (external vs. internal) on likelihood of **receiving HIV test results** in SFHR (coverage of internal)

Effect	Coverage (α, α')	Unadjusted RD	Unadjusted 95% CI	Adjusted with interactions RD	Adjusted with interactions 95% CI
Direct	(50%, 50%)	**-0.148**	(-0.230, -0.065)	**-0.160**	(-0.265, -0.055)
Direct	(70%, 70%)	**-0.142**	(-0.246, -0.038)	**-0.162**	(-0.268, -0.055)
Direct	(99%, 99%)	-0.101	(-0.258, 0.056)	-0.130	(-0.268, 0.008)
Indirect	(50%, 70%)	**-0.041**	(-0.071, -0.012)	**-0.031**	(-0.054, -0.008)
Indirect	(50%, 99%)	-0.070	(-0.156, 0.019)	-0.062	(-0.123, 0.000)
Indirect	(70%, 99%)	-0.029	(-0.098, 0.040)	-0.030	(-0.072, 0.011)
Total	(50%, 70%)	**-0.183**	(-0.271, -0.096)	**-0.193**	(-0.286, -0.100)
Total	(50%, 99%)	**-0.172**	(-0.278, -0.066)	**-0.192**	(-0.291, -0.093)
Total	(70%, 99%)	**-0.130**	(-0.254, -0.006)	**-0.161**	(-0.272, -0.049)
Overall	(50%, 70%)	**-0.067**	(-0.096, -0.038)	**-0.065**	(-0.089, -0.041)
Overall	(50%, 99%)	**-0.097**	(-0.183, -0.010)	**-0.111**	(-0.190, -0.032)
Overall	(70%, 99%)	-0.030	(-0.095, 0.035)	-0.046	(-0.105, 0.013)

Associations with Recent Medical Visit - Model 2

Table 5: Estimated risk differences (RDs) with 95% CIs of **locus of control** (external vs. internal) on likelihood of **a recent medical visit** in SFHR (coverage of internal)

Effect	Coverage (α, α')	Unadjusted		Adjusted with interactions	
		RD	95% CI	RD	95% CI
Direct	(50%, 50%)	0.211	(-0.286, 0.708)	0.090	(-0.271, 0.451)
Direct	(70%, 70%)	0.003	(-0.296, 0.301)	-0.111	(-0.346, 0.123)
Direct	(99%, 99%)	-0.227	(-0.463, 0.009)	**-0.280**	(-0.470, -0.089)
Indirect	(50%, 70%)	-0.001	(-0.260, 0.257)	-0.008	(-0.181, 0.165)
Indirect	(50%, 99%)	0.208	(-0.298, 0.715)	0.077	(-0.311, 0.464)
Indirect	(70%, 99%)	0.210	(-0.063, 0.482)	0.085	(-0.136, 0.305)
Total	(50%, 70%)	0.001	(-0.537, 0.539)	-0.119	(-0.496, 0.258)
Total	(50%, 99%)	-0.019	(-0.491, 0.453)	-0.203	(-0.559, 0.153)
Total	(70%, 99%)	-0.017	(-0.255, 0.220)	-0.195	(-0.409, 0.018)
Overall	(50%, 70%)	-0.105	(-0.316, 0.106)	-0.131	(-0.265, 0.003)
Overall	(50%, 99%)	-0.122	(-0.358, 0.114)	**-0.246**	(-0.430, -0.061)
Overall	(70%, 99%)	-0.017	(-0.082, 0.048)	**-0.114**	(-0.181, -0.047)

Causal Inference: IPW estimation - Model 3

Table 6: Estimated risk differences (RDs) with 95%CIs of **blame** (others vs. self) on likelihood of **receiving HIV testing results** in SFHR (coverage of self-blame).

Effect	Coverage (α, α')	Unadjusted RD	Unadjusted 95%CI	Adjusted with interactions RD	Adjusted with interactions 95%CI
Direct	(50%, 50%)	-0.043	(-0.164, 0.079)	-0.045	(-0.159, 0.069)
Direct	(70%, 70%)	-0.035	(-0.159, 0.088)	-0.034	(-0.154, 0.085)
Direct	(99%, 99%)	-0.077	(-0.250, 0.096)	-0.065	(-0.230, 0.100)
Indirect	(50%, 70%)	-0.002	(-0.047, 0.044)	-0.001	(-0.043, 0.041)
Indirect	(50%, 99%)	0.034	(-0.077, 0.145)	0.034	(-0.066, 0.134)
Indirect	(70%, 99%)	0.036	(-0.037, 0.109)	0.035	(-0.032, 0.102)
Total	(50%, 70%)	-0.037	(-0.164, 0.090)	-0.035	(-0.154, 0.083)
Total	(50%, 99%)	-0.043	(-0.200, 0.115)	-0.031	(-0.175, 0.113)
Total	(70%, 99%)	-0.041	(-0.197, 0.115)	-0.030	(-0.176, 0.116)
Overall	(50%, 70%)	-0.005	(-0.048, 0.038)	-0.003	(-0.042, 0.036)
Overall	(50%, 99%)	-0.021	(-0.135, 0.094)	-0.008	(-0.113, 0.097)
Overall	(70%, 99%)	-0.015	(-0.095, 0.064)	-0.005	(-0.079, 0.068)

Associations with Recent Medical Visit - Model 4

Table 7: Estimated risk differences (RDs) with 95%CIs of **blame** (others vs. self) on likelihood of **reporting a recent medical encounter within the past year** (coverage of self-blame)

		Unadjusted		Adjusted with interactions	
Effect	Coverage (α, α')	RD	95%CI	RD	95%CI
Direct	(50%, 50%)	0.017	(-0.141, 0.175)	0.002	(-0.156, 0.160)
Direct	(70%, 70%)	-0.054	(-0.205, 0.096)	-0.076	(-0.213, 0.060)
Direct	(99%, 99%)	-0.209	(-0.467, 0.050)	**-0.269**	(-0.527, -0.011)
Indirect	(50%, 70%)	0.076	(-0.001, 0.153)	0.086	(-0.014, 0.186)
Indirect	(50%, 99%)	**0.238**	(0.053, 0.423)	**0.272**	(0.072, 0.472)
Indirect	(70%, 99%)	**0.162**	(0.019, 0.305)	**0.186**	(0.038, 0.335)
Total	(50%, 70%)	0.022	(-0.099, 0.143)	0.009	(-0.126, 0.144)
Total	(50%, 99%)	0.029	(-0.159, 0.218)	0.003	(-0.214, 0.219)
Total	(70%, 99%)	-0.047	(-0.263, 0.170)	-0.083	(-0.299, 0.133)
Overall	(50%, 70%)	0.029	(-0.022, 0.081)	0.031	(-0.054, 0.117)
Overall	(50%, 99%)	0.023	(-0.119, 0.164)	0.005	(-0.178, 0.187)
Overall	(70%, 99%)	-0.007	(-0.148, 0.134)	-0.027	(-0.183, 0.130)

Discussion

- Additional benefit to reporting internal locus beyond being around those who have internal for likelihood of receipt of HIV test result
- Among those with external locus, having more community members with internal increased likelihood of receipt of HIV test
- Protective overall association of internal locus with recent medical visit and additional benefit for those with internal among 99% coverage networks
- Attitudes are an important determinant of health-seeking behavior among PWIDs
- Future interventions could consider this influence in the network to increase and sustain impact

Acknowledgements

- Thank you to my mentor, Dr. Spiegelman, and collaborators, Drs. Halloran, Katenka, Friedman, and Kogut, and recent graduates and students, Ayako Shimada, Hilary Aroke, and Tianyu Sun.
- We thank Dr. Friedman for access to the SFHR data. Data from the SFHR study were obtained with support from the National Institute on Drug Abuse (NIDA), under National Institutes of Health (NIH) grant 1R01DA006723.
- This work was supported by NIH Avenir grant 1DP2DA046856-01, Advance Clinical and Translational Research (Advance-CTR) U54GM115677, and the RI Foundation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or RI Foundation.

References

Brian G Barkley, Michael G Hudgens, John D Clemens, Mohammad Ali, and Michael E Emch. Causal inference from observational studies with clustered interference. *arXiv preprint arXiv:1711.04834*, 2017.

Stephen R Cole and Constantine E Frangakis. The consistency statement in causal inference: A definition or an assumption? *Epidemiology*, 20(1):3–5, 2009.

Debarchana Ghosh, Archana Krishnan, Britton Gibson, Shan-Estelle Brown, Carl A Latkin, and Frederick L Altice. Social network strategies to address hiv prevention and treatment continuum of care among at-risk and hiv-infected substance users: a systematic scoping review. *AIDS and Behavior*, 21(4):1183–1207, 2017.

Sihan Huang and Yang Feng. Pairwise covariates-adjusted block model for community detection. *arXiv preprint arXiv:1807.03469*, 2018.

Eric D Kolaczyk. *Statistical Analysis of Network Data*. Springer, 2009.

Temina Madon, Karen J Hofman, Linda Kupfer, and Roger I Glass. Implementation science. *Science*, 318(5857):1728–1729, 2007.

Miller McPherson, Lynn Smith-Lovin, and James M Cook. Birds of a feather: Homophily in social networks. *Annual Review of Sociology*, 27(1):415–444, 2001.

Mark EJ Newman. Modularity and community structure in networks. *Proceedings of the national academy of sciences*, 103(23):8577–8582, 2006.

Nancy S Padian, Charles B Holmes, Sandra I McCoy, Rob Lyerla, Paul D Bouey, and Eric P Goosby. Implementation science for the US President's Emergency Plan for AIDS Relief (PEPFAR), 2011.

Georgia Papadogeorgou, Fabrizia Mealli, and Corwin Zigler. Causal inference for interfering units with cluster and population level treatment allocation programs. *arXiv preprint arXiv:1711.01280*, 2017.

Donald B Rubin. Randomization analysis of experimental data: The Fisher randomization test comment. *Journal of the American Statistical Association*, 75(371):591–593, 1980.

Eric J Tchetgen Tchetgen and Tyler J VanderWeele. On causal inference in the presence of interference. *Statistical methods in medical research*, 21(1):55–75, 2012.

Eric J Tchetgen Tchetgen, Isabel Fulcher, and Ilya Shpitser. Auto-g-computation of causal effects on a network. *arXiv preprint arXiv:1709.01577*, 2017.

Original PWIDs Network in SFHR

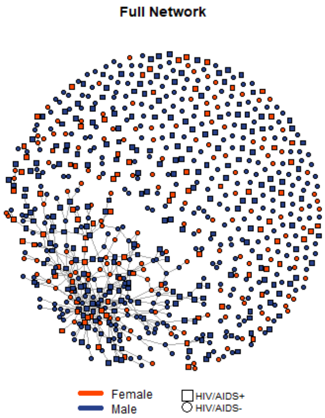


Figure 4: Full Network.