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# SOCIAL NETWORK OPTIMIZATION FOR HIV PREVENTIVE CARE

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**ABSTRACT**

The objective of this dissertation is to investigate how epidemiologic methods can be advanced through the use of social network analysis. Social network analysis (SNA) provides critical insights into the dynamics of health outcomes. Traditional epidemiologic methods have focused on the attributes and behaviors of individuals as the unit of analysis. However, a person's risk for disease often depends on the risk factors and norms of the individuals within their social networks. This dissertation focuses on HIV infection to demonstrate the importance of social networks, as HIV is an inherently social disease that disproportionately affects particular socio-demographic groups in the United States (U.S.).

HIV incidence in the U.S. has remained generally stable in recent years, with the exception of the number of new infections among young Black Men who have Sex with Men (YBMSM). According to the CDC, HIV diagnoses increased by 87% among YBMSM from 2005-2014.[1] Concurrently, only 3% of HIV funding is allocated for HIV prevention.[2] Previous research has focused on individual-level risk factors as a means to explain the disparate trends in HIV prevalence and inform the design of HIV prevention interventions. This approach has been largely ineffective. Consequently, focus has now turned toward social network analysis (SNA).

SNA can be organized into two general analytic approaches: ego-centric (examination of the ties, attributes and local structure in one's personal network) and socio-centric (examination of "whole" network structural characteristics). Social networks have been utilized to effectively promote HIV risk reduction and to recruit hard to reach populations and visualize where HIV transmission clusters occur. The potential of social network interventions, however, has not been actualized, primarily due to the dominance of individualism culturally and thus the domination of people with these views on review committees and funding agencies. **The research described in**

**this dissertation furthers HIV prevention research and epidemiologic methodology through the utilization and evaluation of two longitudinal social network based HIV interventions on the South Side of Chicago (SSC).** Specifically, this dissertation employs the two SNA analytic approaches to:

**Aim 1: Develop an HIV risk network metric to predict HIV acquisition over time. This metric (the "network viral load") is based on the HIV viral loads of the sexual partners of an HIV negative individual.**

- **Hypothesis 1.1** Individuals with higher **"**network viral load" will be more likely to acquire HIV, and this relationship will be moderated by HIV risk behaviors, other network member attributes, and network position.

**Aim 2: Describe social network stability among YBMSM ages 16-29 over an 18-month period and determine how factors related to social disorder, such as unstable housing, criminal justice involvement, and exposure to violence and resilience factors affect the composition of social networks over time**

- **Hypothesis 2.1** Individuals with greater exposure to social disorder will experience higher rates of network instability, but this will be alleviated by resilience factors.

**Aim 3: Determine whether a social network based HIV testing intervention in networks of individuals who were recently infected or recently diagnosed with HIV is a cost-effective strategy for locating people with undiagnosed HIV infection compared with the expanded HIV testing initiative in a hospital setting.**

- **Hypothesis 3.1** The social network based testing will be more costly than expanded testing, but also more effective at yielding new HIV diagnoses.

## 1. SIGNIFICANCE

**This dissertation forwards a new approach to epidemiologic methods.**

Traditional epidemiologic methods have focused on attributes of the individual as a means to assess correlates of health status. The goal of social network analysis is to explain the behavior of individuals within a network and of the system as a whole by focusing on specific features of the interconnections among individuals.[3] Relationships influence a person's behavior beyond the influence of his or her individual attributes.[4] The role of linkages in a social setting is therefore a critical feature of health and the spread of behavior. In the context of HIV, reaching a high-risk population targeted for HIV prevention is not straightforward due to the influence of peers. At-risk individuals often obtain and transmit information primarily through their informal social networks, especially their friends, making the examination of social networks necessary for HIV risk reduction. [5]

Social network analyses have examined the relationship between social networks and health since the 1970s.[6] The significant role that sexual networks play in the spread of HIV and Sexually Transmitted Infections (STI) has been widely recognized, primarily in the context of sexual mixing patterns. Sexual and injection mixing patterns have been posited as a mechanism to explain disparities in HIV/STI prevalence observed among particular racial/ethnic groups in the United States. [7,8,3]

Data from the National Health and Social Life Survey combined with a simulated sexual network have been used to explain a marked disparity between the high prevalence of STIs among African-Americans and low prevalence of STIs among White Americans. After controlling for traditional risk factors for STI infection, African-Americans had significantly higher rates of STIs as a result of a combination of assortative and dissortative sexual mixing

patterns.[7] Specifically, individuals of the same race/ethnicity tended to partner sexually with one another (assortative mixing), and this preference was more common among African-Americans than it was among White individuals. However, the partnerships within race/ethnicity were dissortative in terms of risk. African-Americans who only had one sex partner in the past year (African-Americans on the "periphery") were significantly more likely to choose sex partners with four or more sex partners in the past year (African-Americans in the "core") than were White individuals on the periphery to choose White individuals in the core. [7]

Similarly, socio-centric examinations of the networks of drug injectors have been used to explain the occurrence of stable, high HIV prevalence rates among this group (as opposed to HIV-prevalence rates that commonly lead to outbreaks). Specifically, the types of linkages between HIV positive and HIV negative individuals are important in limiting disease outbreaks. A network structure that contains small sub-networks of linked HIV negative individuals within a larger network of individuals with mixed HIV serostatuses limits outbreaks. The small size of the HIV negative sub-network serves as a structural form of herd immunity. In addition to these sub-networks, the presence of individuals in the larger network who have long-term HIV infection "firewalls" also help limit outbreaks due to their lower potential of transmitting disease (as a result of a lower viral load at their stage of infection) and their insusceptibility to primary infection. [9]

An examination of individual level risk factors alone is therefore inadequate for identifying the determinants of disease trends, highlighting the utility of SNA for epidemiologic purposes.

**YBMSM represent a highly vulnerable population and longitudinal social network analyses on this population are limited.**

Black Men who have Sex with Men aged 13-29 are more heavily impacted by the HIV epidemic in the United States than any other group that is at risk for HIV.[10] The rate of new HIV infections increased by 87% among YBMSM aged 13-29 between 2005-2014, distinguishing the group as the only risk group to experience a statistically significant increase in new infections during the time period.[4] The state of the HIV epidemic is similar in the city of Chicago. In 2009, 39% of new HIV infection diagnoses occurred among individuals under 30 years of age, with Men who have Sex with Men (MSM) contact accounting for the majority of transmissions within this age group.[12] The rate of new HIV diagnoses among YBMSM aged 13-29 in Chicago increased from 13.2% of all new infections in 2006 to 18.5% in 2009.[12] HIV prevention in this young population has considerable impact on future health-care resources given the need for lifelong antiretroviral treatments. Network data in this population is essential, yet a meta-analysis of HIV related network studies noted a paucity of network studies on YBMSM, particularly those with a longitudinal design.[13] Longitudinal data on YBMSM are crucial for the development of effective and sustainable interventions because social networks change rapidly among this population over time.

**2. INNOVATION**

The questions addressed in this dissertation are some of the first to be assessed among YBMSM using a network approach. The studies utilized for this dissertation (detailed below) are both novel in their design, allowing for the assessment of these AIMS. The uConnect study is the first social network study that longitudinally evaluates and includes personal, non-sexual social networks in a model of risk and risk reduction in YBMSM. It is also one the largest single-site cohorts of YBMSM in the U.S. to date. The Transmission Reduction Intervention Project (TRIP) is one of few studies to trace the risk networks of individuals who were recently infected with

HIV over time. Very little is known about the network dynamics of YBMSM, particularly with regard to network change over time and how social factors impact this change.

The increase in HIV incidence being limited to one specific risk group is encouraging in that it may indicate the possibility of HIV elimination in the U.S. In order to actualize this possibility, a socially-integrated trans-disciplinary approach is needed[14] that harnesses the benefits of biomedical advancements by being informed by social science. This combination approach will optimize the benefits of biomedical advancements via increasing the precision by which they are indicated, increasing their accessibility, and decreasing operational barriers to their use. The AIMS in this dissertation accomplish this on both a macro-level (AIM 1) and micro-level (AIM 2) level, in addition to assessing the economic feasibility of implementing a social network intervention on a large scale (AIM 3).

**3. APPROACH**

To advance the aims of utilizing SNA to develop epidemiologic methods, data from two longitudinal social network based HIV interventions on the South Side of Chicago will be used. Both studies target individuals and members of their social networks who are at heightened risk of HIV infection, with the purpose of preventing and treating HIV transmission. Previous research exists on individuals at risk for HIV in this region, but the aforementioned studies are the first to provide information on the people who are socially influential to those at risk. Both studies are also the first in this population with a longitudinal study design.

The two studies recruited respondents from the South Side of Chicago, a 95 mi² region including 34 of the city's 77 community areas. It is one of the largest contiguous Black communities in the US (71% of 869K people).[15] This region contains 9 of the 10 poorest communities in Chicago. Disparities in basic resources are reflected in the range of People

Living with HIV rates reported in 2012. Communities in this area such as Englewood, Woodlawn, South Shore, Grand Boulevard and Washington Park range from 913-1296/100,000. This exceeds the overall prevalence of Chicago (829.9/100,000).[12] This region also lacks services targeted at YBMSM, making this population difficult to reach and thus amenable to social network recruitment strategies.

## 4. AIM 1: Network Viral Load: A Critical metric for HIV elimination

### 4.1 BACKGROUND

HIV prevention interventions, such as pre-exposure prophylaxis (PrEP) and treatment as prevention (TasP) offer potential for great reductions in HIV transmissions.[16-18] In recent years, the number of new HIV diagnoses in the United States (U.S.), for example, has remained stable at around 50,000 cases per year,[19,20] indicating the need for more effective HIV prevention programs to achieve further reductions in new HIV diagnoses.

TasP has been shown to reduce the number of phylogenetically linked HIV transmissions by 96%.[16] The TasP approach is effective because it lowers HIV viral load, which limits onwards transmission.[21,22] Some public health departments have utilized this association on a population level for the targeting of HIV prevention resources: The San Francisco Department of Public Health, for example, calculated an aggregate viral load measure for different geographic areas within the city, the "community viral load" (CVL), and considered associations between CVL and new HIV diagnoses by geographic area.[23] Decreasing CVL was found to be associated with a decline in the number new HIV diagnoses over a five year period.[23] While these findings are promising, the CVL approach has several limitations,[24] most notably that it may be prone to ecologic fallacy. The CVL assumes that individuals transmit HIV primarily to other individuals in the same geographic area as them. With the advent of hook-up apps and easier mobility within

and across cities,[25] HIV transmission has increased potential to occur in more heterogeneous contexts and networks. A recent phylogenetic analysis in Chicago for example, demonstrates that the HIV virus of Black YMSM in Chicago was phylogenetically similar throughout geographically diverse areas where HIV infected YMSM reside. This indicates that HIV is transmitted across communities, and that the CVL may therefore be discounting these cross-community exposures.[26] Recent articles published in *The Lancet* journals by Miller et al.[24] and Herbeck and Tanser[27] discuss other weaknesses of the aggregate CVL measure and call for a model that better understands the affected population and avoids ecologic conclusions.

A more precise metric would account for the composite viral loads of the risk networks of an HIV negative individual, regardless of the geographic location of either the individual or the network member. Here, we develop this new metric, the Network Viral Load (NVL)[28] that accounts for the composite viral loads of a risk network sample of an HIV negative individual. We test its association with HIV infection among a population-based cohort of YMSM.

## 4.2 METHODS

### Study Population

Data come from the baseline sample of uConnect, a longitudinal study of YMSM ages 16-29 who reside in Chicago, conducted from 2013-2016.[29-32] Respondent Driven Sampling (RDS) was used for recruitment. RDS seeds were selected from a distribution of social spaces that YMSM occupy (both physical spaces and virtual spaces such as Facebook). Eligibility criteria included: 1) self-identification as African American or Black, 2) born male, 3) between 16 and 29 years of age (inclusive), 4) report of oral or anal sex with a male within the past 24 months 5), willing and able to provide informed consent at the time of the study visit, 6) Primary residence in South Chicago, the most populous contiguous Black community in the U.S.[29]

Respondents were given up to six vouchers to recruit others they know who they have frequent contact with who fit the eligibility criteria. Each respondent was given $60 for participation and $20 for each successful recruit enrolled into the study. Respondents were administered a behavioral questionnaire and tested for HIV and HIV RNA. The Institutional Review Board at the University of Chicago and the National Opinion Research Center at the University of Chicago approved all procedures.

**Laboratory Testing**

HIV infection was determined by three assays applied to samples eluted from dry blood spot samples: ARCHITECT HIV Ag/Ab Combo; Multispot HIV-1/HIV-2 Bio-Rad; and Realtime HIV-1 RNA, Abbot. In cases where test data were missing at the study visit, available HIV viral load and serostatus surveillance data were used from the Health Department. We obtained a Release of Information from each respondent to obtain these data.

**Network Construction**

HIV risk networks were constructed from the RDS recruitment network as previously defined by Tsang and colleagues, consisting of RDS referrals and referees.[33] This "risk environment network" definition exploits the RDS referral structure in a novel way by situating the referrals and referees as part of a respondent's HIV risk environment network.[33-37] The risk network as we define it represents a sample of network members from their immediate risk environment. Risk environments have been previously defined as the composition of risk factors external to the individual, such as community level norms and practices.[37] This definition is particularly relevant to YMSM by virtue of their tendency to recruit and be recruited by individuals who share close social connections. Given the high HIV prevalence in this population, the significant overlap between the sexual and social networks of Black MSM[38] and

the notable influence that social networks have on HIV preventive behaviors and transmission patterns,[38-39] this more broad definition of one's HIV-related network should be useful for effective HIV prevention efforts.

**Analytic Plan**

**Measures**

The outcome of interest was HIV serostatus, defined by laboratory testing during the study visit. The primary independent variable of interest was a respondent's NVL, defined as the sum of the viral loads in a respondent's network at baseline, divided by the number of HIV seropositive people in the network (**Figure 1**). The total number of HIV-seropositive people were chosen as the denominator rather than the total number of connections due to the potential dilution of the NVL effect among those with large networks. The NVL was then summarized into the following categories: all network members were HIV seronegative, at least one network member was HIV infected and the average NVL ranged from <200 to <10,000 copies/mL, at least one network member was HIV infected and the average NVL ranged from 10,000 to <60,000 copies/mL, and at least one network member was HIV infected and the average NVL was ≥60,000 copies/mL. These categories reflect relative cutoffs that designate risk of transmissibility[22] and the distribution of the NVL in the sample.

Other covariates include 1.) Non-injection drug use or alcohol use during sex (drugs included marijuana, MDMA, volatile nitrates, cocaine, heroin, psychoactive drugs, methamphetamines, and prescription pain killers). Sex-drug use was a dichotomous measure indicating use of any of the aforementioned substances); 2.) Frequency of condomless anal sex in the past 6 months (defined as the sum of the number of times the respondent reported sex with each sexual partner they reported inconsistent condom use with in the past 6 months; 3.) Self-

reported syphilis diagnoses in the past 12 months; 4.) Degree (total number of sex partners and confidants reported by the respondent combined); 5.) Other demographics and social characteristics. Injection drug use was not assessed due to its low prevalence in the sample. Analyses excluded respondents in the last RDS wave because their networks were incomplete because they were unable to recruit others as a result of the sample design.[33]

**Analysis**

Multivariate logistic regression was used to assess the relationship between HIV serostatus and NVL at baseline. Variables significant at the $p \leq 0.1$ level in bivariate analysis were considered in the multivariate model. All variables retained in the final model were significant at the $p \leq .05$ level.

An additional exploratory analysis was conducted which assessed the association between NVL and HIV seroconversion over the 18-month study period. Seroconversion was defined as having a HIV negative lab result at baseline and having an HIV infected lab result at either of the two follow-up visits. NVL was summarized into 3 categories for this analysis due to limited sample size: all network members are HIV negative, at least one network member is HIV infected and the average NVL ranges from <200 to <10,000 copies/mL, at least one network member is HIV infected and the average NVL is ≥10,000 copies/mL.

Lastly, we calculated mean CVL using Enhanced HIV/AIDS Reporting System data (state mandated laboratory data) from the Health Department. We assessed associations between CVL and respondent HIV serostatus using logistic regression. All regression analyses were conducted using Stata version 14.[40] Permutation analyses were conducted in R version 3.3.1.[41]

**Sensitivity Analysis**

Assumptions of independence between observations assumed by the logistic regression[42]

are violated by network data. A series of permutation tests were conducted to verify the associations found in the multivariate logistic regression model. Each permutation retained the original network structure, but randomly assigned the viral loads and HIV serostatuses throughout the network. This null hypothesis was that one's own HIV serostatus is unrelated to the viral loads of the individuals in one's egocentric network. Five hundred permutations were performed to obtain an estimate of the permutation distribution for the odds ratios, and the likelihood of the observed odds ratios were evaluated relative to this distribution, yielding a 2-sided permutation p-value.[33]

We also repeated the NVL analysis replacing NVL with the proportion of respondents' networks that are HIV infected to determine if there is any added benefit of assessing NVL over network HIV infection alone, which we have conducted previously.[33] HIV-seropositive network environment proportions were coded as 0%, 1%- 49%, 50%-≤75% and ≥75%. Categories were selected based upon the distribution of the HIV-seropositive network proportions in the sample.

**4.3 RESULTS**

Our sample included 65 seeds that generated a baseline sample of 618 respondents. Referred network members were mostly individuals known to the index, with 77% of the referrals including close confidants, sex partners, or family members (largely family of choice rather than biological family). Only productive seeds (n=38), defined as seeds that recruited at least one participant, were included in the analyses. Excluded from the analyses were 89 respondents in the final RDS wave, because they were unable to recruit by design, and thus the size of their networks was restricted in a way that the networks of other respondents were not. The total sample size after these exclusions was 502; of these, we had laboratory data on 91%, yielding a total sample size of 457.

The mean age of the participants was 23 (range 16-29), 100% were Black/African-American, 34 (7%) had less than a high school degree, 331 (66%) and 138 (27%) identified as gay and bisexual respectively, 163 (33%) were unemployed, 258 (51%) had health care coverage, 20 (4%) had ever used PrEP, 129 (26%) were unstably housed in the past 12 months, and 233 (46%) had ever experienced criminal justice involvement (**Table 1).** The HIV prevalence in the sample was 39% (n=182).

The mean risk environment network size was 1.9 (range 1-7). The distribution of NVL in the sample of these networks was as follows: 187 (43%) had entirely HIV-seronegative networks, 159 (37%) had a NVL of <200 to <10k copies/mL, 63 (15%) had a NVL of ≥10k to <60k copies/mL, and 21 (5%) had a NVL of ≥60k copies/mL. HIV-seropositive network proportions were as follows: 187 (43%) had 0% HIV-seropositive network partners, 45 (11%) had 1%– 49% HIV-seropositive network partners, 68 (16%) had 50% to ≤75% HIV-seropositive network partners, and 131 (30%) had ≥75% HIV-seropositive network partners. Respondents had an average of 2 male or transgender anal sex partners in the past 6 months (range 1-6) and reported having condomless sex with an average of 1 in the past 6 months (range 0-6).

After controlling for age, substance use during sex, frequency of anal sex in the past 6 months, degree, and syphilis diagnosis in the past 12 months, we found increased odds of HIV infection with increased NVL score (**table 2**). The odds of HIV infection with a NVL of <200 to <10k copies/mL were 2·17 times that of a network with all HIV-seronegative members (OR 2.17; 95% C.I. 1.34-3.51), the odds with a NVL of ≥10k to <60k copies/mL were 2·44 times that of a HIV-seronegative network (OR 2.44; 95% C.I. 1.30-4.55), and the odds with a NVL of ≥ 60k copies/mL were 2.88 times that of a HIV-seronegative network (OR 2.88; 95% C.I. 1.11-7.44)(**table 2**). A test for trend of the NVL was significant at p=0.001, indicating increased odds

of HIV infection with increasing levels of NVL. Increasing age was also associated with increased odds of HIV infection (OR 1.10; 1.02-1.18) as well as being diagnosed with syphilis in the past 12 months (OR 4.39; 2.40-8.02). Drug use during sex was a strong confounder of the relationship between NVL and HIV infection. No effect modification was found between NVL and any of the covariates in the model.

The permutation test results reveal that observed odds ratios of 2.17, 2.44, and 2·88 comparing <200 NVL to <10k NVL, 10k NVL to <60k NVL, and 60k+ NVL to the reference group of a completely HIV-seronegative NVL are all located on the extreme tails of the permutation distributions, yielding estimated p-values of <0.001 (0/500), <0·001 (0/500) and 0·03 (16/500) respectively (**Figure 2**). This finding indicates that the observed associations were unlikely under the null hypothesis.

Of the 271 respondents who were HIV negative at baseline, 242 (89%) had follow-up data. Of those, 27 (11%) seroconverted to HIV-seropositive over the 18 months of follow-up. While this rate is high, it is not substantial enough to be adequately powered for multivariate analysis. Nevertheless, descriptive results using lower NVL thresholds show signs of a potential association between NVL and HIV seroconversion. A slightly lower proportion of those who seroconverted had entirely HIV-seronegative networks at baseline (46%) compared to those who remained negative over the course of the study (52%). Additionally, a slightly higher proportion of those who seroconverted had a NVL of 10k+ copies/mL (23%) compared to those who remained negative (17%). These differences were not statistically significant (p=0.71)

To further assess geographically defined community viral load type metrics, we present the geographic distribution of sex partners of respondents relative to the recruitment location on the South Side of Chicago (**Figure 3**). The figure reveals notable geographic diversity between

the residence of the respondents (highlighted in grey) and the residence of their sex partners. Just above half (764) of the 1360 total sex partners elicited reside in the same region of the city as the respondents, further indicating that sex partners of our respondents did not necessarily reside in the same geographic communities as the respondents. The city of Chicago is organized into 77 community areas.[64] We calculated mean CVLs for each community area in Chicago using Health Department data and assessed whether it was associated with HIV serostatus using logistic regression. We found insignificant results in a bivariate analysis between CVL and respondent HIV serostatus (OR 0.99; 95% C.I. 0.99-1.00) as well as in a multivariate analysis including the covariates from the NVL multivariate model (OR 0.99; 95% C.I. 0.99-1.00).

**4.4 DISCUSSION**

The current analysis establishes the relationship between a new metric, Network Viral Load (NVL), and HIV serostatus. We found that the strength of the association between NVL and HIV serostatus was positively associated with the magnitude of the NVL and that the association was significant after adjusting for other common drivers of HIV infection including age, non-injection drug use or alcohol use during sex, frequency of condomless anal sex, syphilis diagnosis and degree social connectivity.

The U.S. CDC recommends monitoring of CVL as a mechanism for measuring progress towards the National HIV/AIDS Strategy goals.[44] However, shortly after this recommendation an article in *Lancet Infectious Diseases* emphasized the limitations of an aggregate viral load measure, highlighting the importance of considering the composition of an individual's sexual network.[24] The NVL is a response to this criticism as it is a more precise metric for addressing HIV transmission potential.

There is at least one other index that has been explored previously. An analysis by Little et al. of recently HIV infected adults and adolescents in San Diego examined multiple factors, such as a transmission network score (an individual's degree in a phylogenetic transmission network), viral load, and number of sex partners.[31] The study found that the numeric transmission network score, viral load, and number of sex partners (all measured at baseline) predicted risk of HIV transmission during a 12-month period.[31] The NVL model, in contrast, considers a variation of these factors, but focuses on the risk of acquisition among HIV seronegative individuals rather than the transmission capacity of those recently infected as done by Little and colleagues.

The utility of the NVL is enhanced because health departments can easily create it by combining partner services and electronic laboratory surveillance data. The NVL is also different from other approaches in that it focuses on the risk of acquisition of an *HIV negative* individual, which may have important implications for precision PrEP delivery.

Furthermore, the NVL may also be useful for identifying HIV infected index individuals who have uncontrolled viremia given their propinquity to others who also have high viral loads. We examined the association between viral load of the index and NVL and found a correlation between the respondents' viral loads and the viral load of their networks ($r=0.16$, $p=0.001$). Higher NVL cut-points (100k+ copies/mL) were also examined and demonstrated signs of an increase in the magnitude of the association between NVL and HIV (data not shown).

Our study is limited in its ability to infer causality between NVL and HIV acquisition due to the cross-sectional nature of the study design and the fact that infections of the seropositive could have taken place long ago (and their networks and NVL may have changed during this time). However, our longitudinal seroconversion results indicate that baseline NVL may be

associated with incident HIV infection in larger samples. Another potential concern is whether or not NVL is a better indicator of HIV risk than assessing the proportion of HIV+ individuals in one's network as we have measured previously.[21] A sensitivity analysis replacing NVL with HIV network proportions in the multivariate logistic regression model showed that when compared to an entirely HIV seronegative network, only networks consisting of $\geq$ 50% HIV infected members are associated with HIV infection. The NVL is a more precise measure of circulating virus in the risk environment than the proportion of HIV seropositive individuals who may or may not be virally suppressed. Studies of YMSM in the U.S. with longer follow-up time which allows for a greater number of seroconversions is warranted. The metrics should also be tested in international settings among populations with higher incidence rates in order to assess their effectiveness.

The NVL association with HIV serostatus could likely be strengthened if all sexual connections and HIV viral loads of those partners are included. However, sex network data is rarely complete.[46] We assessed a model with an interaction between NVL and one's frequency of anal sex but found null results, perhaps due to the possibility that anal sex occurred with individuals who were unobserved in these analytic networks. The risk network as currently defined, however, may be a more realistic representation of the network that would be obtained through partner services. In partner services, less than 50% of contacts are typically ever identified.[46] Targeting YMSM through strictly defined sex networks has proven unsuccessful in Chicago and in North Carolina in the U.S., given stigma and the fact that an increasing percentage of sex partners are being found online.[25] Another concern is that the current model implies that a person's risk frequency with a given network member is unrelated to the total number of people in their network. However, Miller et al. point out that the HIV prevalence of a

population must be considered in addition to viral load and frequency of contact in order to accurately predict ongoing HIV transmission (i.e. incidence rate=prevalence rate x average contact x per contact transmission probability).[24] Given the high HIV prevalence among YMSM, our model assumption should not significantly affect the NVL serostatus relationship because the probability of having contact with an HIV seropositive individual is high. We tested the effect of NVL averaged over the total number of network members in the multivariate model and found attenuated results in the >60k+ copies/mL category due to the dilution of the NVL leading to fewer people in this category. Nevertheless, our study serves as a valid starting point for development of the NVL metric and further supports the importance of examining risk environments in terms of HIV transmission.

The NVL has potential to improve public health practice in the U.S. Current state laboratory reporting laws combined with existing contact tracing practices and the increase in uptake of electronic lab reporting could allow for a NVL calculation of individuals at risk for HIV infection. Currently, 36 states plus the District of Columbia require laboratory reporting of all levels of CD4 and viral loads of all HIV seropositive individuals, and this number is expected to increase.[47] This information is becoming more accessible as a result of the CDC providing supplemental HIV surveillance funding to support the implementation and maintenance of electronic lab reporting for all HIV related test results.[48,49] Concurrently, partner services is already the standard of care for syphilis and HIV control efforts by local Public Health Services, which helps identify large numbers of individuals who are of negative or unknown HIV serostatus. Combining these two pre-existing public health data sources would allow for the calculation of NVL, which could then be used for a public health approach towards HIV prevention interventions where interventions such as PrEP are focused upon HIV seronegative

individuals who have a high NVL. Guidelines for PrEP[50] for example are still based upon individual level behaviors, which may be inadequate (half of seroconverters in the uConnect cohort were not eligible for PrEP according to CDC guidelines, data not shown). A paradigm shift in how we use PrEP that includes characteristics of the network, which could include NVL, is needed. Future studies should test the association between NVL and HIV seroconversion to further validate the metric and advance efforts towards HIV elimination.

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**Tables**

| **Table 1. Demographics, behavioral characteristics, and HIV serostatus, uConnect (n=457)** | |
|---|---|
| | **n (%)** |
| **Age at interview (years)** | |
| 16-18 | 33 (7) |
| 19-20 | 83 (18) |
| 21-24 | 211 (46) |
| 25+ | 130 (28) |
| **Education** | |
| < High school Degree | 61 (13) |
| High school graduate or equivalent | 112 (25) |
| Some college or higher | 284 (62) |
| **Unemployed (previous year)** | |

| **Table 1. Demographics, behavioral characteristics, and HIV serostatus, uConnect (n=457) cont.** | |
|---|---|
| Yes | 149 (33) |
| **Health care coverage*** | |
| Yes | 235 (51) |
| **Ever used PrEP** | |
| Yes | 20 (4) |
| **Unstably housed (previous year)*** | |
| Yes | 129 (26) |
| **Number of Residences (previous year)** | |
| 1 | 252 (55) |
| 2 | 124 (28) |
| 3+ | 80 (18) |
| **Criminal justice involvement in lifetime[a]** | |
| Yes | 233 (46) |
| **Drug Use (previous year)** | |
| Marijuana | 388 (77) |
| Volatile Nitrates | 33 (7) |
| MDMA | 43 (9) |
| Psychoactive drugs | 3 (<1) |
| Methamphetamine | 3 (<1) |
| Cocaine/Crack | 23 (5) |
| Heroin | 3 (<1) |
| **Sex drug use (previous 6 months)** | |
| Yes | 118 (24) |
| **Sexual orientation** | |
| Gay | 331 (66) |
| Straight | 20 (4) |
| Bisexual | 138 (27) |
| Other | 12 (2) |
| **Number of male sex partners (previous 6 months) (median, IQR)[b*]** | 2 (1,3) |

| **Table 1. Demographics, behavioral characteristics, and HIV serostatus, uConnect (n=457) Cont.** | |
|---|---|
| **Number of condomless male sex partners (previous 6 months) (median, IQR)** [b] | 1 (0,1) |
| **Frequency of anal intercourse (previous 6 months) (median, IQR)** [b] | 11 (3,15) |
| **Frequency of condomless anal intercourse (previous 6 months) (median, IQR)** [b] | 2 (0,11) |
| **Number of social & sexual connections "Degree" (median, IQR)** [b] | 5 (3,7) |
| **HIV Characteristics** | |
| **HIV Serostatus** | |
| Positive | 182 (39) |
| **Use of ARVs (Current)** [c] | |
| Yes | 88 (48) |
| **Percentage of risk network members HIV+ (median, IQR)** | 25% (0%, 100%) |
| **Network Viral Load*** | |
| All HIV-seronegative network | 187 (44) |
| <200 to <10k copies/mL | 159 (37) |
| ≥10k to <60k copies/mL | 63 (15) |
| ≥60k copies/mL | 21 (5) |

O.R.=Odds Ratio, CI=Confidence Interval
[a]Includes jail/parole
[b]Obtained from network elicitation
[c]% among HIV+ aware
*Missing data (n):Healthcare coverage (11), unstably housed (2), detained (1), # males sex partners (20), NVL (27)

| **Table 2. Multivariate Logistic Regression: Factors Associated with HIV serostatus: uConnect Study (n=425)** | | | | |
|---|---|---|---|---|
| | | **OR** | **95% CI** | **p-value** |
| **Age** | | 1·10 | 1·03-1·18 | 0·006 |
| **Syphilis Diagnosis (previous year)** | No | 1·00 | - | - |
| | Yes | 4·39 | 2·28-7·57 | <0·0001 |
| **Frequency of condomless anal intercourse (previous 6 months)** | | 0.99 | 0·97-1·03 | 0·94 |

| Table 2. Multivariate Logistic Regression: Factors Associated with HIV serostatus: uConnect Study (n=425) Cont. | | | | |
|---|---|---|---|---|
| **Number of social & sexual connections (Degree)** | | 0·99 | 0·96-1·02 | 0·61 |
| **Sex Drug Use** | No | | | |
| | Yes | 1·37 | 0·84-2·25 | 0·21 |
| **Average Network Viral Load** | 0 | 1·00 | - | - |
| **(copies/mL)** | <200-<10k | 2·17 | 1.34-3·50 | 0·002 |
| **(copies/mL)** | ≥10k-<60k+ | 2·44 | 1·30-4·55 | 0·005 |
| **(copies/mL)** | ≥60k | 2·88 | 1·11-7·44 | 0·03 |
| OR=Odds Ratio, CI=Confidence Interval | | | | |

**Figures**

**Figure 1. Example sociogram depicting Network Viral Load calculation**

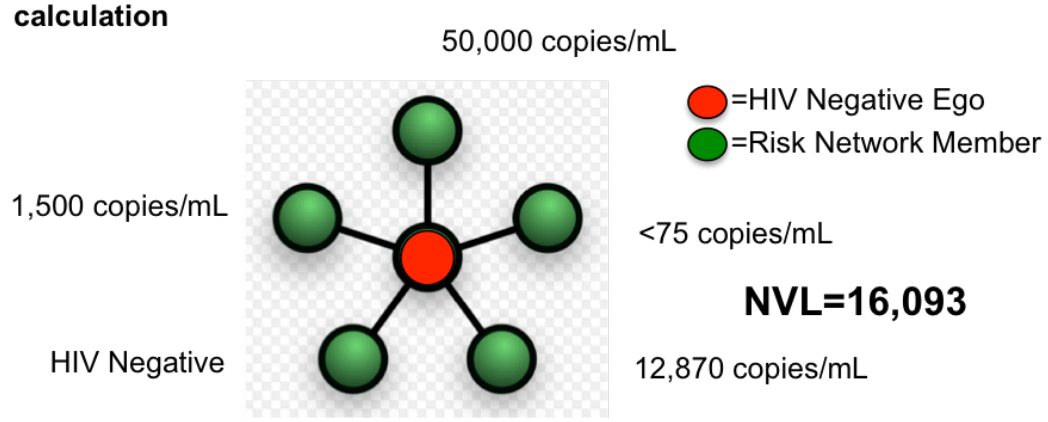
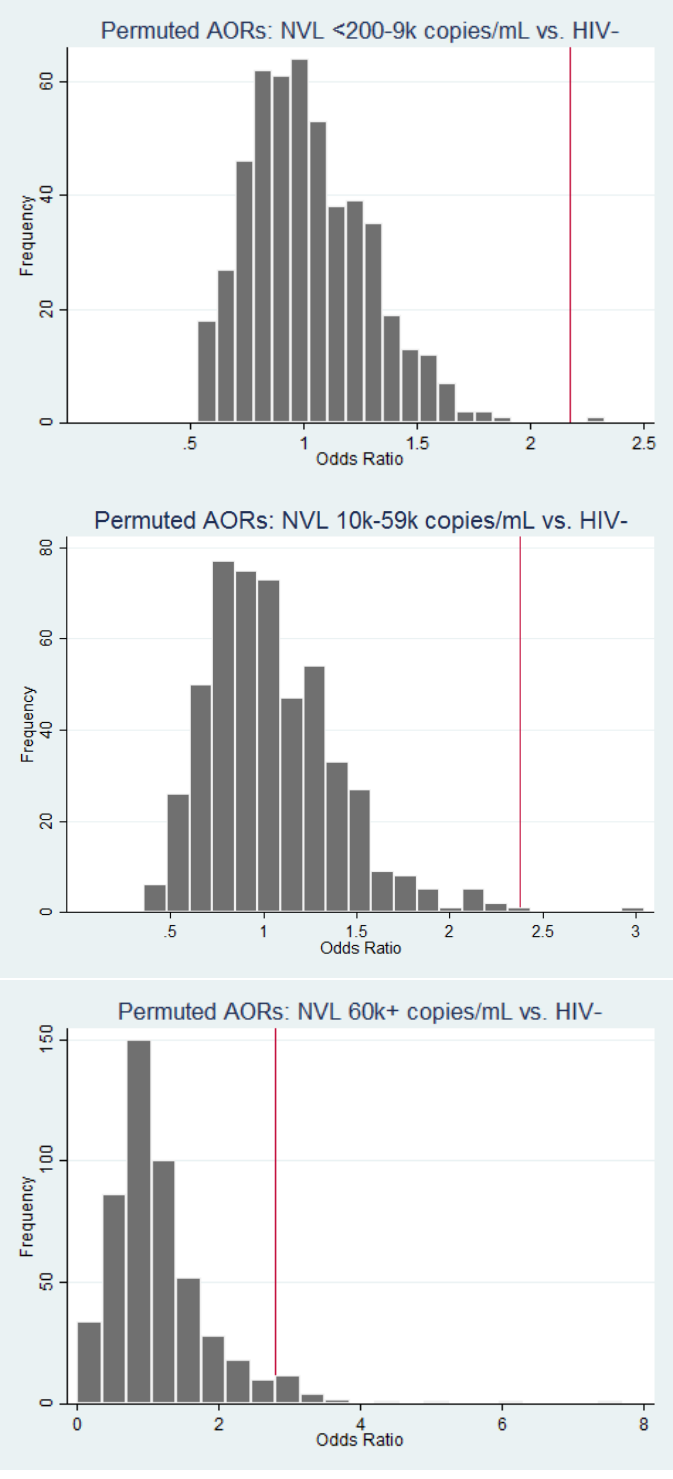


**Figure 2. Comparison of observed NVL results and 500 randomly generated networks (reference line indicates observed Odds Ratio)**

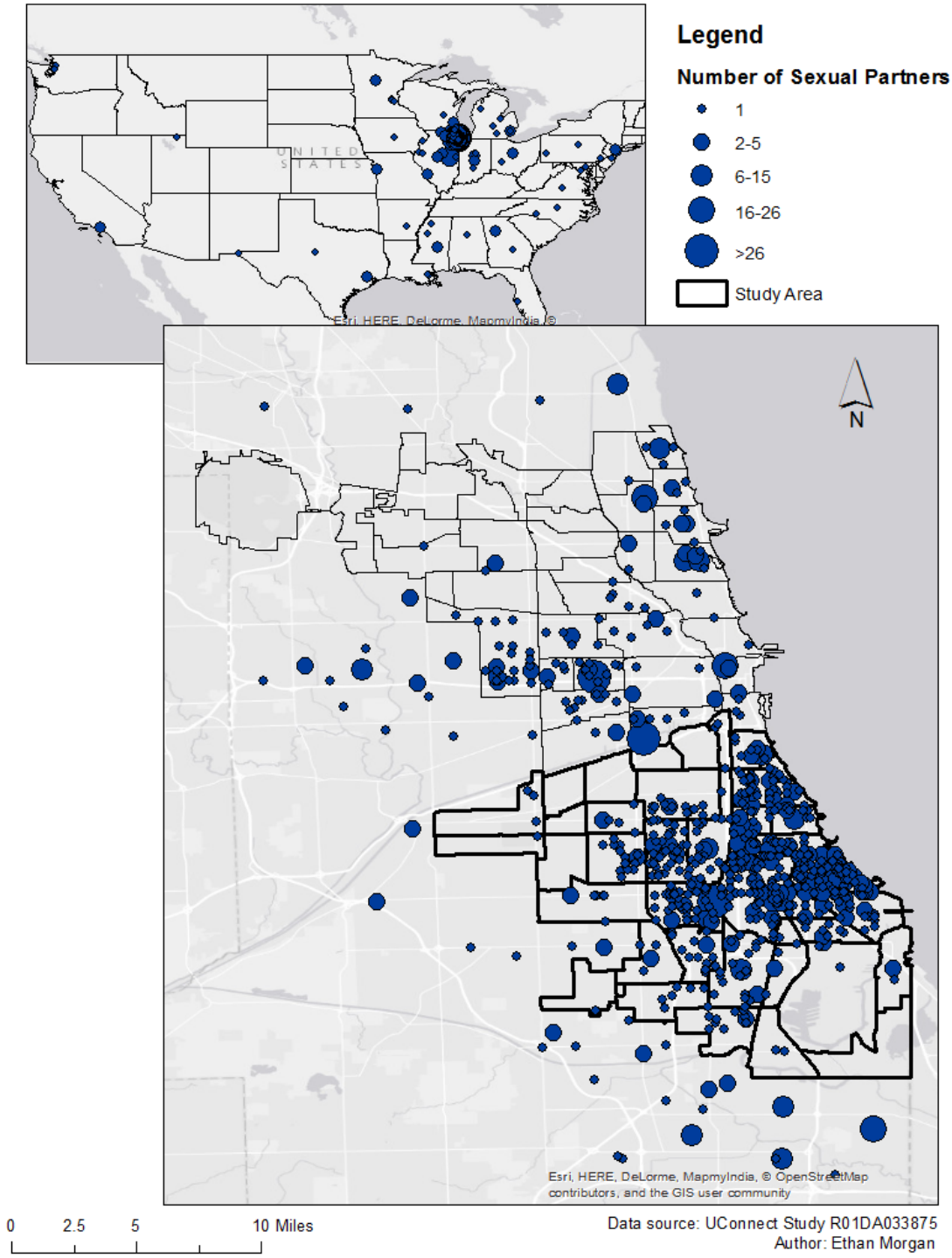



Observed OR: 2.17
p=<0.001

Observed OR: 2.44
p=<0.001

Observed OR: 2.88
p=0.03

**Figure 3. Map of respondents' sex partner locations and the uConnect study area**



## 5. AIM 2: Social-Environment Factors and Network Dynamics among YBMSM in Chicago

### 5.1 BACKGROUND

Young Black Men who have Sex with Men (YBMSM) age 16-29 are heavily impacted by HIV infection in the United States (U.S).[1] Explanations for the disproportionate rates among YBMSM have been varied, potentially due to the limited number of studies with large samples of the population, precluding investigation of behaviors and norm differences within the population.[51] Most of the research on YBMSM and HIV risk draws comparisons between Black MSM and MSM of other race/ethnicities, leading to small samples of each group.[52,53] Despite these limitations, a meta-analysis by Millet and colleagues comparing disparities in HIV infection between Black and White MSM suggests that the epidemic among Black MSM in the U.S. may be, "inextricably linked to social and economic environments" such as unemployment, low income, criminal justice involvement, and low education.[53] The mechanism by which these social and economic factors relate to HIV risk, however, has not been widely elucidated. It has also been previously established that social networks can be utilized to describe the spread of HIV and Sexually Transmitted Infections (STI) beyond individual risk factors alone due largely to one's position in the network and to the influence of their network connections.[68-71] Therefore, the current paper examines whether the stability of one's social network over time serves as a mechanism linking social-environment factors and HIV risk among the largest single-site, longitudinal cohort of YBMSM in the U.S.

Social-environment factors such as criminal justice involvement, exposure to community violence, and increased rates of unemployment have been associated with greater odds of transactional sex, substance use during sex, condomless sex, gang involvement and general substance use among YBMSM and adolescents.[71,72] Likewise, Millet and colleagues also found

that among MSM of all ages, disparities exist in the association between low income, low education, criminal justice involvement, unemployment, health insurance access for HIV-positive MSM and HIV risk outcomes between Black MSM and MSM of other race/ethnicities.[53] How exposure to these social-environment factors leads to HIV risk, however, has not been well explained.

We hypothesize that exposure to social-environment factors affects the stability of one's social network, and that stability is in turn linked to HIV risk. Networks and social-environments are related in that physical proximity, shared interests and shared norms commonly influence network formation.[69] The intersection of these factors allows for a confluence of effects on HIV risk, with each factor having the potential to be either protective or detrimental. For instance, factors related to social disorder are of particular importance when assessing the formation of social networks because they lead to changes in one's network that are against one's will, such as the loss of a close confidant due to death or incarceration.[70] These forced social network losses are more detrimental to one's health and social capital than losses by choice due to the difficulty in recovering from the loss and therefore difficulty in replacing the quality of the social tie.[70,71] The weak, fleeting, nature of the connections in unstable networks leads to poor health outcomes. Longitudinal network data from the National Social Life, Health, and Aging Project found that Black and low-SES respondents lost more confidants and had more difficulty replacing them than their higher SES counterparts later in life.[70] On the contrary, elements of one's social network can also be protective with regard to HIV risk.[72] In a sample of YBMSM, having a social network comprised of two or more family members was associated with decreased odds of sex-drug use and group sex, and increased odds of discouraging these behaviors in others.[72] In this paper, we assess the extent to which protective factors and exposure

to adverse social-environment circumstances affect network stability over time.

We define network stability as the extent by which an individual connects otherwise unconnected groups, known as "bridging" in social network analysis.[62] By our definition, the more likely one is to be a bridge, the less stable their network. Previously, bridges have been examined primarily in the context of social capital.[63,64] Previous literature has demonstrated that there is a link between bridge status and high social capital as a result of a bridge's exposure to non-redundant information and subsequent opportunity for innovation.[65] Bridge metrics are useful for assessing network instability because the bridging position tends to be temporary; approximately 90% of people who hold bridge positions only hold them for a year or less.[64] Network theory suggests that this is because the maintenance of social ties requires frequent interaction, which results in the strengthening of some ties and the degradation of others, thus terminating the bridge position.[62] Likewise, ties between individuals in groups that were otherwise unconnected often develop when relationships are maintained, terminating the bridge position.[64]

In the context of infectious disease transmission, bridges serve as essential targets for reducing disease transmission because they introduce disease to multiple clusters of susceptible individuals. Previous literature has shown that immunization based on bridge position is more effective than immunization based on number of contacts alone.[66] High network turnover (instability) has also been associated with HIV transmission among Intravenous Drug Users.[67] In other words, bridge status has different implications for those who are HIV-seropositive versus HIV-seronegative. Those who are HIV-seropositive who are in a bridge position may introduce the virus to different susceptible populations if they have uncontrolled virus, and could therefore be engaged in treatment to prevent onward transmission. Likewise, those who are HIV-

seronegative who are in a bridge position could be engaged in HIV preventive care, such as linkage to pre-exposure prophylaxis, to prevent acquisition and consequent future transmission.

Much of the literature on YBMSM networks in the context of HIV has focused on sexual networks exclusive of social networks.[68] The addition of social connections is necessary with regard to HIV risk assessment because social connections have influence on behavior,[68] and in high-prevalence populations, recruitment of the social connections of YBMSM is effective at identifying new infections because the probability of seroconversion is high.[69] Few studies have assessed the role of bridging on HIV risk over time as there are very few HIV oriented network studies with longitudinal data.[13,68] This paper is therefore unique in that it assesses the influence of social-environment factors on network stability in a combined social and sexual network of YBMSM over an 18-month period. Specifically, we assess how factors related to social disorder, such as unstable housing, criminal justice involvement, and exposure to violence affect the composition of social and sexual networks over time, and how this network stability affects HIV risk **(figure 4)**. We also investigate whether there are protective factors that can moderate the relationship between the social-environment and HIV risk.

## 5.2 METHODS

### Study Population

Data comes from uConnect, a longitudinal study of YMSM ages 16-29 who reside in Chicago, conducted from 2013-2016.[29-32] Respondent Driven Sampling (RDS) was used for recruitment. RDS seeds were selected from a distribution of social spaces that YBMSM occupy (both physical spaces and virtual spaces such as Facebook). Eligibility criteria included: 1) self-identification as African American or Black, 2) born male, 3) between 16 and 29 years of age (inclusive), 4) report of oral or anal sex with a male within the past 24 months 5), willing and

able to provide informed consent at the time of the study visit, 6) Primary residence in South Chicago, the most populous contiguous Black community in the U.S.[29] Respondents were given up to six vouchers to recruit others they know who they have frequent contact with who fit the eligibility criteria. Each respondent was given $60 for participation and $20 for each recruit successfully enrolled into the study. Respondents were administered a behavioral questionnaire and tested for HIV and HIV RNA at each study period. Respondents were evaluated every 9 months for 18-month period (3 study visits total). The Institutional Review Board at the University of Chicago and the National Opinion Research Center at the University of Chicago approved all procedures.

**Laboratory Testing**

HIV infection was determined by three assays applied to samples eluted from dry blood spot samples: ARCHITECT HIV Ag/Ab Combo; Multispot HIV-1/HIV-2 Bio-Rad; and Realtime HIV-1 RNA, Abbot. In cases where test data were missing at the study visit, available HIV viral load and serostatus surveillance data were used from the Health Department. We obtained a Release of Information from each respondent to obtain these data.

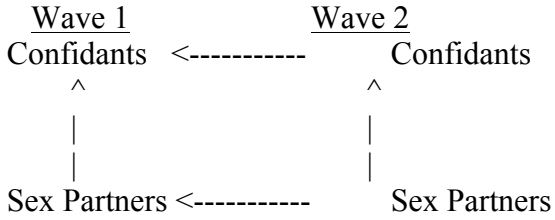
**Network Generation and Construction**

Social Network Data Collection

A set of name-generating and interpreter (descriptor) questions was used at each study visit to collect data on participants' social and sexual networks as described previously.[32] In brief, participants were asked to list up to five confidants with whom they "discuss things that are important to you." Participants were asked to provide demographic information on each, such as first name, last name, nickname, gender (male, female, transgender), age, education, employment status, ethnicity (Hispanic or not), and race. Participants were also asked to list their

(up to) five most recent sexual partners in the past six months. After providing this list, respondents were further prompted with a question asking if they were in a relationship with someone they consider their main sexual partner. If they listed someone and that person was not listed initially, this person was added as a sixth sexual partner. The same demographic information was collected for sex partners. At their first visit, participants were asked if any of their sex partners were the same as persons listed as confidants and matches were recorded. The same name generators were used in each wave. Verification of matches between network partners differed slightly between waves. At their wave 2 visit, after generating their list of confidants, participants were asked if the confidants listed were the same as any of their confidants named in wave 1. Later when they generated the list of their most recent sex partners, they were asked if any of these corresponded to confidants they had just named and if any were the same as any of their sex partners named at their previous visit. It should be noted that the respondent was *not* asked to compare their confidants with sex partners from Wave 1 nor were they asked to compare their sex partners in Wave 2 with the confidants from Wave 1. (See diagram)

**Comparisons of alter lists between network generators and interviews**




A similar procedure was used in Wave 3, except that the confirmation list was cumulative. For example, respondents in Wave 3 were asked whether any of the confidants listed corresponded to a combined list of confidants and sex partners from the previous

interview. And in Wave 3, similarly respondents were asked whether the sex partners listed corresponded to a cumulative list of the confidants and sex partners from the current and previous interview waves. Matches were recorded.

Construction of Matched Network

A multiple step process combining computerized scoring and manual verification was used to construct a de-duplicated network of all respondents and social and sexual network partners across all three waves. The first step was to run a computer program on the initial list of 8,522 respondents, social, and sexual network partners listed and described in all interviews to create a file information on and a "matched score" for pairs of nodes. The score was based on and ordered by information on the following: phoneticized last name, phoneticized first name, phoneticized nickname, age, gender, and race (defined as Black/African American versus not Black/African American due to the sample being predominately Black/African American).

The file produced at this step contained all pairs with scores that met a threshold that allowed us to consider them potential matches as well as their demographic information. This list was compared with and updated to include missing pairs based on a list of all matches that had been reported by respondents (i.e. confidants who were also sex partners, or either confidants or sex partners who appeared in multiple waves from one respondent) resulting in a file with 205,127 pairs.

Two independent coders then independently reviewed and scored the composite list of paired nodes. The reviewers manually scored each pair on a 4-point scale from 3 indicating that they were "extremely confident that it is the same person" to 0 indicating that they were "extremely confident that it is not the same person". Senior research staff reviewed the file with the manual scores to resolve any discrepancies. After an initial pass to resolve coder differences,

a computer program was run to verify that matched pairs were transitive and to add missing pairs to achieve transitive sets of pairs (i.e., if A matched B and B matched C, if a match between A and C was missing it was generated, etc.) Comparisons with a score of 3 were considered to be a "match" (the same person). A new set of unique IDs was created for all nodes with matched nodes receiving the same the ID. An edge (tie) list was created for all Egos (respondents) and Alters (social and sexual network partners) based on the new unique IDs. The complete network was generated and checked for coherence (e.g., respondents being matched). This allowed us to identify a small number of incorrect matches which were then removed and the renumbering with unique IDs was redone. This resulted in 5,994 unique IDs for the original list of 8,522 nodes from all the interviews.

**Analytic Plan**

**Measures**

The outcome of interest was network stability measured by the effective size bridging metric developed by Ronald Burt.[65] Effective size can be conceptualized as the number of, "non-redundant contacts in an individual's network."[65] In other words, it measures the number of disconnected groups that an individual connects as depicted by **figure 5**. The ego in **figure 5** has 8 network connections, but 4 of them know each other and are hence redundant. The effective size in this figure is therefore 4. Higher effective size indicates more bridging. Effective size was dichotomized at the median due the shortage of information on its distribution among this population.

The primary independent variables of interest were exposure to community violence, economic hardship indicators, and criminal justice involvement. Exposure to community violence was assessed using the Lifetime Exposure to Violence Probe at baseline and Wave 3.[75]

The probe consisted of seven items that assess the level of exposure to witnessing or being a victim of community violence. Each item was on a 7-point scale, ranging from 0 (never) to 6 (6 or more times). A continuous measure of the total violent exposures experienced was used in the multivariate analysis. Criminal justice involvement was defined as having ever previously been detained, arrested, or spent time in jail or prison. We also assessed how many separate occasions respondents had been detained, arrested, or spent time in jail or prison. These measures were collected at all three waves. Finally, social economic hardship was assessed by summing responses captured on two items, unstable housing in the past year [Yes/No] and a question assessing how often in the past 6 months there was not enough money in the household for rent, food, or utilities [Ever/Never]. The items in the index were strongly associated with each other and with the outcome. Overall index scores ranged from 0 to 2, with higher scores indicating more economic hardship.

Resilience measures included: 1.) The level of emotional support received from a mother figure and/or father figure [Very supportive/<Very supportive], feeling close to the gay community and/or close to the Black community [Very close/< Very close], and the importance of religion in the respondent's life [Very important/<Very important].

Other measures included: 1.) Non-injection drug use or alcohol use during sex (drugs included marijuana, MDMA, volatile nitrates, cocaine, heroin, psychoactive drugs, methamphetamines, and prescription pain killers). Sex-drug use was a dichotomous measure indicating use of any of the aforementioned substances in the previous year before or during sex; 2.) Condomless anal sex in the past 6 months; 3.) Number of male/transgender anal sex partners in the past 6 months; 4.) Transactional sex in the previous year, defined as paying or receiving pay for sex [yes/no]; 5.) Participation in group sex in the past year [yes/no]; 6.) Other

demographics and social characteristics. Injection drug use was not included in the model due to its low prevalence in the sample. Analyses excluded seeds that did not recruit other respondents (n=27).

**Statistical Analysis**

The outcome A longitudinal logistic Generalized Estimating Equations (GEE) model with an unstructured correlation structure was conducted to assess the relationship between network stability and social-environment factors, and network stability and HIV risk factors over time. Separate models were run to assess the relationship between the two constructs (social environment and HIV risk) and network stability. Variables significant at the $p \leq 0.1$ level in bivariate analysis were considered in the multivariable model. All variables retained in the final model were significant at the $p \leq 0.05$ level. Gile's Sequential Sampling (SS) estimators were used to weight our sample to enable probabilistic inference as a result of the RDS recruitment methodology.[77] All regression analyses were conducted using Stata version 14.[41]

**5.3 RESULTS**

Our sample included 65 seeds that generated a baseline sample of 618 respondents. Only productive seeds (n=38), defined as seeds that recruited at least one participant, were included in the analyses. The total sample size after this exclusion was 591. The follow-up rate for Wave 2 was 522 (88%) and the follow-up rate for Wave 3 was 505 (85%). At baseline, the mean age of the participants was 23 (range 16-29), 100% were Black/African-American, 34 (7%) had less than a high school degree, 389 (66%) and 163 (28%) identified as gay and bisexual respectively, 318 (55%) had health care coverage, 124 (25%) faced housing instability in the past year, 254 (43%) did not have enough resources to fulfill basic needs, and 273 (46%) had ever experienced criminal justice involvement. The HIV prevalence in the sample was 31% (n=195), and 52% of

those infected were virally suppressed (**table 3).**

The mean network size was 5.3 (SD 2.3) at baseline and 4.9 (SD 2) at both Waves 2 and 3. Respondents retained an average of 1.40 (SD 1.23) network members between baseline and Wave 2, and 1.14 (SD 1.05) between Wave 2 and Wave 3. The mean effective size was 4.9 (SD 2.17) at baseline and decreased by an average of 0.21 (SD 2.9) over the entire study period. Rates of community violence exposure can be found in **figure 6**. Overall, the mean total exposure to violence was 16 (SD 13) and the most common exposure was having a close friend or family member robbed or attacked (86%). Approximately 62% had at least 1 close friend or family member die violently. The most common resilience factor was having a mother figure who is very emotionally supportive 364 (68%).

After controlling for age and social economic hardship in the logistic GEE models assessing bridging and HIV risk (**table 4**), bridging was positively associated with multiple anal sex partners (OR 5.22; 95% CI 3.32-8.23), condomless sex (OR 1.57; 95% CI 1.19-2.06), group sex (OR 3.20; 95% CI 2.09-4.89), transactional sex (OR 4.35; 95% CI 2.32-8.17), and using drugs or alcohol during sex (OR 1.89; 95% CI 1.37-2.61).

In the logistic GEE model assessing social-environment factors and bridging (**table 5**), we found that after controlling for age and all other factors in the model, the outcome of being in a bridge position was positively associated with total community violence exposures (OR 2.70; 95% CI 1.14-6.40), having a sexual dating application account (OR 2.27; 95% CI 1.54-3.35), and experiencing both unstable housing and having insufficient resources combined (OR 1.75; 95% CI 1.02-2.99). Bridging was inversely associated with having an emotionally supportive mother figure (OR 0.64; 95% CI 0.43-0.96). In a sub-analysis of the HIV seropositive respondents, we found that having a sexual dating application account (OR 2.54; 95% CI 1.31-4.94), and

experiencing both unstable housing and having insufficient resources combined (OR 3.21; 95% CI 1.06-9.67) were positively associated with bridging after controlling for age. We also found an interaction between viral suppression and having an emotionally supportive mother figure (**figure 7**). For those who are virally suppressed, having an emotionally supportive mother figure was not associated with being a bridge (OR 1.07; 95% CI 0.46-2.53). However, for those who are not virally suppressed, having an emotionally supportive mother figure was inversely associated with being a bridge (OR 0.26; 95% CI 0.09-0.77).

**5.4 DISCUSSION**

We found that being in a bridge position (having an unstable network) was positively associated with both adverse social-environment factors and HIV risk, indicating that network stability may be on the explanatory pathway between social-environment factors and HIV risk. The odds of having multiple anal sex partners, condomless sex, group sex, transactional sex, and using drugs or alcohol during sex were all higher among those with high bridge scores versus those with a low bridge scores after controlling for age and economic hardship. Similarly, those with high bridge scores were more likely to experience unstable housing, community violence, and have limited economic resources compared to those with low bridge scores.

In addition, we found that having an emotionally supportive mother figure may be protective in terms of HIV risk as it was inversely related to bridge status, and that this relationship is particularly important for those who are HIV-seropositive and not virally suppressed. Having an emotionally supportive mother figure was also inversely associated with odds of repeated involvement with the criminal justice system and sex drug use (data not show). These findings indicate that engaging family members in HIV interventions may be worthwhile with regard to HIV prevent efforts.

The high rates of exposure to community violence coupled with its association with increased odds of bridging shed light on the increased need for violence prevention resources geared towards sexual minorities. In addition, our rates of exposure to violence are likely underestimated because they do not capture exposure to police brutality or inter-partner violence. Future studies should collect these data and assess the impact of varying types of violence exposure to better inform intervention.

Our study is limited in that much of the data are self-report, including the elicited network members. Thus, there could be concern about missing data within the network. However, network data are rarely complete,[47] and our rigorous network matching methodology allowed us to link individuals who did not elicit one another, increasing the completeness of the network. Another question about our analysis is whether the commonly used bridging metric, constraint,[64] should be used instead of effective size to designate network stability. Constraint also calculates redundancy, but there are assumptions about the intensity of the relationships between people.[64] We re-ran all analyses with constraint as an outcome and got very similar findings to the models using effective size. However, we feel that effective size is more intuitive by definition and therefore more useful for disseminating our findings to non-network audiences.

Despite these limitations, this study is the first to assess network stability as a mechanism to explain the association between the social environment and HIV risk. Engaging those with high exposure to community violence and high rates of social economic hardship may be an effective way to reach people who are HIV positive due to the network stability association found in this paper coupled with the association between bridging and HIV positivity established elsewhere.

**ACKNOWLEDGEMENTS**

We would like to thank the uConnect study participants for the time they contributed to this study. We would also like to thank staff for the collection of the data as well as Stuart Michaels, Phil Schumm, Lindsay E. Young, Ethan Morgan, Aditya Khanna, and Nicola Lancki for their contributions. This work received funding from the National Institutes of Health grants R01 DA039934, R01 DA033875, T32 HS000084 as well as the University of Chicago, Biological Sciences Division, Office of Diversity & Inclusion. The funding sources did not have involvement in the development of this work.

**Figures**

**Figure 4. Example of network stability pathway concept**

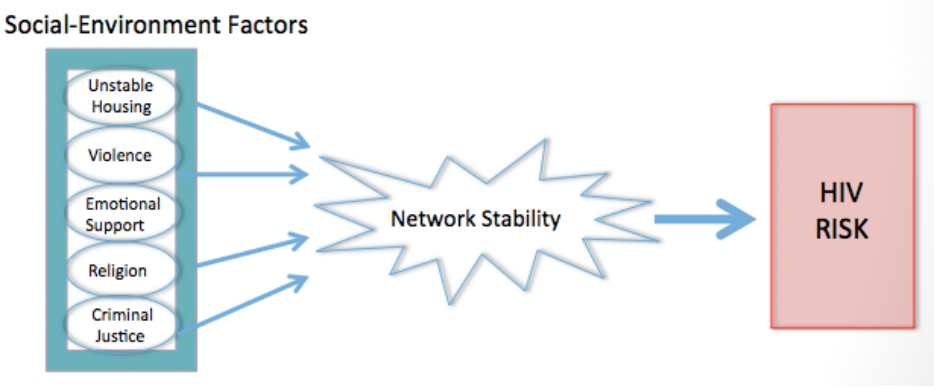



**Figure 5. Example of Effective Size Calculation (Effective Size=4)**

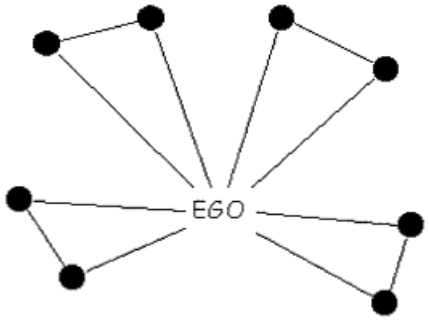



Figure 2. Adapted from Figure 1.1B of Burt (1992:17).

**Figure 6. Cumulative Community Violence Exposure (n=505)**

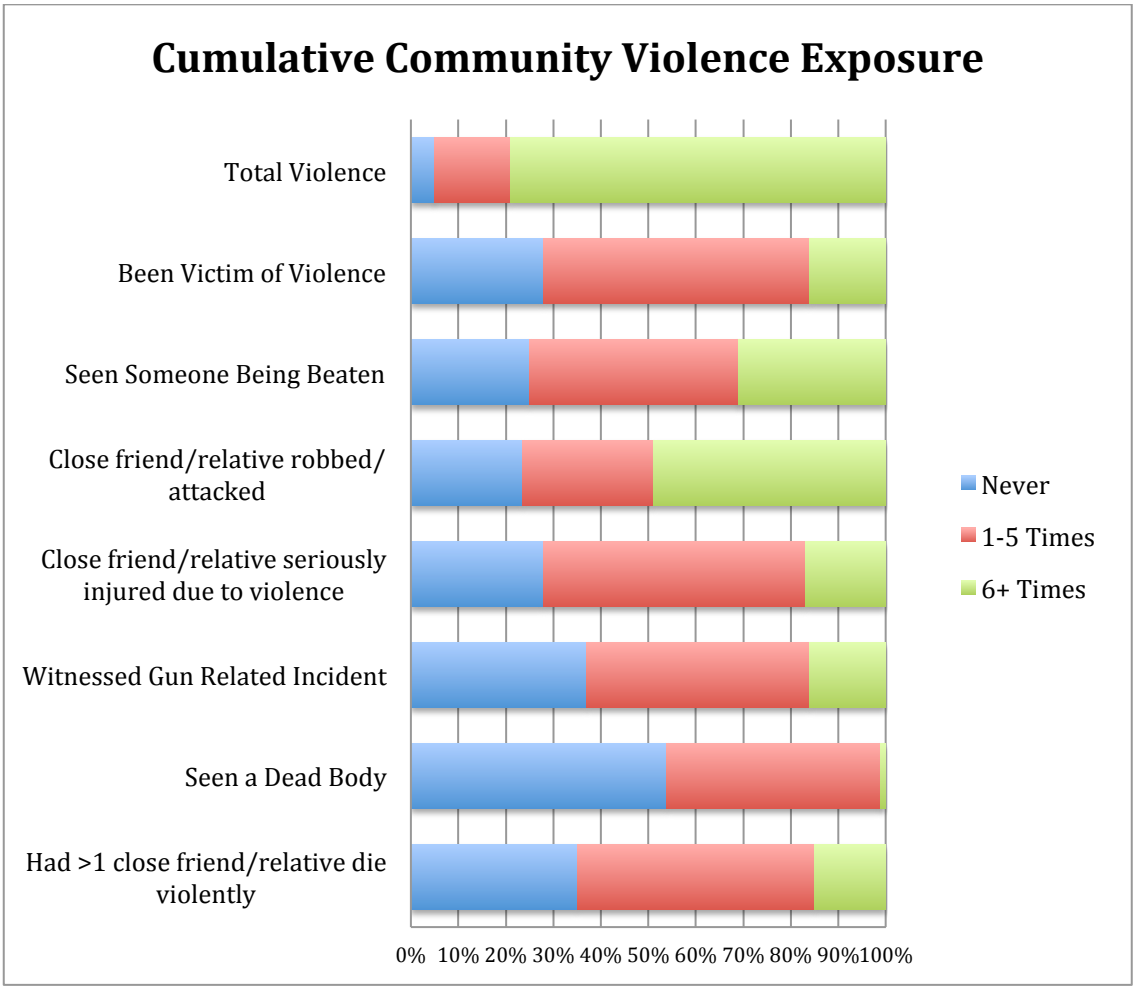
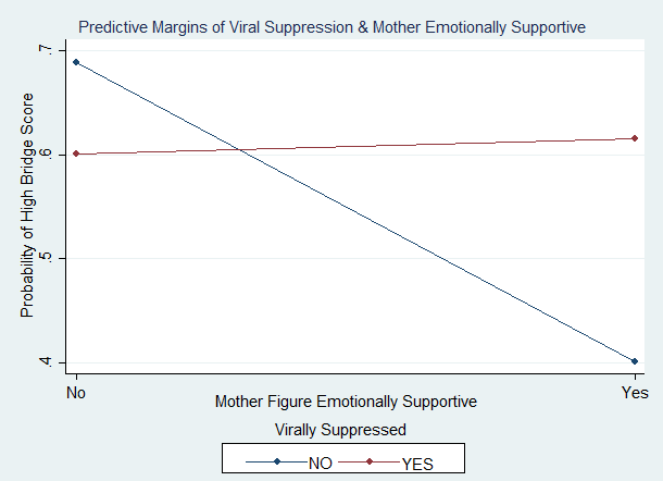



**Figure 7. Predictive Margins of Viral Suppression & Mother Emotional Support**



**Tables**

| **Table 3. Baseline demographics, behavioral characteristics, and HIV serostatus, uConnect (n=591)** | | |
|---|---|---|
| | Unweighted | Weighted |
| | **n (%)** | **(%)** |
| **Age at interview, median (IQR)** | 23 (20,25) | - |
| **Health care coverage** | | |
| Yes | 318 (55) | 55% |
| **Sexual Orientation** | | |
| Gay | 389 (66) | 66% |
| Bisexual | 163 (28) | 28% |
| Straight | 22 (4) | 4% |
| **Unstably housed (previous year)** | | |
| Yes | 124 (25) | 25% |
| **Not enough resources for basic needs (previous 6 months)** | | |
| Very Often | 254 (43) | 43% |
| **Criminal justice involvement in lifetime**[a] | | |
| Yes | 273 (46) | 46% |
| **# Criminal justice exposures** | | |
| 1 | 104 (39) | 39% |
| 2 | 59 (22) | 22% |
| 3+ | 107 (39) | 39% |
| **Have Father Figure** | | |
| Yes | 369 (62) | 63% |
| **Have Mother Figure** | | |
| Yes | 534 (90) | 90% |
| **Mother figure emotionally supportive** | | |
| Yes | 364(68) | 68% |
| **Father figure emotionally supportive** | | |
| Yes | 167 (46) | 46% |
| **Feel close to Gay community** | | |
| Yes | 130 (22) | 22% |
| **Feel close to Black community** | | |
| Yes | 275 (47) | 47% |
| **Feel religion is important** | | |

| Table 3. Baseline demographics, behavioral characteristics, and HIV serostatus, uConnect (n=591) Cont. | | |
|---|---|---|
| Yes | 296 (50) | 50% |
| **Sex drug use (previous year)** | | |
| Yes | 142 (24) | 24% |
| **Transactional sex (previous year)** | | |
| Yes | 68 (12) | 12% |
| **Group sex (previous year)** | | |
| Yes | 118 (20) | 20% |
| **Number of male sex partners (previous 6 months) (median, IQR)[b]** | 2 (1,3) | - |
| **Any condomless male sex partners (previous 6 months)** | 288 (49) | 49% |
| **HIV Serostatus** | | |
| Positive | 196 (41) | 41% |
| **Suppressed viral load[c]** | | |
| Yes | 95 (52) | 52% |
| [a]Includes jail/parole<br>[b]% among those with CJI<br>[c]Obtained from network elicitation<br>[d]% among HIV+ aware | | |

| Table 4. Associations between bridge position and HIV risk factors among uConnect participants in Chicago, 2013-2015 | | | | | | |
|---|---|---|---|---|---|---|
| | **Unadjusted OR** | | | **Adjusted OR[b]** | | |
| | N=591 | | | n=591 | | |
| | OR | 95% C.I. | p-value | OR | 95% C.I. | p-value |
| **Condomless anal sex (previous 6 months)** | 1.61 | 1.23-2.09 | 0.001 | 1.57 | 1.19-2.06 | 0.001 |
| **≥2 male/transgender partners (previous 6 months)** | 5.21 | 3.36-8.07 | <0.001 | 5.22 | 3.32-8.23 | <0.001 |
| **Transactional Sex** | 4.68 | 2.51-8.72 | <0.001 | 4.35 | 2.32-8.17 | <0.001 |
| **Sex Drug Use** | 1.93 | 1.40-2.64 | <0.001 | 1.89 | 1.37-2.61 | <0.001 |
| **Any Group Sex** | 3.33 | 2.19-5.06 | <0.001 | 3.20 | 2.09-4.89 | <0.001 |
| **STI Diagnosis** | 1.31 | 0.87-1.97 | 0.19 | 1.27 | 0.85-1.89 | 0.24 |
| OR indicates Odds Ratio, C.I. indicates Confidence Interval<br>[b]Adjusted for age and SES index | | | | | | |

| Table 5. Multivariable Logistic Regression assessing bridging and social-environmental factors | | | | |
|---|---|---|---|---|
| | **Total (n=540)** | | **HIV+ (n=211)** | |
| | OR | 95% C.I. | OR | 95% C.I. |
| **Total community violence exposures** | **2.70** | **1.14-6.40** | 4.46 | 0.96-20.61 |
| **Age** | 1.01 | 0.95-1.08 | 1.07 | 0.97-1.18 |
| **Has sexual dating application account** | **2.27** | **1.54-3.35** | **2.54** | **1.31-4.94** |
| **Economic Hardship Scale** | | | | |
| 0 | Ref. | | | |
| 1 | 1.28 | 0.88-1.88 | 1.01 | 0.53-1.92 |
| 2 | **1.75** | **1.02-2.99** | **3.21** | **1.06-9.67** |
| **Virally suppressed** | - | - | | |
| **Mother emotionally supportive** | **0.64** | **0.43-0.96** | 1.07 | 0.46-2.53 |
| **Not virally suppressed** | - | - | | |
| **Mother emotionally supportive** | - | | **0.26** | **0.09-0.77** |
| ***Interaction p-value*** | | | | **0.04** |

OR indicates Odds Ratio, C.I. indicates Confidence Interval
All ORs adjusted for income and variables present in the table

## 6.AIM 3: Social network based HIV testing: a cost-effective strategy for locating people with undiagnosed HIV infection?

### 6.1 BACKGROUND

Approximately 18.1% of people living with HIV are unaware of their infection, and an estimated 49% of HIV transmissions occur from individuals who are unaware of their infection.[79] In 2006, the Centers for Disease Control and Prevention (CDC) made a recommendation to include routine HIV screening as a part of regular medical care. Routine screening has been shown to be cost-effective from a societal perspective (all costs and effects are incorporated no matter who pays the costs or receives the effects[80]), increasing life

expectancy by an average of 5.48 days (4.70 quality adjusted days) at $194 per screened patient.[81] However, little data exists on the real-world costs of broadly implementing routine screening programs, or on how the costs of routine screening programs compare to the real-world costs of alternative screening strategies.

Although the United States (U.S.) continues to experience new HIV diagnoses, the number of new HIV diagnoses has remained stable at around 50,000 cases per year.[81] In 2011, the CDC established a, "High-Impact HIV Prevention" approach to reducing HIV infection in response to limited HIV prevention resources. This approach considers five factors in determining whether an intervention should be considered high-impact. Two of these considerations are effectiveness and cost as well as the feasibility of full-scale implementation.[82] Recently, the CDC has promoted the Social Network Strategy (SNS) as an effective HIV testing intervention. This strategy identifies HIV positive individuals and individuals who are at-risk for acquiring HIV and asks them to recruit their social network for testing in exchange for an incentive. Pilot data have found SNS to be effective in terms of finding new diagnoses. These data show that 6% of those tested through SNS were newly identified HIV infections, which is five times the prevalence found via publicly funded counseling, testing, and referral sites.[83] However, data on the costs of broadly implementing the SNS strategy are limited. A recent cost-utility analysis of HIV testing programs among Men who have Sex with Men (MSM) in the United States had mixed findings about the cost-effectiveness of SNS strategies with only half of the SNS sites showing the strategy to be cost saving.[84]

The goal of this AIM, therefore, is to expand on the pilot findings of the SNS by specifically recruiting and testing the risk networks of individuals who were recently infected with HIV. Individuals who recently acquired HIV (within the past year) are more likely to

transmit the disease to others if they remain untreated due to heightened viral load during this time.[7] Preliminary data show that this approach yields a higher proportion of newly diagnosed HIV infections than traditional voluntary counseling and testing (VCT) in Chicago. Therefore, this paper compares the cost and effectiveness of testing through the risk networks of individuals recently infected or diagnosed with HIV to testing through an integrated routine HIV screening program on Chicago's south side in the identification of new HIV infections. If proven effective, this intervention would be considered, "high-impact" and could potentially be implemented on a large scale.

## 6.2 METHODS

### Data

### Social Network Strategy

TRIP is a longitudinal network intervention that identifies recently HIV-infected persons using a combination of testing history and viral load. Contact tracing was used for recruitment. Seeds include those recently infected with HIV (in the previous 9 months) in addition to two sets of controls: those who are recently diagnosed with HIV (diagnosed in the previous 9 months, but not recently infected) and those who are HIV negative. Network and venue members of those recently infected and those who are recently diagnosed are recruited. All respondents were at least 18 years of age. Each respondent was given $10 for the time required for the testing component of the baseline survey and $20 for each successful recruit enrolled into the study. Only the baseline sample was considered for this analysis. Testing occurred between September 13, 2013 and February 29, 2016. Blood samples were tested by AxSYM HIV-1/2 gO (Abbott) and confirmed by Western Blot (MP Diagnostics).

### Expanded Testing

X-TLC is a large-scale, multi-site HIV screening program for populations disproportionately affected by HIV-infection on the south side of Chicago. Testing occurred between February 1, 2011 and December 31, 2013 among 27 sites, which included outpatient clinics, emergency departments, and hospitals. However, for comparability purposes, we have focused on one site, the Academic Medical Center (AMC). Consent for HIV testing was obtained through opt-in oral consent which was prompted by reminders in the electronic medical record system. Test technologies included standard third-generation blood-based enzyme immunoassay and confirmatory Western blot or fourth-generation HIV testing with Multispot confirmation.

A cost-effectiveness analysis was conducted utilizing an ingredients-based approach (where each cost component is identified and assigned a cost value) comparing social network based HIV testing via TRIP to an integrated routine HIV screening via X-TLC. Ingredients included training, HIV testing, labor, materials, and facility costs. A list of costs and assumptions can be found in **table 6**.

**Analysis**

Cost per new HIV diagnosis was calculated and compared to a cost-saving threshold. We determined the cost-saving threshold for the cost per new HIV diagnosis by estimating the value of the gain in life expectancy that results from early identification of HIV. Sanders et al. estimate that early identification of HIV for an individual 30 years of age increases overall life expectancy by just over 1.8 years, and quality adjusted life expectancy by 1.52 years.[80] We derived a dollar value per QALY from a literature review by Hirth et al. that combined estimates from several valuation methodologies (human capital, contingent valuation, revealed preference/job risk, and revealed preference/non-occupational safety).[86] The median value of a QALY derived from the Hirth analysis was $385,133.80 after conversion to 2013 dollars.[86] Therefore, we valued of the

overall increase in life expectancy to be $693,240. We valued of a quality-adjusted increase in life expectancy to be $585,403 per HIV diagnosis.[80, 86]

A decision tree analysis model (a graphical depiction of decisions, probabilities, outcomes, and their associated costs) was also conducted comparing the two interventions with each other and to the cost of not screening for HIV. HIV prevalence rates for the decision tree analysis were set to the HIV prevalence rate on the south side of Chicago for the no screening arm and the HIV prevalence rates found in each of the screening programs for the expanded testing (0.5%) and the social network (25%) arms. Benefits in the HIV positive arm of each program were determined by subtracting the cost of the program from the value of the gain in life expectancy. Costs in the HIV negative arm were defined as the cost of the program. Costs in the HIV positive arm of the "no screening" option were defined as the cost of not receiving a gain in life expectancy. There was no cost associated with the HIV negative arm of the "no screening" option.

**6.3 RESULTS**

Demographics for each study can be found in **table 7**. Network testing participants were primarily Black/African-American (91%), male (84%), and under the age of 30 (median age 26, IQR 23-31). Demographics for the expanded testing program were only available for 73% of the tested population. Of those with demographic information, most were Black/African-American (75%), male (64%), and over the age of 30 (median age 32, IQR 24-47). The expanded testing program completed 30,438 HIV tests over the study period, which resulted in 167 (0.5%) HIV positive tests and 78 new HIV diagnoses (0.3%). The social network strategy completed 172 HIV tests over the study period, which resulted in 79 (46%) HIV positive tests and 8 new HIV diagnoses (5%). After removing the initial respondents, the HIV prevalence estimate was 25%

for network testing. The 25% prevalence rate excludes those who were selected to start the network recruitment chains because we identified them based upon their HIV status.

The overall cost breakdown for each program can be seen in **figure 8** and **table 8**. The overall cost for the expanded testing program was $835,088.21, with tests (44%) and labor (33%) accounting for the bulk of the total costs. The overall cost for the network-testing program was $489,322.97, with labor accounting for 72% of the total costs. Therefore, the estimated cost per new HIV diagnosis for the expanded testing program was $10,706.26 and the estimated cost per new HIV diagnosis for the network-testing program was $61,165.37, deeming both as cost-effective when compared to a threshold of $585,403-$693,240 per additional life-year gained.

The decision tree analysis showed that after considering the HIV prevalence in each arm, the cost of each program, and the added value assigned to the increase in life expectancy, the network-testing program provided the most value overall. The net value was $170,474 for network testing, $3,438 for expanded testing (**figure 9**).

**Sensitivity Analysis**

The value of each program is heavily dependent upon both the HIV prevalence in the population and the value assigned to the additional life-years gained. Therefore, a sensitivity analysis was conducted varying both of these factors. We conducted a two-way sensitivity analysis varying the prevalence of HIV for the expanded testing program from 0% to 40% and the value of additional life years gained from $0 to $1 million. We chose to vary the prevalence for the expanded testing program because it is currently much lower than the prevalence on the south side of Chicago (where the AMC is located) at 0.5% versus 0.65%.[9] The expanded testing program is currently opt-in. If it changes to opt-out we would expect to find a higher HIV prevalence rate. Likewise, network-testing programs engage populations with high prevalence

rates in order to find those who are otherwise hard to reach within the at risk population. Therefore, the prevalence will typically be higher and more predictable in network testing settings than in expanded testing settings. Finally, the dollar value assigned to a QALY has received much criticism. Our sensitivity analysis accounted for most estimates provided in the literature.[86] Other cost components were also varied, but did not have an impact on the results given the influence of HIV prevalence and the value assigned to the gain in life expectancy (data not shown). The results of the sensitivity analysis are shown in **figure 10**. We found that XTLC is rarely a better option when assigning any value to an additional life-year unless the HIV prevalence of XTLC approaches the HIV prevalence in TRIP. For instance, when an additional life-year is valued at $250,000, TRIP is the more beneficial choice until the HIV prevalence in XTLC exceeds 20%.

**6.4 DISCUSSION**

Our analyses showed that both the expanded testing and social network strategies are worthwhile when compared to a threshold of $585,403-$693,240 per additional life-year gained, and that the network testing strategy is the more effective strategy when considering both the HIV prevalence in the population and therefore the overall benefit of life-years gained as a result of detecting HIV infections.

We recognize there are alternative methods for determining a cost-effective threshold. A recent analysis by Zullinger et al. estimates the societal cost of the implementation of a program using the equation, C=AT, where ‘‘C’’ is the societal cost of implementation, ‘‘A’’ is the number of HIV infections averted, and ‘‘T’’ is the lifetime treatment cost of one HIV infection.[6] The number of infections averted is calculated by multiplying the total number of new HIV diagnoses in each strategy by the estimated difference in the transmission rate among those unaware of

their HIV status and those aware. The transmission rates were determined defined by the percentage of individuals expected to be at each stage of the HIV care cascade.[85,89,91]

We repeated this analysis for comparison purposes for both of our HIV screening programs. Since the network-based study is comprised primarily of Young Black Men who have Sex with Men (YBMSM), we determined the number of infections averted for our program by using the frequencies at each step of the HIV care cascade among YBMSM established by Morgan et al.[91] The number of infections averted for the expanded testing program was determined by HIV care cascade rates for the overall HIV positive population, as established by Skarbinski et al.[90] The transmission rate for those unaware of their HIV status is 7.3 per 100 HIV infected persons for MSM[87] and 6.6 per 100 persons for the general HIV positive population.[82]

Morgan et al. estimate that approximately 20% of YBMSM are unaware of their HIV infection. Of those who are aware, 45% are not retained in care, 24% are retained but are not virally suppressed, and 31% are retained and virally suppressed.[91] The transmission rate for those aware of their status in the network studies therefore was 3.00 (45% x 5.3 + 24% x 2.1 + 31% x 0.4) per 100 person years.[11, 12] This yields a rate of 0.043 (7.3-3.00)/100)) HIV transmissions averted per HIV diagnosis. Skarbinski et al. estimate that approximately 20% of the general HIV positive population is unaware of their HIV infection. Of those who are aware, 55% are not retained in care, 14% are retained but are not virally suppressed, and 31% are retained and virally suppressed.[91] The transmission rate for those aware of their status in the expanded testing program therefore was 3.33 (55% x 5.3 + 14% x 2.1 + 31% x 0.4) which yields a rate of HIV transmissions averted of 0.032 (6.6-3.33)/100)) per HIV diagnosis.

The discounted lifetime cost to treat an HIV infection (T) was as determined by in 2001 dollars was US $402,238, which assumes CD4 at diagnosis to be 501-900 cells/mL and 32.1 year

life-expectancy of 38 years. We used these parameters because they are relevant with Treatment as Prevention guidelines,[92] and appropriate for our primarily young population in the network study. In 2013 dollars, this cost translates to $475,050. Therefore, a program will be considered cost saving if the cost per new diagnosis is less than $20,427 for the network testing programs and less than $15,202 for the expanded testing program. Using just this calculation, neither of our programs would be considered cost effective. However, this calculation does not consider the overall prevalence in the population, so we feel that our analysis captures societal costs more accurately.

Our study is limited in that it may not be completely generalizable due to the assumptions made which allowed us to compare a service based intervention to a research based intervention. However, we enumerated costs in a way that others could evaluate site-specific costs associated with implementation. This analysis is also limited in that it does not incorporate all economic perspectives. Future analyses will work to integrate these perspectives and compare additional strategies. Despite this limitation, our analysis is likely an underestimate of the total benefit received from both HIV screening programs because it does not evaluate the effect of re-engaging those lost to HIV care. As stated above, only 45% of YBSMSM who are aware of their HIV status are retained in care and only 31% are virally suppressed. Poor retention is both detrimental to those HIV positive and to preventing future transmission. Future studies should evaluate the cost-effectiveness of HIV retentions interventions.

Future studies should also conduct additional sensitivity analyses that assess treatment costs and productivity gains associated with effective HIV treatment. The results of this analysis demonstrate that different strategies may be more or less effective depending upon the phase of the epidemic. A hybrid approach that consists of routine screening in combination with network

testing may be the most effective approach at identifying new HIV infections.

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**Figures**

**Figure 8: Breakdown of costs per HIV screening program**

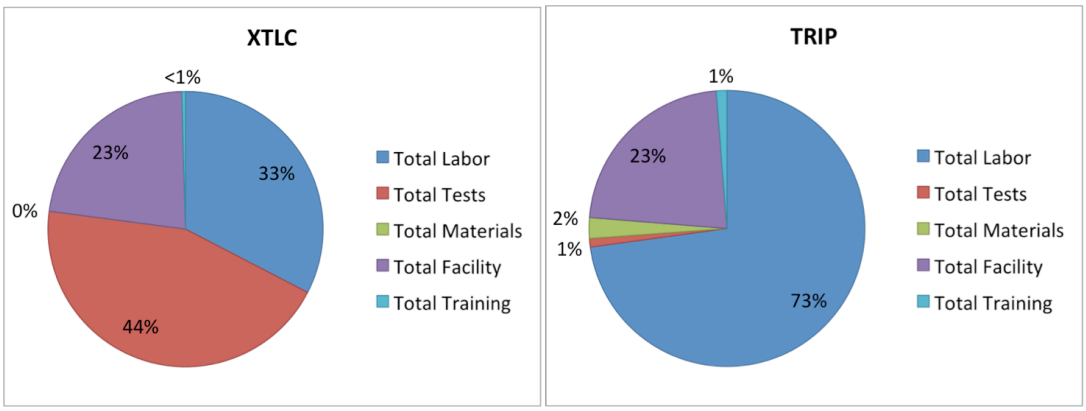



**Figure 9: Decision tree analysis of HIV screening programs vs. no screening**

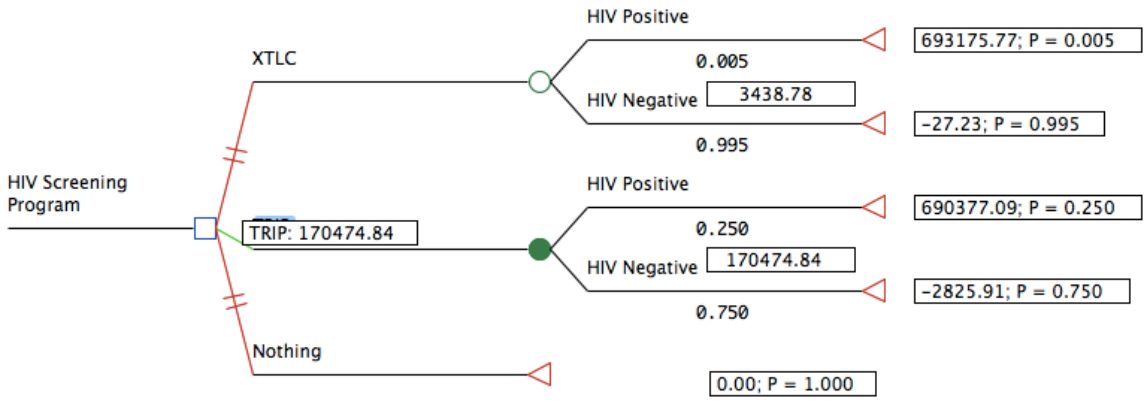
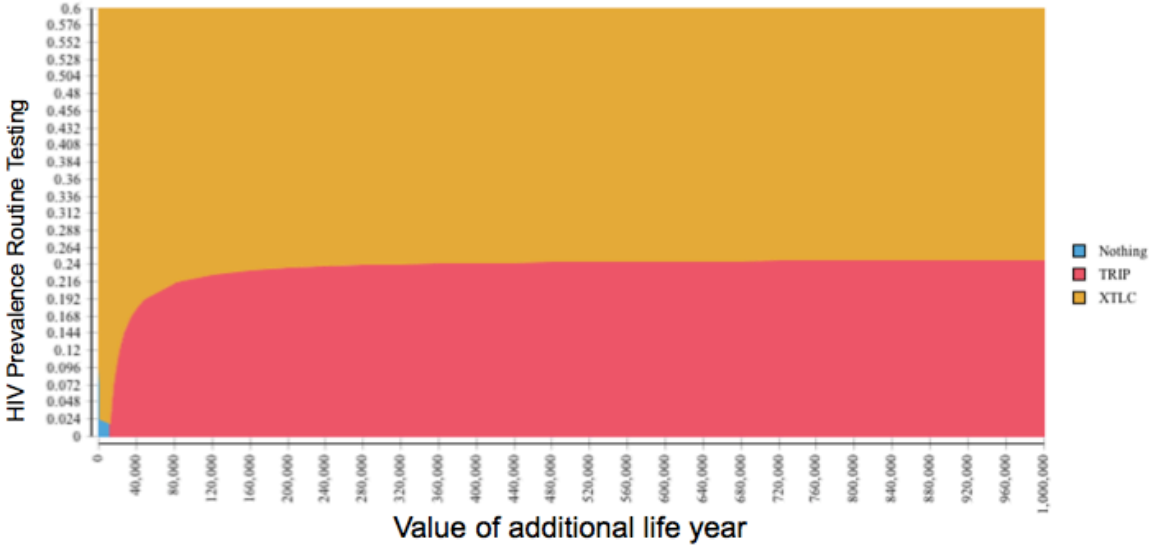


**Figure 10: Sensitivity analysis varying the value of life-years gained & XTLC HIV Prevalence**




## Tables

| Table 6. Input Variables and Assumptions | |
|---|---|
| **Variable** | **Assumption** |
| Labor | Occupational salaries were standardized across sites using data from the Bureau of Labor Statistics [14] |
| Materials* | Incentives were $10 for test time, $20 for network referrals |
| Tests | Testing costs were standardized across sites at $12 per ELISA and $37 per Western Blot, assuming 100% uninsured |
| Facility | We used an indirect rate of 29% as applied by service grants. |

| Table 7. Demographics by HIV Screening Strategy | | |
|---|---|---|
| | **TRIP (n=172)** | **X-TLC (n=22,226)*** |
| **Age (Median, IQR)** | 26 (23,31) | 32 (24,47) |
| **Race/Ethnicity** | | |
| Black/African American | 157 (91%) | 15,021 (75%) |
| White | 3 (2%) | 4097 (20%) |
| Other | 12 (7%) | 1063 (5%) |
| **Gender** | | |
| Male | 144 (84%) | 14,235 (64%) |
| Female | 22 (13%) | 7,987 (36%) |
| Transgender | 5 (3%) | |
| *Of those with demographic information | | |

| Table 8. Total program costs, HIV testing results, and cost analysis results | | |
|---|---|---|
| | **TRIP** | **X-TLC** |
| **HIV Testing** | | |
| # Tested | 172 | 30438 |
| # HIV Positive | 79 | 167 |
| # Newly Diagnosed | 8 | 78 |
| **Costs** | | |
| **HIV Testing Costs** | $4,987.00 | $371,435.00 |
| **Labor Costs** | $353,858.03 | $272,264.56 |
| **Training Costs** | $4,987.00 | $3655.64 |
| **Materials Costs** | $12,141.00 | - |
| **Facility Costs** | $112,131.17 | $187,733.01 |
| **Total Program Cost** | $489,322.97 | $835,088.21 |

## 7. CONCLUSION

This dissertation demonstrates the utility of social network analysis in advancing both epidemiologic methods and as a tool for HIV elimination. All three chapters shed light on the influence of networks on individual behaviors and disease acquisition. AIM 1 shows how personal networks can be used to engage and identify individuals at risk for HIV acquisition, AIM 2 links social-environment factors to network composition, and AIM 3 demontrates the effectiveness of using networks as a recruitment strategy for identifying new HIV infections.

While these findings highlight the effectiveness of social network analysis, there are challenges in the fullscale implementation of social network interventions. As noted in AIM 1, health department databases need to be updated and linked to one another in order to calculate metrics. This is an arduous task, but possible given the increasing electronic medical record infastructure.[49] Likewise, as elucidated in AIM 3, network interventions can be very resource intensive, especially in terms of labor. Both of these challenges can be mitigated through public health department and academic partnerships. These partnerships would be benefical through their use of shared skills and resources as well as their ability to span the reach of interventions by engaging those not in touch with the public health system. Despite these challenges, the

findings from all of these AIMs reveal that they are a factor that we cannot ignore in the context of health.

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