THE UNIVERSITY OF CHICAGO

SOCIAL, MOLECULAR, AND HIV TRANSMISSION NETWORKS: A SOCIOMOLECULAR APPROACH TOWARD HIV PREVENTION

A DISSERTATION SUBMITTED TO THE FACULTY OF THE DIVISION OF THE BIOLOGICAL SCIENCES AND THE PRITZKER SCHOOL OF MEDICINE IN CANDIDACY FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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DEDICATION

To my husband, Michael.

For all your love and support.

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ABSTRACT

Determining how network-level factors influence individual risk of human immunodeficiency virus (HIV) acquisition is vital in preventing disease transmission. Debate remains as to how risk of HIV acquisition is affected given one's network composition of those recently infected with HIV or those with long-term HIV infection, but who are not virally suppressed. Additionally, phylogenetic analysis can be utilized to build molecular networks and identify clusters of HIV transmission by determining similarities among HIV genetic sequences from persons infected with HIV. In this dissertation work social and sexual network data were combined with HIV molecular network data: 1) to determine characteristics associated with both membership in an HIV molecular cluster and the number of clustered sequences within these clusters; 2) to examine whether new HIV seroconversions occurring among young Black men who have sex with men (YBMSM) are proximal to either recently or long-term HIV infected individuals; and 3) to examine potential overlap and to ascertain the benefits of combining these types of analyses.

A cohort of YBMSM (N = 618) was generated through respondent driven sampling with survey data collected across three waves from 2013 through 2016. Dried blood spots were obtained at each wave and were assessed for HIV seropositivity and/or acute HIV infection using 4^{th} generation HIV immunoassay, HIV-1/-2 Ab differentiation, and HIV RNA testing. Chicago Department of Public Health (CDPH) HIV surveillance data was utilized to determine date of HIV diagnosis in combination with survey data. Pairwise genetic distances of HIV-1 *pol* sequences were used to identify potential molecular ties among HIV-infected persons whose sequences were $\leq 2.0\%$ genetically distant. Putative molecular clusters were defined as ≥ 1

connection to another individual. We then determined demographic and risk attributes associated with both membership in an HIV molecular cluster and the number of ties to other persons within the cluster. RDS-weighted Cox and logistic regressions were utilized to examine proximity of HIV transmission events to other recent or long-term HIV infected individuals in the risk network. Finally, confidant, sexual, and Facebook® network data were matched between named partners across all three waves utilizing a computer algorithm with all matches confirmed manually by two separate analysts.

An absence of tie overlap was observed between the molecular network and first, second and third degree confidant network as well as the molecular network and first, second and third degree sexual network. We did, however, find that of the 15 individuals with both molecular and Facebook© data available, 3 (25.0%) of the 12 network ties overlapped between the two networks. We also found a consistent 45-50% overlap of network ties between the social, sexual, and Facebook© networks.

Across all waves, 266 (43.0%) participants were identified as HIV-positive with 139 identified as having an undectecable viral load. Of the remaining HIV-positive individuals, we successfully sequenced the *pol* region of the viral genome for 42 (30.2%) individuals. We obtained a further 44 viral sequences from CDPH HIV surveillance data for a total of 86 (61.9%) available sequences., Thirty-five (40.7%) of these sequences were tied to ≥1 other sequence with a total of 55 ties between all individuals. Through multivariable analyses, we determined that those who identified as straight and those who reported symptoms of depression were significantly less likely to be members of a molecular cluster. Additionally, as the number of confidants in a participant's social network increased, the odds of membership in a molecular cluster decreased significantly. We also found that those who identified as straight, had stable

housing, and reported less frequent marijuana use had significantly fewer ties to other individuals' sequences in molecular clusters.

Within the cohort, 343 (55.5%) participants were identified as HIV seronegative at baseline. Of these, 33 (9.6%) seroconverted during the study period. We found that the odds of seroconversion increased significantly with each additional recently HIV infected individual in one's network (AOR = 12.96; 95% CI: 5.69-29.50). The number of long-term infected individuals in one's network did not significantly alter odds of seroconversion. We also found that for each additional member of one's network who used PrEP, the odds of seroconversion decreased significantly, adjusting for overall network size as well as the number of HIV-negative individuals in one's network (AOR = 0.44; 95% CI: 0.20-0.96).

This work presented in this dissertation demonstrates the potential for combining molecular, social, and other individual and network attributes in a sociomolecular approach to target HIV control efforts to persons with potentially higher transmission risk. This work also suggests some unappreciated specific predictors of transmission risk among YBSM in Chicago for future study. An increase in the number of recently HIV infected individuals in one's network was associated with an increased rate of seroconversion and the odds of seroconversion are significantly reduced by an increase in the number of network members who use PrEP. Limited overlap was also observed between reported social network ties and molecular ties in this young MSM population, suggesting that transmissions may have occurred in networks that existed more than six months ago (limited by the recall period) before the observed networks.

Increasing the social network cluster size by two and three degrees only marginally improved overlap between reported social and molecular network ties. Virtual network data, such as Facebook, may be particularly useful in developing a more complete picture of one's risk

environment and identify	most at risk comm	unity members not o	observed in phylogenetic
networks.			

CHAPTER 1

INTRODUCTION AND MOTIVATION

Nationally, young black men who have sex with men (YBMSM) are at high risk for human immunodeficiency virus (HIV) infection. In the United States, the rate of new HIV diagnoses varies widely by gender, race, and transmission group. Both black men (1 in 20) and Hispanic men (1 in 48) experience a higher lifetime risk of HIV infection compared to white men (1 in 132)¹ while men who have sex with men (MSM) (1 in 6) experience higher HIV infection rates than both heterosexual men (1 in 473) and women (1 in 241).¹ HIV infection rates among MSM are higher across all race categories and follow the same pattern of disparity: 1 in 2 for black MSM, 1 in 4 for Hispanic MSM, and 1 in 11 for white MSM.¹ Among younger MSM, those aged 13-24, young black MSM (YBMSM) account for twice as many new HIV infections as young white or Hispanic/Latino MSM.²

Compared with national rates, rates of HIV infection are higher in Chicago. In the United States, the rate of new HIV diagnoses is 15.0 cases/100,000 persons.³ Two-thirds of new diagnoses occur among MSM, and during 2010-2014 that proportion has been increasing.³ Comparatively, the burden of HIV in Chicago is more severe.⁴ In 2013, the rate of new HIV diagnoses was 2.5 times that of the United States overall. However, since 2009, a decline has occurred in new diagnoses among all risk categories except MSM, who have experienced a 5 % increase in new diagnoses.⁴

Geography is also a key factor in HIV risk and transmission. According to American Community Survey estimates,⁵ demographic characteristics vary widely across Chicago's 200 neighborhoods. The neighborhoods on the North side of Chicago are majority white, with some exceeding 80 % of the population, although certain neighborhoods, particularly those on the far

North side, have a diverse population of blacks, whites, and Hispanics. The neighborhoods located on the South side are majority black with most of these exceeding 80 % of the population. Those located on the West side of the city are divided between majority black and majority Hispanic populations, although few neighborhoods have a single racial/ethnic group exceeding 80 % of the population. The South and West side neighborhoods experience the highest percentage of households below the poverty line and the lowest per-capita income. Neighborhoods with high HIV diagnosis rates are located throughout Chicago and, in 2014, include Edgewater (North, 100 cases/100,000 persons), Uptown (North, 132/100,000), West Garfield Park (West, 100/100,000), Washington Park (South, 98/100,000) and Pullman (South, 89/100,000).

Previous studies have been conducted to examine and understand HIV transmission dynamics and the associated characteristics of persons identified as potential transmission partners because they have highly similar HIV strains.⁷ Results from these analyses can highlight differences in transmission between subtypes,⁸ over time,⁹ and by presence of drug resistance.¹⁰ These methods also can be used to assess differences across geographic regions¹¹ and to understand the characteristics of persons in social clusters.¹² Still other studies have reported that these types of analyses can be used to understand to what extent transmission occurs between demographic or risk groups.^{7,13} Perhaps most importantly, molecular network data can be used to prioritize interventions to disrupt transmission and ultimately to control outbreaks of infectious diseases,^{14,15} including HIV.

Prior work has shown that, compared to young white or Hispanic MSM, YBMSM are more likely to be present in molecular clusters¹⁶ in Chicago and are more likely to have a higher degree of connectivity within those clusters.¹⁷ Young black MSM, however, exhibit fewer risk

taking behaviors and use fewer illicit substances than their white counterparts yet have higher rates of HIV transmission, ^{18,19} making social network analyses (SNA) potentially important for developing novel intervention strategies. Past research has focused on sexual contact networks; however, data related to sexual contacts and behavior are often missing and are subject to information biases. Social network data are typically more complete and reliable than sexual network data. Social contacts may become sexual partners and vice versa, particularly among MSM. Prior research has not examined the dynamics of social and sexual networks, particularly among YBMSM.⁷

Social network analysis (SNA) is an important method for studying risk among YBMSM. It can be used to characterize social network size or composition, social relationships between network members, and the influence of both on health outcomes. At the most basic level networks are described via nodes, the individual members of the network, and the ties, or the relationships between persons that connect them. While social network data is still likely to contain missing ties between persons (which can be modeled), it is less susceptible to the same sensitive data collection issues as those observed in sexual contact networks. Importantly, social networks have been shown to overlap with sexual networks, ²⁰ making them particularly useful for assessing social context, the influence of social context on behavior, and network formation among high risk populations. ²¹ Past research has combined sexual contact network analyses with molecular networks²⁰; however, little work has characterized how social networks themselves may be related to or overlap with molecular networks, a gap which will be filled by the work proposed in this dissertation.

The work presented in this dissertation combines molecular network analyses and social network analyses to better understand the dynamics of HIV transmission among YBMSM. Prior

research has also shown a necessity for including network factors²² in successful HIV interventions. The work presented here describes and assesses local, inferred HIV molecular networks among YBMSM (Chapter 3), examines the interrelation of molecular and social network analyses and presents novel methods for the expansion of partner services (Chapter 4), and investigates characteristics of persons who become HIV-positive (Chapter 5). These analyses and results have the potential to drive public policy and disrupt forward transmission of HIV through a greater understand of how HIV moves through networks of YBMSM.

CHAPTER 2

uCONNECT DATA

Setting and Population

uConnect is a longitudinal population-based cohort study^{23,24} which aims to examine factors associated with HIV risk and transmission within a socially diverse sample of young Black men who have sex with men (YBMSM) within South Chicago and adjacent south suburbs, the largest contiguous Black community area in the United States⁵. In 2011, BMSM accounted for 39% of newly-diagnosed HIV infections in the United States despite representing only 0.2% of the overall population²⁵. Further, young MSM in Chicago have experienced a 5% increase in the number of new HIV diagnoses since 2009, compared to a decline across all other risk categories across the city⁴.

Eligibility Criteria

Study respondents were eligible to participate if they 1) self-identified as African American or Black, 2) were born male, 3) were between 16 and 29 years of age (inclusive), 4) reported oral or anal sex with a male within the past 24 months, 5) were residing on the South side of Chicago, and 6) were willing and able to provide informed consent at the time of the study visit.

RESPONDENT DRIVEN SAMPLING

Respondent Driven Sampling (RDS) is a widely used approach that provides a design for sampling using seeds and subsequent recruits, and a methodology for estimating statistical properties of the target population²⁶. These strengths of RDS have prompted its wide use in public health studies, especially when populations are stigmatized or not accessible through

traditional rosters^{26–29}. Inference from RDS data requires strong assumptions to treat the sampling scheme as probabilistic, and may be biased due to a number of underlying assumptions, which are discussed in detail elsewhere^{23,24}. Methodological research to improve estimation of parameters and standard errors from RDS studies has received much recent attention^{30–33}.

Recent recommendations for estimation of population parameters from RDS data include an estimator that treats the RDS recruitment process as a successive sampling (SS) process when the size of the population is known or can be reliably estimated^{34,35}. Previously, the population of YBMSM in South Chicago was estimated to be 5500³⁶. To assess the sensitivity of our results to this estimator, we compared our results with weights generated by another commonly used estimator³³.

Implementation of RDS Sampling

The implementation of respondent driven sampling began by purposively selecting a diverse set of YBMSM to serve as initial respondents or seeds. The research team gathered a group of twenty community partners to help with identifying potential seeds. A meeting was convened with the community partners in May 2013 to explain the goals and importance of the study and to ask attendees to invite up to three eligible candidates who were social in the community and likely to bring others into the study. Table 1 summarizes the main types of methods and venues from which our team members and partners were recruited, including sources of seeds. Our goal was to recruit a diverse group of seeds who would be interested and willing to participate in the study and who would be able to recruit others like themselves. Ten seeds were recruited via connections to the House/Ball Community. Most of the rest of the seeds

were recruited via avenues that were less specific, e.g., via web sites, Facebook postings, community events, college campuses etc. for a total of 62 seeds.

Table 1. Sources of seeds

	Productive Seeds, $n(\%)$	All Seeds, <i>n</i> (%)
Source	(n=37)	(n=62)
FQHC HIV Clinic	10 (27.0)	17 (27.4)
YMSM CBO for HIV Prevention	6 (16.2)	12 (19.4)
Direct Community Contact - unaffiliated	6 (16.2)	7 (11.3)
House/Ball Weekly Meeting Group	4 (10.8)	5 (8.1)
BMSM CBO	3 (8.1)	4 (6.5)
Facebook	3 (8.1)	4 (6.5)
Website	2 (5.4)	5 (8.1)
Ball Community Member - unaffiliated	1 (2.7)	5 (8.1)
HIV Support Group	1 (2.7)	1 (1.6)
College	0 (0.0)	1 (1.6)
Unknown	1 (2.7)	1 (1.6)

Each participant was invited and given instructions about recruiting other eligible MSM they knew using six coupons with unique ID numbers. The distribution of successful referrals were 0 (6.4%), 1 (44.3%), 2 (24.4%), 3 (15.1%), 4 (5.9%), 5 (2.5%) and 6 (1.4%). This was repeated for each new participant whether they were a seed or a sprout. Each respondent, seed and recruit, were offered \$60 for their participation in the interview and were told they would receive an additional \$20 for each recruit who participated. Sensitivity analyses that excluded

referrals of 4, 5 and 6 did not change our main findings. In addition, in our primary analysis we included all seeds because there is no current consensus as to whether seeds should be included or excluded from analyses (1, 2). The ratio of seeds to recruits of approximately 10% is consistent with other RDS samples of YBMSM (3). Our main findings were robust and did not change when analyses included all seeds, productive seeds, or no seeds.

Computation of Finite Population Correction

If the sample size is denoted as n, and the population size is denoted by N, then sampling fraction in our population is 618/5500=11.2%. Our sampling process was also without replacement, and with such a large proportion of the population being sampled, we need a finite population correction, to treat our sampling scheme as without replacement.

This correction implies that the multiplicative scale factor for the variance of our parameter estimates is 1-(618/5500) = 0.888. Since we treat each seed as a separate cluster, the number of clusters is 62. The scale factor is computed as 1-sample.psu/population.psu, where sample.psu = 62. Therefore population.psu = 556.

We therefore compute the finite population correction as 1-62/556 = 0.888 (Thomas Lumley, personal communication).

Sensitivity Analyses

Substituting the VH weights for the Gile's SS weights did not change the significance of any of the variables in our multivariate models for the full population and the HIV-positive, unaware subsample (data not shown). The odds ratios changed by less than 5% for each (data not

shown). In the full sample, the complete-case analysis ignored observations in varying numbers due to missing data at each level of the continuum of care. Additionally, excluding non-productive seeds from our analysis did not change our final results (data not shown).

UCONNECT MATCHING METHODOLOGY

Social Network Data Collection

A set of name-generating and interpreter (descriptor) questions were used at each study visit to collect data on participants' social and sexual networks as described previously (cite network science paper). 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 with 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 (Figure 1).

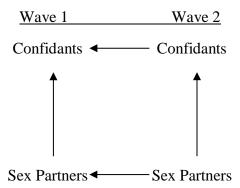


Figure 1. Comparisons of alter lists between network generators and interviews

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. 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 with 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 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 were 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.

SURVEY INSTRUMENT

Interview

Between August 2013 and July of 2014, YBMSM were recruited in Chicago using respondent-driven sampling (RDS) All interviews were conducted using Computer Aided Personal Interviewing (CAPI). Some sections of the interview were self-administered. Measures were assessed for background and socio-demographic factors, self-reported substance use, HIV care continuum measures (e.g. linkage to care, retention in care, adherence to antiretroviral mediation, etc.), and HIV status.

A multi-disciplinary team of medical, public health and social science researchers with expertise in HIV research and prevention, social networks, survey research, sexuality, and community violence in minority communities worked for over a year developing the survey design and instrument. The questionnaire covered demographic and background information, family life, Black and MSM community involvement, sex and sex-drug risk/reduction practices, exposure to violence and the criminal justice system, STI/HIV testing and treatment, social

media use, and numerous self-administered scales including depression, knowledge and attitudes toward safe sex and risk. During this period, pilot interviews and cognitive testing of questions was conducted by the Survey Research Lab at the University of Chicago.

Additional covariates measured

Additional covariates measured include: education, employment, housing instability, insurance status, alcohol use, other substance use, and depression. Education was defined as less than high school education, completed high school education, some college education, Associate's degree, Bachelor's degree, and Master's degree. Employment status was defined as currently working full-time (> 30 hours/week), part-time (< 30 hours/week), or unemployed. Housing instability was defined as self-reported homeless status in the past twelve months. Insurance status was defined as currently having health insurance coverage or currently having no coverage. Alcohol use was defined as never, one to two per year, one to two per month, or one to two per week/everyday over the course of the participant's lifetime. Finally, depression was analyzed using the Brief Symptom Inventory 18-question survey (BSI-18), a self-report measure of psychological symptoms over the previous week. Raw scores for the BSI-18 were converted to T-scores and defined as present if the T-score was greater than 62.

CHAPTER 3

DETERMINANTS OF HIV PHYLOGENETIC CLUSTERING IN CHICAGO AMONG YOUNG BLACK MEN WHO HAVE SEX WITH MEN FROM THE UCONNECT COHORT

ABSTRACT

Phylogenetic analysis determines similarities among HIV genetic sequences from persons infected with HIV, identifying clusters of transmission. We determined characteristics associated with both membership in an HIV molecular cluster and the number of clustered sequences among a cohort of young black men who have sex with men (YBMSM) in Chicago.

Pairwise genetic distances of HIV-1 *pol* sequences were collected during 2013–2016. Potential molecular ties were identified among HIV-infected persons whose sequences were $\leq 1.5\%$ genetically distant. Putative molecular pairs were defined as ≥ 1 tie to another sequence. We then determined demographic and risk attributes associated with both membership in an HIV molecular cluster and the number of ties to the sequences from other persons in the cluster.

Of 86 available sequences, 31 (36.0%) were tied to ≥1 other sequence. Through multivariable analyses, we determined that those who reported symptoms of depression and those who had a higher number of confidants in their network had significantly decreased odds of membership in molecular clusters. We found that those who had unstable housing and who reported heavy marijuana use had significantly more ties to other individuals within molecular clusters, while those identifying as bisexual, those participating in group sex and those with higher numbers of sexual network members had significantly fewer ties.

This study demonstrates the potential for combining phylogenetic and individual and network attributes to target HIV control efforts to persons with potentially higher transmission risk, as well as suggesting some unappreciated specific predictors of transmission risk among YBSM in Chicago for future study.

INTRODUCTION

Phylogenetic analysis can be used to determine similarities between genetic sequences of persons infected with HIV.³⁷ Highly similar viral strains can then be combined with epidemiologic data to identify an inferred molecular network for a particular population.^{15,38}

Results from these analyses can be used to assess demographic or risk characteristics associated with membership in a molecular cluster¹⁶ and number of connections to other individuals within the cluster.¹⁷ Results from these analyses can also highlight differences in transmission by geographic location,^{13,17} infection subtype,⁸ and drug type resistance.¹⁰ Phylogenetic analysis and molecular network analyses are key to targeted interventions and controlling the outbreak of infectious diseases,^{14,15} including HIV.

Previous studies have examined characteristics that are associated with having highly similar HIV strains, termed membership in a molecular cluster. 7.16,17,39 These studies, however, have focused primarily on differences by geography 7.16,17 or basic demographic characteristics. 39 Findings have demonstrated that young, Black, MSM (YBMSM) are those most likely to be members of an HIV molecular cluster in Chicago and are also more likely to be in larger HIV molecular clusters. To appropriately target and disrupt transmission of HIV among YBMSM, especially given the high incidence of HIV among YBMSM, it is necessary to examine specific demographic and risk characteristics which are associated with molecular network membership and size. Understanding these specific characteristics associated with HIV transmission among YBMSM will inform intervention strategies and guide public health department HIV prevention policy.

We examined HIV Type 1 (hereafter referred to simply as HIV) *pol* sequences collected between 2013-2016 from study participants in Chicago, Illinois. From those data, we ascertained the molecular transmission network, identified clusters, and determined the network degree among these clusters. We then determined characteristics associated with both membership in a molecular cluster and the number of persons within each cluster.

METHODS

The setting and population have been described in detail in Chapter 2. Briefly, uConnect is a longitudinal population-based cohort study^{24,40} which was designed to assess factors associated with HIV risk and transmission among a sample of YBMSM. uConnect participants resided mainly in South Chicago and the adjacent southern suburbs, which represents the largest contiguous Black community area in the United States.⁵

Eligibility Criteria — Study respondents were eligible to participate if they 1) self-identified as African American or Black, 2) were assigned male at birth, 3) were between 16 and 29 years of age (inclusive), 4) reported oral or anal sex with a male within the past 24 months, 5) spent the majority of their time on the South side of Chicago, and 6) were willing and able to provide informed consent at the time of the study visit.

Interview – Recruitment utilizing respondent driven sampling and survey follow-up occurred between August 2013 and January of 2016. Surveys were conducted across three waves of study, each separated by nine months. Interviews were conducted using Computer Aided Personal Interviewing (CAPI) with some portions self-administered. The interview itself involved different types of questions and activities: background and socio-demographic

questions, self-administered scales of substance use, and HIV care continuum measures. We developed a matching algorithm to create the social network among respondents in the uConnect network. At each uConnect wave, respondents were asked detailed information regarding their sexual partners and confidants, including name, age, geographic residence and other sociodemographics, if known. These data provided by respondents were then matched across all waves to identify unobserved ties which may exist as a result of different respondents naming the same individual as a network member. The algorithm used to complete the matching process was verified by two separate analysts with all matches confirmed manually, and has been described in detail elsewhere. 41

Molecular Network Inference

Dried blood spots were collected as a portion of each participant's survey at each wave. Each participant's HIV infection status (including acute infection) was determined by 4th generation HIV immunoassay (Abbott ARCHITECT HIV Ag/Ab Combo assay), HIV-1/-2 Ab differentiation (Bio-Rad Multispot HIV-1/-2 Rapid Test) and viral load testing (Abbott ReaLTime HIV-1 assay) applied to samples eluted from dry blood spots (DBS).⁴² HIV *pol* sequences were obtained from all persons whose viral load was ≥2000 copies/mL, the allowable limit for elution from dried blood spots. Specific procedures describing extraction of cell-associated HIV DNA from dried blood spots and HIV *pol* amplicon sequencing, including number of base pairs analyzed and primers used, have been previously described.⁴³ For participants whose viral sequences were unable to be determined, we obtained sequences (if available) collected through routine surveillance by the Chicago Department of Public Health

(CDPH). All participants whose data was accessed through CDPH provided a release of information to obtain any available sequences or HIV related test results.

All available genetic sequences were aligned to the HXB2 reference sequence using MUSCLE (MUltiple Sequence Comparison by Log-Expectation, European Bioinformatics Institute) multiple sequence alignment⁴⁴ in the MEGA v7.0 (Molecular Evolutionary Genetics Analysis) software package.⁴⁵ Phylogenetic tree analyses were performed by using the neighborjoining method,⁴⁶ with distance calculated by TN93⁴⁷ analysis. One sequence was obtained from each participant. Each individual is referred to as a node. A potential molecular transmission event was defined as having a genetic distance $\leq 1.5\%$ between *pol* sequences, and referred to as a tie. It should be noted that phylogenetic analyses cannot define which of those with similar sequences was transmitter versus recipient, or if transmission was indirect via an unidentified individual rather than directly between those with similar sequences. A cluster was defined as ≥ 2 persons linked by ≥ 1 tie. All cluster visualizations were performed by using NodeXL v1.0.1.340 (Social Media Research Foundation).⁴⁸

Dependent variables

We utilized two main outcomes in our analysis: 1) membership in a molecular cluster and 2) number of connections within the cluster, referred to as molecular network degree. Cluster membership was a dichotomous measure indicating membership in an HIV molecular cluster. The network degree, or number of connections, within the cluster was defined as the number of ties each individual had to other individuals in the molecular cluster (e.g. one individual tied to three other individuals would have a value of three).

Independent variables

Sexual identity was categorized as gay, bisexual, or straight/other. The following variables were utilized as dichotomous measures: 1) self-reported possession of health coverage at the time of interview, 2) currently a student, 3) housing instability ("In the past 12 months, have you been homeless at anytime? By homeless, I mean you were living on the street, in a shelter, a Single Room Occupancy hotel (SRO), temporarily staying with friends or relatives, or living in a car?")at any point in the previous 12 months, 4) presence of depressive symptoms (measured using the Brief Symptom Inventory 18-question survey⁴⁹), 5) group sex, and 6) condomless sex. Condomless sex and group sex were defined as at least once instance of each in the past 12 months. Drug use was defined as any use in the past 12 months; due to the high usage of marijuana in this population, use of marijuana was separately categorized as never, intermittent use (up to and including several times per week), and heavy use (at least once per day). All other drugs were combined into a single variable (including ecstasy/molly/E, poppers, crack/cocaine, heroin, psychedelics, methamphetamines, or prescription drugs).

Sexual network degree, confidant network degree, and total (combined sexual and social) network degree were determined using the full matched data across all three waves. In each type of network, network degree was utilized as a continuous variable. Confidants were asked as, "Please list the names of the people with whom you discuss things that are important to you." Number of sexual partners was asked as "How many people, including men, women, and transgender women have you had sexual activity with, even if only one time?"

Participants were asked a series of questions which would allow for the construction of both a sexual and confidant network. Participants were asked "Thinking back over the past six

months, that is since MONTH, how many people, including men, women, and transgender women have you had sexual activity with, even if only one time" and "So I can ask some follow-up question, please list the names of the people with whom you discuss things that are important to you", to elicit number of sexual partners and confidants, respectively. For sexual partners, participants were asked identifying information and a series of questions regarding their relationship and risk behaviors with each partner. For confidants, participants were asked identifying information and a series of questions regarding their relationship with up to five confidants.

Statistical Analyses

Association of all variables with both membership in a cluster and molecular network degree within the cluster were first analyzed by using unadjusted logistic and Poisson regressions, respectively. RDS-weighted multivariable logistic and Poisson regressions were then used to estimate the association between all variables with membership in a molecular cluster and the molecular network degree as the dependent variables. All covariates identified as statistically significant at the $p \leq .05$ level, using Wald test statistic, were included in the multivariable regression model. Effect modification was assessed by using cross-products individually between sexual and social network degree and each of the covariates. All analyses were performed in Stata v14.0. 50

RESULTS

Sample characteristics

The final analytic sample included 266 HIV-positive participants, among which, 139 had an undectecable viral load. Of the remaining HIV-positive individuals, we successfully sequenced the *pol* region of the viral genome for 42 (30.2%) individuals. We obtained a further 44 viral sequences from CDPH HIV surveillance data for a total of 86 (61.9%) available sequences. There were no differences in sociodemographics or risk behaviors between participants who did, and did not, have a sequence available (not shown). Characteristics of those with sequence data are presented in Table 2, and are stratified by presence in a molecular cluster. The majority of participants with sequence data did not have health insurance (42, 48.8%), had low income (72, 83.7%), self-identified as gay (59, 68.7%), and reported condomless sex in the past 12 months (49, 57.0%).

Figure 2 depicts the HIV molecular clusters identified by phylogenetic analysis in the study sample. Among participants with available viral sequences, 31 (36.0%) were determined to be members of a molecular cluster. Connections between nodes represented an inferred HIV transmission as determined by phylogenetic analysis of the *pol* region with a maximum genetic distance of 1.5% (0.015 nucleotide substitutions per site).

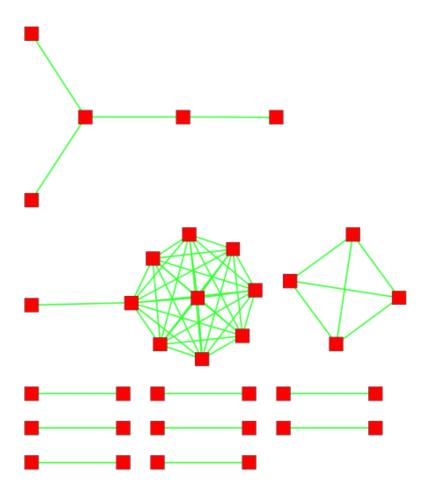


Figure 2. HIV transmission network among persons in clusters (n = 31, 40.7% of total persons with sequences) in the uConnect cohort. Connection between nodes represents an inferred transmission between persons, assessed through phylogenetic analysis of the *pol* region with a maximum genetic distance of 1.5% (0.015 nucleotide substitutions per site).

Table 2. Sample characteristics stratified by presence in a molecular cluster¹ among young Black MSM in Chicago, uConnect (N = 86)

				t in a		n a	р-
	Total		cluster ¹		cluster ¹		value ²
Characteristic	No.	%	No.	%	No.	%	
Total	86	100	55	64.0	31	36.0	-
Demographics , $n(\%)$							
Currently insured	42	48.8	29	52.7	13	41.9	0.336
Currently a student	24	27.9	15	27.3	9	29.0	0.956
Low income ³	72	83.7	45	83.3	27	90.0	0.403
Housing instability ⁴	28	32.6	16	29.1	12	40.0	0.306
Sexual identity							0.660
Gay	66	77.7	42	77.8	24	77.4	
Bisexual	14	16.5	8	14.8	6	19.4	
Straight or other	5	5.9	4	7.4	1	3.2	
Mental Health ⁵ , $n(\%)$							
Depressive Symptoms	11	12.8	9	16.4	2	6.5	0.186
Risk behaviors ⁴							
Condomless sex	49	57.0	33	60.0	16	51.6	0.451
Group sex	22	25.6	16	29.1	6	20.0	0.360
Drug use ⁴ , $n(\%)$							
Marijuana ⁶							0.956
Never	21	24.4	13	23.6	8	25.8	
Intermittent	30	34.9	19	34.6	11	35.5	
Heavy	35	40.7	23	41.8	12	38.7	
Other Substance Use ^{4,7}	23	26.7	16	29.1	7	22.6	0.513
Network degree							
measures, ⁸ mean (range)							
Confidant network ⁹	4.0	1–9	4.2	1–9	3.6	1–7	0.084
Sexual network	6.4	1–15	6.6	1–15	6.1	1–14	0.238

Abbreviations: MSM = men who have sex with men

 $^{^{1}}$ A cluster was defined as ≥ 2 persons whose pol sequences were <1.5% genetically distant

²Using chi-square analysis

³Defined as <\$20,000 per year

⁴In the past 12 months

⁵Using the Brief Symptom Inventory 18 (BSI-18)

⁶Intermittent use is defined marijuana use less than and including weekly use; heavy use is defined as at least once per day.

⁷Includes the use of ecstasy/molly/E, poppers, cocaine/crack, heroin, psychedelics, methamphetamines, prescription drugs

⁸Degree is defined as the number of ties each individual had to other individuals in the network (e.g. one individual tied to three other individuals would have a value of three)

 $^{^9}$ Confidants were defined as a close social contact, someone with whom the respondent would discuss things that are important to them

There were a total of 9 observed HIV molecular clusters with a total of 51 ties among all clustered individuals. The majority of members of molecular clusters were more likely to have low household income (27, 90.0%), to self-identify as gay (24, 77.4%), and to report at least once instance of condomless sex in the past 12 months (16, 51.6%). We also found that confidant network degree and HIV prevalence were significantly positively correlated (r = 0.12; p = 0.004). None of the characteristics of cluster members, however, differed significantly in unadjusted analyses from those who were not in clusters based on HIV sequence similarity (Table 2).

In contrast, RDS-weighted adjusted logistic and Poisson regression analyses revealed that compared to those who do not report symptoms of depression, those who reported symptoms of depression were significantly less likely to be members of a molecular cluster (AOR = 0.13; 95% CI: 0.02–0.69). Additionally, we found that each additional member of a participant's confidant network significantly decreased the odds of membership in a molecular cluster (AOR = 0.70; 95% CI: 0.50–0.98). Compared to those with stable housing, those without stable housing were significantly more likely to be members of a molecular cluster (AOR = 3.71; 95% CI: 1.08—12.78).

The RDS-weighted multivariable analyses also found associations with molecular network degree (Table 3). Those who reported housing instability had significantly more ties to other individuals in clusters (ARR = 1.95; 95% CI: 1.36–2.81), compared to those who have stable housing (Table 3) Compared to those who do not report low income, those who had low income had significantly fewer connections to other individuals in HIV molecular clusters (ARR = 0.56; 95% CI: 0.37—0.86). Participants who reported using marijuana heavily, compared to those who reported never using marijuana, had significantly more connections to other

individuals in molecular clusters (ARR = 1.96; 95% CI: 1.20–3.19). We also found that each additional member of a participant's sexual network significantly decreased the number of connects to other individuals (ARR = 0.91; 95% CI: 0.86–0.97).

Table 3. Adjusted RDS-weighted logistic and Poisson regression models of association of selected characteristics with both membership in a cluster¹ and molecular network degree ¹ among HIV diagnosed YBMSM with a known viral genetic sequence, uConnect (N = 86)

	Membership in a					
	cluster			of cluster		
Characteristic	AOR	95% CI	ARR	95% CI		
Sexual identity	_		_			
Gay	Ref	_	Ref	- 0.21—0.83		
Bisexual	0.48	0.10—2.18	0.10—2.18 0.41*			
Straight or Other	Empty	_	Empty	_		
Currently insured						
No	Ref	_	Ref	_		
Yes	0.79	0.23 - 2.70	1.02	0.49 - 2.11		
Currently a student						
No	Ref	_	Ref	_		
Yes	1.10	0.50-2.40	0.84	0.59 - 1.21		
Housing instability ²						
No	Ref	_	Ref	_		
Yes	3.71*	1.08-12.78	1.95**	1.36-2.81		
Low income						
\geq \$20,000 per year	Ref	_	Ref	_		
<\$20,000 per year	1.39	0.21-8.98	0.56**	0.37-0.86		
Depressive Symptoms ³						
No	Ref	_	Ref	_		
Yes	0.13*	0.02-0.69	0.49	0.13-1.80		
Group sex ²						
None	Ref	_	Ref	_		
≥1	1.91	0.33-11.06	0.54*	0.31-0.95		
Marijuana ^{2,4}						
Never	Ref	_	Ref	_		
Intermittent	1.86	0.41-8.44	1.20	0.59-2.44		
Heavy	1.95	0.42-9.00	1.96**	1.20-3.19		
Other Substance Use ^{2,5}						
None	Ref	_	Ref	_		
≥1 other drug	0.69	0.15-3.30	0.45	0.17—1.15		
Network degree						
Confidant network	0.70*	0.50-0.98	0.95	0.87—1.04		
Sexual network ⁶	0.97	0.81—1.17	0.91**	0.86—0.97		
Abbreviations: HIV – human immunodeficiency virus YRMSM – young black men who have sex with						

Abbreviations: HIV = human immunodeficiency virus, YBMSM = young black men who have sex with men, AOR = adjusted odds ratio, ARR = adjusted rate ratio, CI = confidence interval

Table 3 Continued.

 1 A cluster was defined as having ≥ 2 connected persons whose *pol* sequences were <1.5% genetically distant. Number of connections within a cluster were defined as the number of ties each individual had others in the cluster (e.g. an individual with three ties had a value of three).

²In the past 12 months

³Self-reported via the Brief Symptom Inventory 18-question survey

⁴Intermittent use is defined as anything less than and including weekly use; heavy use is defined as at least once per day.

⁵Includes the use of ecstasy/molly/E, poppers, crack/cocaine, heroin, psychedelics, methamphetamines, prescription drugs

⁶ Confidants were defined as a close social contact, someone with whom the respondent would discuss things that are important to them

^{*}p <0.05; **p <0.001

DISCUSSION

In this study, we present novel findings regarding characteristics which may influence the spread of HIV through networks of YBMSM. First, we find that nearly one-third of HIV-positive individuals with an available viral sequence in our sample were members of an HIV molecular cluster. Second, we find that having a greater number of confidants in one's network significantly reduces the odds of being in a molecular cluster. Third, we find that participants with symptoms of depression are significantly less likely to be members of molecular clusters. Finally, we find that both housing instability and heavy marijuana use significantly increase the number of connections to other individuals in a molecular cluster.

A higher number of confidants in one's network may reduce the risk of HIV transmission among YBMSM. Past studies have shown that social networks of HIV-positive black MSM exhibit a preponderance of family members and relatives.⁵¹ Additional work has shown that personal networks consisting of greater family network proportion are associated with lower rates of both sex-drug – that is drugs with are used to make sex easier, more enjoyable, or last longer— use and group sex.⁵² BMSM with greater support networks have also been shown to participate less in high-risk sexual behavior and to have a greater number of HIV tests in the previous past two years.⁵³ Further, greater social support has been associated with higher HIV care uptake and adherence to antiretroviral medications.⁵⁴ The findings presented in this study support past work suggesting that greater social support in one's network plays a protective role in the movement of HIV through molecular networks of YBMSM. Future work should be conducted to address factors which are more protective for persistently HIV-negative social and confidant network members.

Contrary to past findings, we found depression to be associated with a lower likelihood of being a member of a molecular cluster. Depression has previously been associated with an overall increase in participation in HIV risk behavior, 55–59 even given knowledge of one's HIV status. These behaviors include inconsistent condom use and a higher number of lifetime sexual partners 2,63; depression has also been associated with poor adherence to antiretroviral medications. Given past research, our findings of depression playing a "protective" role are a bit surprising; it is possible that our association may only be found in relation to HIV molecular clusters and not overall HIV risk. Additionally, our findings may be attributed to our use of the Brief Symptom Inventory 18-question survey (BSI-18), which only indicates the presence of depressive symptoms and does not identify level of depression. Further research is need to fully ascertain the relationship between HIV molecular clusters and depression.

Both housing instability and heavy marijuana are associated with a greater number of connection within HIV molecular clusters. Any marijuana use has previously been associated with participation in HIV risk behaviors including both condomless sex and group sex ⁶⁶ while heavy marijuana use has been associated with being HIV positive and unaware of one's status. ⁴⁰ Our findings support this past research and suggest that engaging heavy marijuana users in HIV prevention efforts may reduce the overall size of molecular clusters and may serve to disrupt forward transmission of HIV through networks of YBMSM.

Similar to past studies we defined housing instability as one's perception of being homeless and not one's physical address.⁶⁷ Early evidence has shown that HIV rates among homeless adults are higher for blacks than whites and for MSM compared to other risk groups.⁶⁸ More recent research has shown that homelessness is also associated with HIV risk among both substance users^{69,70} and street-involved youth.⁷¹ Additionally, survival sex, or trading sex for

basic goods in the face of extreme need, has been shown to be a strong predictor of HIV risk among lesbian, bisexual, and gay homeless youth. 72 AWhile engaging those YBMSM who perceive themselves as homeless in HIV prevention services may aid in disrupting HIV molecular clusters, these individuals may be more impacted through structural interventions visà-vis stable housing.

Our study should be viewed in the context of its limitations. First, our data are cross-sectional and thus do not allow for causal inference. Second, we were able to obtain HIV sequences for only 32.3% of persons who were HIV-positive during the study period, and thus, the molecular network is incomplete (although this was due to a high number of virally suppressed individuals). Due to the small size of our study population, the results are limited in their scope and generalizability, our limited cohort may not necessarily be representative of the larger population of interest in Chicago. Additionally, we only observed one cluster with a high degree and our results may differ widely when more sequences are included, these results should be validated in other settings. We are also unable to determine whether the observed ties between HIV-positive individuals are indirect or direct transmission links, nor can we determine a direction of transmission from our data.

Even considering these limitations we were still able to draw meaningful conclusions from our data. We have shown that an increased number of confidants in one's network may play a role in reducing the likelihood of being a member of a molecular cluster. We have also demonstrated that perception of being homeless and heavy marijuana use may increase the size of HIV molecular clusters. Future work should also be conducted to examine in greater depth the observed relationship between depression and molecular networks. Finally, the prospective use of phylogenetic analyses ought to be evaluated further for incorporation into HIV surveillance

methods in local departments of public health. Our results suggest that determination of sequence clusters may aid in determining factors associated with spread in a population, which may vary in other locales from what we observed among YBMSM and provide a method for prioritizing limited public health resources to limit HIV spread.

CHAPTER 4

SEX, CONFIDANT, FACEBOOK, AND MOLECULAR NETWORK OVERLAP: A SOCIOMOLECULAR APPROACH TOWARDS HIV PREVENTION

ABSTRACT

Determining how network-level factors influence individual risk of human immunodeficiency virus (HIV) acquisition is vital in preventing disease transmission. In this study we combined social-, sexual-, and HIV molecular network data to examine potential network overlap and to ascertain the public health system benefits of combining these types of data.

A cohort of YBMSM (N = 618) was generated through respondent driven sampling with survey data collected across three waves in South Chicago from 2013-2016. HIV serostatus, RNA and genotypes were collected from respondents and through the Chicago Department of Public Health HIV surveillance data. Potential molecular ties were identified via pairwise genetic distance analysis of HIV-1 *pol* sequences with links inferred between individuals whose viral sequences were $\leq 1.5\%$ genetically distant. Putative molecular clusters were defined as ≥ 1 connection to another individual. Entity resolution⁷³ between confidant, sexual, and Facebook® network data was conducted across all three waves utilizing a computer algorithm with all matches confirmed manually by two separate analysts.

Of 266 (43.0%) participants identified as HIV-positive, we obtained 86 (32.3%) viral genetic sequences. Of these, 35 (40.7%) were tied to ≥1 other sequence with a total of 55 ties between all individuals. None of the molecular ties were identified in the first, second, or third degree confidant and sexual networks. We did, however, find that of the 15 individuals with both

molecular and Facebook© data available, 3 (25.0%) of the 12 ties overlapped between the two networks.

There is limited overlap between reported sexual and confidant network ties and molecular ties in this young MSM population, suggesting that transmissions may have occurred prior to elicitation of sex and social network members. Increasing the social network cluster size by two and three degrees only marginally improved overlap between reported social and phylogenetic network ties. Virtual network data, such as Facebook, may be particularly useful in developing a more complete picture of one's risk environment including identification of unobserved network members connected to molecular clusters: these network members are at greatest risk for HIV transmission.

INTRODUCTION

Determining how network-level factors influence individual risk of human immunodeficiency virus (HIV) acquisition is vital to preventing disease transmission. Recent research has moved beyond individual- to network-level analyses examining how these network data can inform and enhance our understanding of HIV prevention. In particular, some differences by race in HIV or other sexually transmitted infections have been explained in part by network factors. Traditional behavioral factors thought to increase the rate of HIV acquisition – those such as substance use and condomless sex have not been found to be significant drivers of the observed disparities. Continued focus on individual risk behaviors is then likely to have limited impact on HIV elimination, suggesting a need to examine network-level risk.

Previous research has leveraged several types of networks to examine factors associated with HIV infection, including social, ^{52,54,77} sexual, ^{20,54,77} and molecular networks. ^{7,16,17} Some work has examined how molecular and sexual contact networks overlap and interact, ^{15,78} highlighting the need to include network analyses when formulating prevention policies. ²¹ Past work utilizing molecular networks has identified HIV molecular clusters and has examined characteristics associated with both cluster membership and size. ^{7,15–17} Due to their nature, molecular networks provide no information on HIV-negative individuals and it is unclear the extent to which these networks are relevant to sexual transmission. Sexual contact networks also are with limitations and have been shown to suffer from missing data, ⁷⁹ from information bias regarding self-reported sexual history and frequency of risk behaviors. ⁸⁰ Further, past research has demonstrated a reluctance among some participants to provide information regarding sensitive behaviors ^{81,82} and some exhibit emotional distress when asked to report on sexual

behaviors.^{83,84} Perhaps most importantly, sexual networks are highly dynamic in younger populations⁸⁵ which challenges existing approaches to categorize them. Put together, molecular networks and observed sexual networks suffer from several biases and limitations and are highly dynamic, making analysis difficult and intervention given the data available subject to error.

Compared with sexual contact networks, social networks provide more complete data and often overlap with sexual networks, particularly among black MSM.²⁰ While social network data is still likely to contain missing ties between persons, it is less susceptible to some of the biases observed in sexual contact networks. In addition, non-sexual social networks tend to be more stable over time.⁸⁵. Examining social context, the influence of social context on behavior, and network formation is vital to the study of sexually transmitted diseases (STIs), including HIV.²¹ Past research has suggested that a socio-molecular approach to studying infectious diseases may yield new interventions,⁸⁶ however, little work has been done to characterize the relationship between non-sexual, social and molecular networks. Understanding how these networks overlap and how each enhances the information provided by the other has the potential to inform prevention strategies and may lead to identification of why disparities in HIV acquisition exist.

In this analysis, we characterized an HIV molecular network among young black MSM (YBMSM) in Chicago. These data were then combined with confidant, sexual and Facebook© network data from the same cohort to examine potential overlap between the networks in order to guide our understanding of how phylogenetic analyses can strengthen and be strengthened by existing network elicitation approaches.

METHODS

The setting and population have been described in detail previously, in Chapter 2. In brief, uConnect is a longitudinal population-based cohort study^{24,40} which was designed to assess factors associated with HIV risk and transmission among a sample of YBMSM. uConnect participants spent most of their time on the South Side of Chicago and the adjacent southern suburbs, which represents the largest contiguous Black community area in the United States.⁵

Eligibility Criteria — Study respondents were eligible to participate if they 1) self-identified as African American or Black, 2) were assigned male at birth, 3) were between 16 and 29 years of age (inclusive), 4) reported oral or anal sex with a male within the past 24 months, 5) spent the majority of their time on the South side of Chicago, and 6) were willing and able to provide informed consent at the time of the study visit.

Interview – Recruitment utilizing respondent driven sampling and survey follow-up occurred between August 2013 and January of 2016. Surveys were conducted across three waves of study, each separated by nine months. Interviews were conducted using Computer Aided Personal Interviewing (CAPI) with some portions self-administered. The interview itself involved different types of questions and activities: background and socio-demographic questions, self-administered scales of substance use, and HIV care continuum measures.

As part of the survey at each wave, participants were asked a series of questions to elicit confidants as well as their past sexual partners, allowing for the separate construction of both a sexual and a confidant network. Participants were asked "Thinking back over the past six months, that is since [MONTH], how many people, including men, women, and transgender women have you had sexual activity with, even if only one time" and "So I can ask some follow-up question, please list the names of the people with whom you discuss things that are important

to you", to elicit number of sexual partners and confidants, respectively. For sexual partners, participants were asked identifying information and a series of questions regarding their relationship and risk behaviors with each partner. Participants were asked to name their five most recent sexual partners, in the past six months, as well as their main partner, if one existed, for a total of up to six recent sexual partners. For confidants, participants were asked identifying information and a series of questions regarding their relationship with up to five confidants.

In addition to the named confidant and sexual partner questions, an application was developed to extract Facebook® friend lists from study respondents. ⁸⁷ Due to changes in Facebook® privacy policies, this process was completed only during waves one and two and was limited to those who consented to this process. Additionally, we were only able to obtain one degree of information regarding the friends of study participants (i.e. not the friends of their friends).

Entity resolution⁷³ was performed for each network type - confidant and sexual - among respondents in the uConnect cohort. At each study wave, respondents were asked detailed information regarding their sexual partners and confidants, including name, age, geographic residence and other sociodemographics, if known. These data provided by respondents were then matched across all waves to identify unobserved ties which may exist as a result of different respondents naming the same individual. The algorithm used to complete the matching process was verified by two separate analysts with all matches confirmed manually, and has been described in detail elsewhere.⁴¹

Molecular Network Inference

Dried blood spots were collected from each consenting participant at each wave. HIV infection status (including acute infection) was determined by 4th generation HIV immunoassay (Abbott ARCHITECT HIV Ag/Ab Combo assay), HIV-1/-2 Ab differentiation (Bio-Rad Multispot HIV-1/-2 Rapid Test) and viral load testing (Abbott ReaLTime HIV-1 assay) applied to samples eluted from dry blood spots (DBS) as described elsewhere.⁴² Given the limit allowable for elution, HIV *pol* sequences were obtained from all persons whose viral load was ≥2000 copies/mL. Specific procedures describing extraction of cell-associated HIV DNA from dried blood spots and HIV *pol* amplicon sequencing, including number of base pairs analyzed and primers used, have been previously described.⁴³ For participants whose viral sequences were unable to be determined, we obtained sequences (if available) collected through routine surveillance by the Chicago Department of Public Health (CDPH). All participants whose data was accessed through CDPH provided a release of information to obtain any HIV related test results.

All available genetic sequences were aligned to the HXB2 reference sequence using MUSCLE (MUltiple Sequence Comparison by Log-Expectation, European Bioinformatics Institute) multiple sequence alignment⁴⁴ in the MEGA v7.0 (Molecular Evolutionary Genetics Analysis) software package.⁴⁵ Those with a viral load below 2000 copies/mL were unable to be sequenced due to the lack of amplifiable virus. Phylogenetic tree analyses were performed by using the neighbor-joining method,⁴⁶ with distance calculated by TN93⁴⁷ analysis. One sequence was obtained from each participant. Each individual is referred to as a node. A potential transmission event was defined as having a genetic distance ≤1.5% between *pol* sequences, and

referred to as a tie. A cluster was defined as ≥ 2 persons linked by ≥ 1 tie. All cluster visualizations were performed by using Visone network visualization software.⁸⁸

All molecular, confidant, and sexual network analyses were limited to only those named partners who were also study respondents. We also included network data for all RDS ties as these were each described as either sexual partners or friends/family by the participants included in this study. Additionally, molecular network formation was limited to the number of individuals for whom we were able to obtain a viral genetic sequence.

In this study, we combined network data in such a way as to logically arrive at one's likely risk environment. We began with molecular network data, having identified these individuals as transmission cases (Figure 3A, panel A). Next, we added the named sexual partner data, or probable cases, to the molecular network (Figure 3A, panel B). Then the named confidants were added to the network as possible cases (Figure 3B, panel A), followed by overlapping networks (Figure 3B, panel B) and all Facebook ties (Figure 3B, panel C).

Sensitivity analysis

Given the large number of Facebook® ties, it is possible that any observed overlap between the social and molecular networks may be due to chance alone. To assess this, a series of simulations were run to test any observed overlap between the networks. Each simulation randomly re-assigned the ties in the network. The null hypothesis was that there was no association between the genetic and Facebook® networks. Ten thousand simulations were performed to obtain an estimate of the distribution of overlap between the networks and the

likelihood of the observed percent overlap between the networks was evaluated relative to this distribution, yielding a one-sided simulation p-value.

RESULTS

The uConnect cohort included 618 participants, of which 266 (43.0%) were identified as HIV-positive through the completion of the study. Among the 266 HIV-positive individuals, 139 had an undectecable viral load, we successfully sequenced the *pol* region of the viral genome for 42 (30.2%) of these individuals individuals. We obtained a further 44 viral sequences from CDPH HIV surveillance data for a total of 86 (61.9%) available sequences. No differences were observed in sociodemographic, risk behaviors or network position among participants who either did or did not have a sequence available nor based on network type. Characteristics of those with genetic sequence data are presented in Table 4, and are stratified by presence in a molecular cluster. Most participants had low income (72, 83.7%), self-identified as gay (59, 68.7%), and reported condomless sex in the past 12 months (49, 57.0%). Forty-one percent of individuals had a Grindr or Jack'd profile of which 30.2% used the services >2 times per week. We also observed an overall mean time since HIV diagnosis of 2.69 years with no significant difference found among those who were and were not in a cluster. Of those with a viral genetic sequence, 35 (40.6%) were present in a molecular cluster, resulting in 55 molecular ties between participants (Figure 3A, panel A).

Table 4. Sample characteristics stratified by presence in an HIV molecular cluster¹ among young Black MSM in Chicago with an available viral genetic sequence, uConnect (N = 86) 2013-2016.

2013-2010.	Total		Not in a cluster ¹		In a cluster ¹		p- value ²
Characteristic	No.	%	No.	%	No.	%	
Total	86	100	55	64.0	31	36.0	-
Demographics , n (%)							
Currently insured	42	48.8	29	52.7	13	41.9	0.336
Currently a student	24	27.9	15	27.3	9	29.0	0.956
Low income ³	72	83.7	45	83.3	27	90.0	0.403
Housing instability ⁴	28	32.6	16	29.1	12	40.0	0.306
Sexual identity							0.660
Gay	66	77.7	42	77.8	24	77.4	
Bisexual	14	16.5	8	14.8	6	19.4	
Straight or other	5	5.9	4	7.4	1	3.2	
Years since HIV diagnosis, mean (range)	2.69	0.75-7	3.11	0.75-7	2.32	0.75-6	0.222
Mental Health, ⁵ n (%)							
Depressive Symptoms	11	12.8	9	16.4	2	6.5	0.186
Risk behaviors, 4 n (%)							
Condomless sex	49	57.0	33	60.0	16	51.6	0.451
Group sex	22	25.6	16	29.1	6	20.0	0.360
Grindr/Jack'd Profile	36	41.9	40	78.4	16	45.7	0.713
Grindr/Jack'd Usage							0.764
Never	50	58.1	31	60.8	19	54.3	
Use ≤2 times per week	10	11.6	5	9.8	5	14.3	
Use >2 times per week	26	30.2	15	29.4	11	31.4	
Drug use, 4 <i>n</i> (%)							
Marijuana ⁶							0.956
Never	21	24.4	13	23.6	8	25.8	
Intermittent	30	34.9	19	34.6	11	35.5	
Heavy	35	40.7	23	41.8	12	38.7	
Other Substance Use ^{4,7}	23	26.7	16	29.1	7	22.6	0.513
Network degree , 8 mean (range)							
Molecular network	1.6	1–9	0	0	1.6	1–9	_
Confidant network	4.0	1–9	4.2	1–9	3.6	1–7	0.084
Sexual network	6.4	1–15	6.6	1–15	6.1	1–14	0.238
Facebook network	33.6	2-98	34.7	2-98	32.0	2-83	0.683

Abbreviations: MSM = men who have sex with men

 $^{^{1}}$ A cluster was defined as \geq 2 persons whose *pol* sequences were <1.5% genetically distant

Table 4 Continued.

The observed pairwise genetic distance ranged from 0.1% to 14.5% (0.001 to 0.145 nucleotide substitutions per site) (Figure 4A). Table 5 depicts overlapping ties between the molecular network and the first degree social, sexual, and RDS networks within the \leq 1.5% genetic distance threshold. An absence of tie overlap was also observed between the molecular network and second and third degree confidant network as well as the molecular network and second and third degree sexual network. We did, however, find rather consistent overlap of 45-50% between the social, sexual, RDS, and Facebook© networks. Out of 12 individuals with both molecular and Facebook© data, we found that 3 (25.0%) of the ties overlapped between the networks. In the sensitivity analysis we found that, under the null hypothesis of no association between the networks, the mean number of overlapping ties was 1.16. We observed a simulation p value of 0.12 (95% CI: 0.11-0.12), indicating that we observed a significant association between the molecular and Facebook© networks.

Table 6, presents network metrics for each network type with the molecular and Facebook© networks having the highest, and similar, density (0.092 and 0.099, respectively), the sexual network having a high average distance (mean \pm SD = 11.63 \pm 6.77), and the Facebook© network having high transitive triads (n = 73,948). Figures 3A and 3B depict the various

²Using chi-square analysis

³Defined as <\$20,000 per year

⁴In the past 12 months

⁵Using the Brief Symptom Inventory 18 (BSI-18)

⁶Intermittent use is defined marijuana use less than and including weekly use; heavy use is defined as at least once per day.

 $^{^{7}}$ Includes the use of ecstasy/molly/E, poppers, cocaine/crack, heroin, psychedelics, methamphetamines, off-label prescription drugs

⁸Degree is defined as the number of ties each individual had to other study participants in the network (e.g. one individual tied to three other individuals would have a value of three)

networks utilized in this analysis including the confidant, sexual, and Facebook© networks with each panel iteratively building upon the previous.

Table 5. Total number of overlapping ties between each type of network among young Black MSM in Chicago with an available HIV genetic sequence, uConnect

	Network Type					
	Molecular	Social	Sexual	RDS	Facebook	
	(n = 12)	(n = 719)	(n = 403)	(n = 716)	(n = 8296)	
Network Type , n (%)						
Molecular	-	-	-	-	-	
Social	0(0.0)	-	-	-	-	
Sexual	0(0.0)	309 (43.0)	-	-	-	
RDS	0(0.0)	321 (44.6)	121 (30.0)	-	-	
Facebook	3 (25.0)	371 (51.6)	199 (49.3)	284 (39.7)	_	

Abbreviations: MSM = men who have sex with men, RDS = respondent driven sampling

Table 6. Network metrics by type of network among young Black MSM in Chicago with an available HIV genetic sequence, uConnect

	Network Type				
	Molecular	Social	Sexual	Facebook	
Network Metric					
Total Ties	55	719	403	8296	
Average degree	3.14	1.96	2.13	39.46	
Density	0.092	0.007	0.005	0.099	
Average distance (± SD)	1.23 ± 0.49	2.85 ± 1.59	11.63 ± 6.77	2.26 ± 0.67	
Transitive triads	88	223	234	73948	
Transitivity	0.98	0.5	0.34	0.36	

Abbreviations: MSM = men who have sex with men, RDS = respondent driven sampling, SD = standard deviation

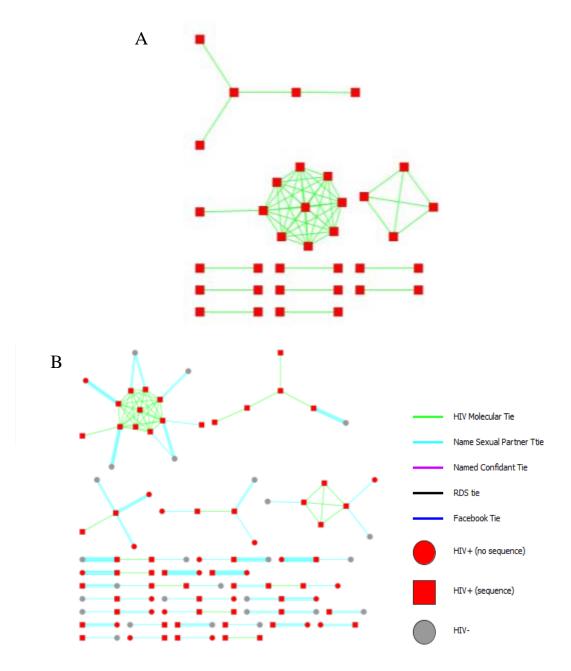


Figure 3A. Network diagrams for all individuals for whom we obtained an HIV genetic sequence: A) molecular transmission network and B) sexual and molecular transmission.

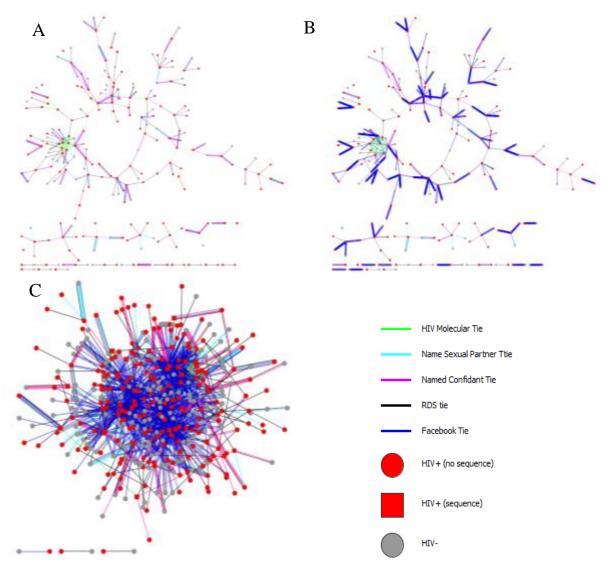
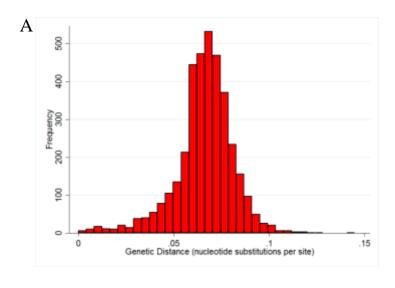


Figure 3B. Network diagrams for all individuals for whom we obtained an HIV genetic sequence: A) molecular, sexual, and confidant networks; B) molecular, sexual, confidant, and partial Facebook© networks; and C) molecular, sexual, social, and complete Facebook© networks.



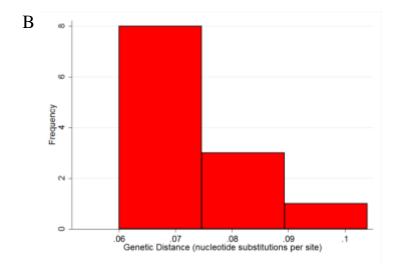


Figure 4. Graphs showing genetic distance (nucleotide substitutions per site) for A) all pairwise genetic distance among uConnect participants for whom we obtained an HIV genetic sequence and B) overlapping ties between the confidant network and the molecular network.

DISCUSSION

In this study, we present new information regarding the extent to which several types of social networks overlap with HIV molecular networks. First, we found that molecular ties have limited overlap with both named confidant and named sexual partners. Second, we find that slightly less than half of the time molecular ties overlap with Facebook® friend ties. These results suggest that a participant's risk network may not be limited to just the sexual connections within the past 6 months, but extend beyond these observed ties. Combining social and molecular network data in a sociomolecular approach may more accurately reflect one's true risk environment and provide information for public health departments to engage individuals not within molecular clusters.

Developing strategies for combining network data in a sociomolecular approach may yield novel strategies for targeting HIV prevention, especially among high risk populations. Young black MSM are one such high risk population and exhibit fewer risk taking behaviors and use fewer illicit substances than their white counterparts yet have higher rates of HIV transmission, ^{18,19} making social network analyses (SNA) particularly important for developing novel intervention strategies. Additionally, past research has shown that role shifting between social and sexual ties is common, ²⁰ particularly among MSM. In this study, we observed overlap between the social and sexual networks, however, observed none between the molecular and social or sexual networks. Past research has found an overlap between named partners and molecular links, however, this work included older populations, heterosexuals and PWID who may have more stable sexual/injecting networks than young MSM. ⁸⁹ The difference observed in our study may be as a result of obtaining viral sequences only for a third of those who are HIV-positive in our cohort. In addition, limited overlap may also be due to having too short of a

framing window (e.g. partners in the past six months), especially given that the mean time since diagnosis was over two years ago. Future research should assess how survey questions can be better tailored to specific populations in order to develop a more complete picture of one's network.

Given the lack of overlap between networks we were concerned that error may exist in our phylogenetic analyses. We did, however, find a normal distribution of distances (Figure 4A), similar to those of previous studies. Additionally, we did find that some named confidants or sexual partners had overlapping ties with our genetic data, however, these were outside our threshold of 1.5% genetic distance (0.015 nucleotide substitutions per site). The minimum observed genetic distance for overlapping molecular and social or sexual networks was 6.0% (0.060 nucleotide substitutions per site), confirming that our threshold did not arbitrarily remove any potential overlap (Figure 4B). Further, the high rate of use of Grindr and Jack'd by this population may suggest that participants are seeking more anonymous sex than previously thought. Past research has shown that, compared to those who do not have a profile on either Grindr or Jack'd, those who do are significantly more likely to be diagnosed with HIV.

It may also be possible to use a sociomolecular network approach to proactively prevent local HIV molecular clusters from growing by incorporating molecular network data into current partner tracing efforts (Figure 5). Figure 5 depicts an example of the expansion of current partner services to include molecular network analyses based upon our findings. Currently, when a new HIV infection (node A) is identified by local public health departments, disease intervention specialist (DIS) officers request that the newly infected individual name their current and past sexual partners. These named partners are then contacted and advised to seek HIV testing and counseling. Here, we are suggesting an additional step to partner tracing efforts,

"network tracing". In this instance, the newly infected individual's (node A) viral sequence can be analyzed using phylogenetic methodologies, yielding a molecular cluster of potentially unnamed or unknown partners (tie 1 and cluster E). Previously named partners (nodes C and D) of the long-term HIV infected individual (node B) can then be re-contacted and advised to again seek HIV testing and counseling, or prioritized to begin PrEP use, given their close proximity to a molecular cluster. It is also feasible that nodes C and D will come into contact with the molecular clusters given that Tie 1 is supported 25.0% of the time by Facebook® data (Tie 1) while Tie 2 is supported 10.0% of the time.

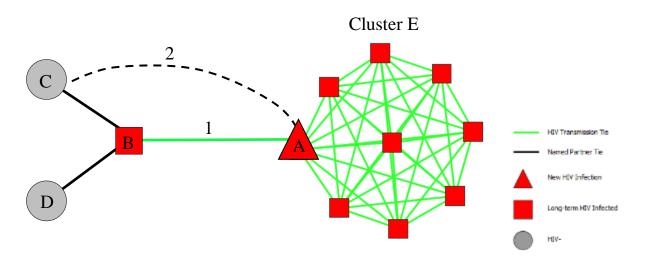


Figure 5. Suggested "network tracing" model for proactively incorporating molecular network data into current partner tracing methods in local public health departments. In this method, molecular ties would be used to identify previously unknown links between HIV-positive individuals. Previously named partners could then be re-contacted to advise further HIV testing or to encourage PrEP or PEP use in order to prevent transmission clusters from growing.

The data presented in this study suggests there is potential for the individuals from one's social network to enter, and grow, HIV molecular clusters. To prevent growth of local molecular clusters, next generation partner tracing efforts could be enhanced in local health departments to identify individuals for additional prevention services with minimal additional effort and using data which is widely becoming available. Padditionally, while current efforts aimed at getting all at-risk individuals on PrEP should be continued, the methods presented here may allow public health departments to prioritize those who should be most prioritized for PrEP engagement. In this manner, HIV-negative individuals who are found to be in close proximity to large molecular clusters can be prioritized. Future research should assess whether the network tracing method is comparable in scope and feasibility to traditional partner tracing efforts.

Our data should be viewed in the context of its limitations. First, we were able to obtain viral sequences for only a third of those who were diagnosed with HIV, thus the molecular network is likely incomplete. We were also unable to determine whether our molecular ties were indirect or direct nor were we able to determine the direction of transmission. Additionally, we only have survey data on the named confidants and sexual partners who are also study respondents and not on the other alters they named; thus we are not viewing a complete risk network.

Even with these limitations we were able to draw meaningful conclusions from our data. We have shown that it is necessary to incorporate many sources of information in order to better illuminate an individual's risk environment. We have also shown that social media networks, such as Facebook, may be useful in developing a more complete picture of one's risk environment. Finally, we presented a case example of how social network data can enhance molecular network data for next generation partner services approaches — "network services".

CHAPTER 5

HIV SEROCONVERSIONS AMONG YOUNG MEN WHO HAVE SEX WITH MEN ARE ASSOCIATED WITH SOCIAL NETWORK PROXIMITY TO ACUTE OR RECENTLY HIV-INFECTED INDIVIDUALS

ABSTRACT

Debate remains as to the relative HIV transmission contributions from individuals who are recently HIV infected and individuals who have long-term infections. In this study, we examine the relationship between new HIV seroconversions occurring among young Black men who have sex with men (YBMSM) and network proximity to recently or long-term HIV infected individuals.

A cohort of YBMSM (N = 618) was generated through respondent driven sampling with survey data collected across three waves. Dried blood spots were obtained at each wave and were assessed for HIV using 4^{th} generation HIV immunoassay, HIV-1/-2 Ab differentiation, and HIV RNA testing. A recent HIV infection was defined as either: 1) a confirmed seroconversion \leq 9 months prior to interview date; or 2) a laboratory confirmed acute infection. Meanwhile long-term HIV infected individuals were defined as a diagnosis date \geq 9 months prior to interview date. RDS-weighted survival analysis and logistic regression were utilized to examine network proximity of HIV transmission events to other recent or long-term HIV infected individuals in the social network.

Within the cohort, 343 (55.5%) participants were identified as HIV seronegative at baseline. Of these, 33 (9.6%) seroconverted during the study period. We found that the odds of seroconversion increased significantly with each additional recent HIV infected individual in

one's network (AOR = 12.96; 95% CI: 5.69-29.50). The number of long-term infected individuals in one's network did not significantly alter odds of seroconversion. We also found that for each additional member of one's network who used PrEP, the odds of seroconversion decreased significantly, adjusting for overall network size as well as the number of HIV-negative individuals in one's network (AOR = 0.44; 95% CI: 0.20-0.96).

An increase in the number of recently HIV infected individuals in one's network is associated with an increased odds of seroconversion while the odds of seroconversion were significantly reduced by an increase in the number of network members who use PrEP. Early diagnosis and treatment is a critical first step in the HIV care continuum and together with PrEP awareness and use are critical targets for disrupting the transmission of HIV through most at risk networks.

INTRODUCTION

High viremia during acute or recent HIV infection may translate into an increased probability of disease transmission ⁹³ and has been shown to have a disproportionate effect on HIV transmission among heterosexual networks. ⁹⁴ There is still debate, however, as to whether new HIV infections are more likely to be a result of closer network proximity to those who are recently infected or those with long-term HIV infection, but are unsuppressed. Previous research demonstrates that one-third of HIV-infected adults have not reached sustained viral suppression ⁹⁵ and that there is continued, albeit limited, risk of transmission even among those who are on antiretrovirals for >6 months. ⁹⁶ Long-term infected individuals may also be contributing to ongoing transmission risk by increasing the number of people already infected in a stable epidemic. To appropriately identify HIV transmission risk and accurately target interventions within defined networks, it is necessary to determine how transmission events are positioned within these networks with proximity to recently and long-term HIV infected individuals.

Risk of HIV acquisition is not limited to behaviors exhibited solely by the individual but rather are influenced by both individual- and network-level behaviors. ^{97–99} Previous research has demonstrated that individual-level intervention among people who inject drugs (PWID) can reduce HIV risk among the overall network. ¹⁰⁰ A review of networks of men who have sex with men (MSM) has found that the risk of HIV acquisition among black MSM (BMSM) increases among networks with high density and high racial homogeneity. ⁵⁴ In addition larger social support networks are associated with reduced engagement in risk-related sexual behaviors such as condomless sex and exchange sex. ^{53,101} Further, past work has demonstrated that network-level behaviors within YBMSM networks are associated with individual-level behaviors ⁹⁸ and

that network-level HIV prevention approaches are feasible when attempting to engage BMSM, who are at increased risk of HIV acquisition. 102

In this analysis, we focus on Black MSM, a group at disproportionate risk for HIV infection. The majority (2 in 3) of new HIV diagnoses occur among MSM³ and some have estimated an overall lifetime risk of HIV infection of 1 in 2.¹ Because network phenomena are more likely to concentrate HIV and other STIs within racially homogeneous groups⁷⁴, examination of transmission processes within large cohorts of Black MSM is critical to limiting ongoing infection in this community. We use data from the uConnect Cohort (2013-2016) to explore the relative extent to which new HIV infections among young Black MSM are associated with proximity to recently infected persons or those with long-term infections.

METHODS

Setting, sampling and visit procedures have been described in Chapter 2. In brief, uConnect is a longitudinal population-based cohort study designed to determine factors associated with HIV risk and transmission within a sample of YBMSM primarily residing on the South Side of Chicago including adjacent southern suburbs, one of the largest contiguous Black community areas in the United States.⁵ Participants were enrolled at wave one and followed-up at waves two and three, no new participants were enrolled after wave one.

Eligibility Criteria — Study respondents were eligible to participate if they 1) self-identified as African American or Black, 2) were assigned male at birth, 3) were between 16 and 29 years of age (inclusive), 4) reported oral or anal sex with a male within the past 24 months, 5)

spent the majority of their time on the Southside of Chicago, and 6) were willing and able to provide informed consent at the time of the study visit.

Interview – Between August 2013 and January of 2016, YBMSM were recruited in Chicago using respondent-driven sampling (RDS) across three waves, each separated by nine months. All interviews were conducted using Computer Aided Personal Interviewing (CAPI) with some portions of the interview self-administered. The interview itself involved different types of questions and activities: background and socio-demographic questions, self-administered scales of substance use, HIV care continuum measures, and collection of dried blood spots for HIV related testing.

As part of data collection at each wave, participants were asked detailed information regarding sexual partners and confidants, including names, if known. Entity resolution⁷³ was conducted across all participants and waves for network members reported in order to identify unobserved ties which may exist. The algorithm used to complete entity resolution was verified by two separate analysts and any new matches were confirmed manually; this process has been described in detail elsewhere ⁴¹, and is described in Supplementary Materials 1.0.

Measures

Our main outcome indicated whether an HIV seronegative individual at baseline seroconverted during the study period and was treated as a binary variable. HIV infection status (including acute infection) was determined by 4th generation HIV immunoassay (Abbott ARCHITECT HIV Ag/Ab Combo assay), HIV-1/-2 Ab differentiation (Bio-Rad Multispot HIV-1/-2 Rapid Test) and HIV RNA testing (Abbott ReaLTime HIV-1 assay) applied to samples

eluted from dry blood spots (DBS)⁴². Chicago Department of Public Health (CDPH) HIV surveillance data were utilized to determine date of HIV diagnosis. Acute infections were defined as individuals who had 4th gen antigen positivity in the absence of antibody confirmed via HIV RNA. These individuals and those found to have HIV antibody or HIV RNA in the absence of antibody at prior waves of the study were categorized as seroconverted participants. Separately, individuals identified as HIV-positive at baseline were stratified to either recently infected or long-term infected. A recent HIV infection was defined as either: 1) a confirmed seroconversion ≤9 months prior to interview date; or 2) a laboratory confirmed acute infection. Long-term HIV infected individuals at baseline were defined as those who were HIV-positive with a diagnosis date ≥9 months prior to interview date.

Separate network typologies were examined in order to remove the effects of individual network size from any observed association between infection type and seroconversion. These included each individual's total network size defined as the summation of non-repetitive ties to non-sexual confidant network and sexual network parnters (referred to herein as "total network"). Participants were able to self-report up to six sexual partners in the past six months and five confidants. Only named partners who were also study participants were included in this analysis as these were the only individuals on who we had laboratory confirmed HIV status. The confidant and sexual networks are not mutually exclusive; however, duplicate ties were removed when analyzing the total network. The network typology included entity resolution⁷³ across waves and were operationalized as a continuous variable, network degree. Network degree is defined as the number of connections each individual has to all other individuals in the network. Similar to total network degree, we also separately assessed, and included, the number of ties to HIV-negative individuals in one's network.

To examine whether seroconversions were more likely to be associated with the number of recent or long-term HIV-infected individuals in one's network, we determined the number of recent and long-term infected individuals in each individual's total network. Recent network degree was defined as the number of ties to those with a recent HIV infection. Likewise, long-term network degree was defined as the number of ties to those with a long-term HIV infection.

Demographic and Risk Characteristics

Demographic and risk characteristics are operationalized as in previous work.^{23,40} Employment was categorized as not employed, part-time employment (<30 hours/week), or fulltime employment (>30 hours/week). Health coverage was defined as having any health insurance public or private plan. Student status was defined as being an active high school or postsecondary school student. Relationship status was defined as currently in a main or casual relationship or single. Sexual identity was categorized as gay, bisexual, or other. Criminal justice involvement was defined as any arrest, detention, or parole in the respondent's lifetime. Housing stability was defined as being homeless at any point during the past 12 months. Risk behaviors included condomless sex and group sex and were each defined as at least one occurrence in the past 12 months. Due to the high usage of marijuana in this population it was treated as a separate variable with use of marijuana categorized as never, intermittent (up to and including multiple times per week), and heavy (at least once per day). All other drugs were combined into a single, binary variable (including: ecstasy, E or molly (MDMA); poppers (volatile nitrates); crack (cocaine); acid, LSD, mushrooms, G or GHB, K or special K, PCP (psychedelics); oxycodone, Vicodin, T3, etc (prescription pain killers)). Other drug use was defined as any use in the past 12

months. Alcohol use was categorized as never, one to two drinks per year, one to two drinks per month, one per week, and greater than one per week. Number of PrEP users in each participant's network was utilized as a continuous variable ("Have you ever used PrEP?"). Having a profile on the social networking site Grindr© or Jack'd© was utilized as a binary variable.

Statistical Analyses

Unadjusted and adjusted RDS-weighted logistic regression models were utilized to examine characteristics associated with odds of serconversion over the study period. Individuals who were HIV-positive did not contribute to the regression analysis. All covariates identified as statistically significant at the $p \le .05$ level, using the log-rank test, or known confounders were included in the multivariable regression model.

All analyses were performed in Stata v14.0.⁵⁰

RESULTS

Sample characteristics

The final analytic sample included 343 respondents identified as HIV seronegative at baseline. These respondents were generated through RDS chains of up to 13 waves in length and with a median of 2 recruits per participant. Sample characteristics for respondents are presented in Table 7 and are stratified by seroconversion during the study period. Our sample contained 310 (90.4%) individuals who remained HIV-negative throughout the study and 33 (9.6%) who seroconverted during the study period. Among those who were HIV-positive at baseline, and

who had an available date of diagnosis (n = 156), 54 (34.4%) were recent infections and 103 (65.6%) were long-term infections. At baseline, the majority of total respondents were employed at least part-time (184, 53.6%), had health coverage (180, 52.5%), had condomless sex at least once in the past 12 months (195, 56.9%), and used marijuana at least intermittently (241, 70.3%). We found that in the past 12 months, 60 (17.5%) participants used the following substances: MDMA (ecstasy, E, or molly) 28 (8.2%), prescription pain killers (oxycodone, Vicodin, T3, etc.) 20 (5.8%), alkly nitrates (poppers) 17 (5.0%), cocaine and/or crack 7 (2.0%), psychoactive drugs (acid, LSD, mushrooms, G or GHB, K or special K, PCP) 3 (0.9%), heroin 4 (1.2%), and methamphetamines 2 (0.6%), (data not shown).

Among study respondents who seroconverted during the study period, the majority were unemployed (27, 81.8%), had never been incarcerated (21, 63.6%), had health coverage (18, 54.5%), had condomless sex during the past 12 months (19, 57.6%), and used marijuana at least intermittently (24, 72.7%). Compared to those who did not seroconvert (mean = 0.2; range: 0-2), those who seroconverted (mean = 1.7; range: 0-5) had a significantly higher number of recent HIV infected individuals in their network (p < 0.001). There was no significant difference between those who did and did not seroconvert with reference to the number of long-term HIV infected individuals in their network. Nor were there any significant differences in the total, confidant, or sexual network sizes between those who seroconverted and those who did not.

Table 7. Sample characteristics stratified by seroconversion among young Black MSM who were confirmed as seronegative at baseline via laboratory analyses in Chicago, uConnect (N = 343 persons)

,	To	otal	Seron	egative	Seroconverted		p- value ²
Characteristic	No.	%	No.	%	No.	%	
Total	343	100	310	90.4	33	9.6	
Demographics , $n(\%)$							
Employment							0.250
Unemployed	159	46.4	140	45.2	27	81.8	
< 30 hours/week	93	27.1	84	27.1	17	51.5	
> 30 hours/week	91	26.5	86	27.7	6	18.2	
Housing Instability ³	85	24.8	78	25.2	7	21.2	0.611
Have health coverage	180	52.5	162	52.3	18	54.5	0.384
Current student	126	36.7	110	35.5	16	48.5	0.141
In a relationship	128	37.3	116	37.4	12	36.4	0.840
Risk behaviors, $n(\%)$							
Condomless sex	195	56.9	176	56.7	19	57.6	0.930
Group sex	57	16.8	49	16.0	8	24.2	0.226
Drug and alcohol use , $^3 n(\%)$							
Marijuana use ⁴							0.341
Never	102	29.7	91	29.4	11	33.3	
Intermittent	141	41.1	125	40.3	16	48.5	
Heavy	100	29.2	94	30.3	6	18.2	
Other Substance Use ^{3,5}	60	17.5	52	16.8	8	24.2	0.283
Alcohol use							0.453
Never	47	13.7	41	13.2	6	18.2	
≤ Once per day	217	63.3	195	62.9	22	66.7	
At least once per day	79	23.0	74	23.9	5	15.2	
Network degree measures,							
mean (range)							
Total network	10.0	1-24	9.8	1-24	11.6	7-20	0.028
Recent HIV	0.6	0-13	0.4	0-11	2.2	0-13	< 0.001
Long-term HIV	1.3	0-11	1.2	0-7	2.0	0-11	0.001
HIV-negative	9.45	1-24	9.44	1-24	9.64	4-18	0.799

¹Defined as HIV seropositive and HIV seronegative in a prior wave.

²Using chi-square analysis or T-test

³In the past 12 months

⁴Intermittent use is defined as less than and including weekly use; heavy use is defined as at least once per day.

⁵Includes the use of ecstasy/molly/E, poppers, cocaine/crack, heroin, psychedelics, methamphetamines, prescriptions.

Logistic regression analysis

In the adjusted RDS-weighted logistic regression models (**Table 8**), we found that the rate of seroconversion increased significantly with each additional recent HIV infected individual in one's network (Adjusted Odds Ratio [AOR] = 12.96; 95% CI: 5.69-29.50). Total network size significantly increased the odds of seroconversion (Adjusted Odds Ratio [AOR] = 1.22; 95% CI: 1.01-1.46). We also found that the rate of seroconversion increased significantly among those who had health coverage (AOR = 4.15; 95% CI: 1.11-15.53), compared to those who did not have health coverage. Heavy marijuana users, compared to those who never use marijuana, were significantly less likely to seroconvert (AOR = 0.12; 95% CI: 0.02-0.72). Additionally, use of at least one substance other than marijuana, compared to those who do not use any other substance, significantly increased the odds of seroconversion (AOR = 5.63; 95% CI: 1.44-22.02).

We found that the rate of seroconversion decreased significantly with each additional network member who used PrEP (AOR = 0.44; 95% CI: 0.20-0.96). We also found that the rate of seroconversion decreased for each additional HIV-negative member in one's network (AOR = 0.14; 95% CI: 0.07-0.26). We continued to find that an increase in one's overall network size significantly increased the odds of serconversion (AOR = 8.91; 95% CI: 4.53-17.52). We found that the odds of seroconversion increased significantly among those who were unemployed (AOR = 5.27; 95% CI: 1.19-23.41) and those who used at least one other substance (AOR = 4.96; 95% CI: 1.33-18.54), compared to those employed full-time and those did not use any other substances, respectively.

Table 8. Adjusted RDS-weighted logistic regression models of selected characteristics with odds of seroconversion, ¹ uConnect

	Netwo	ork Model	PrEP Model		
	(n :	= 326)	(n = 304)		
Characteristic	OR	95% CI	OR	95% CI	
Recent network members	12.96**	5.69-29.50	-	-	
Long-term network members	0.74	0.14-3.82	-	-	
Total network members	1.22*	1.01-1.46	8.91**	4.53-17.52	
HIV-negative network members	-	-	0.14**	0.07-0.26	
PrEP users in network	-	-	0.44*	0.20-0.96	
Condomless sex ²					
Never	Ref	-	Ref	-	
$\geq 1 \text{ time}$	-	-	0.51	0.16-1.63	
Employment					
>30 hours	Ref	-	Ref	-	
<30 hours	1.37	0.23-8.19		0.27-13.00	
Unemployed	3.25	0.76-16.38	5.27*	1.19-23.41	
Have health coverage					
No	Ref	-	Ref	-	
Yes	4.15*	1.11-15.53	2.64	0.85-8.16	
Current student					
No	Ref	-	Ref	-	
Yes	0.77	0.31-1.92	0.76	0.37-1.54	
In a relationship ²					
No	Ref	_	Ref	-	
Yes	0.79	0.24-2.65	0.76	0.25-2.36	
Marijuana use ³					
Never	Ref	-	Ref	-	
Intermittent	0.42	0.08-2.40	0.42	0.10-1.77	
Heavy	0.12*	0.02-0.72	0.08**	0.02-0.41	
Other Substance Use ⁴					
None	Ref	-	Ref	-	
≥ One other substance	5.63*	1.44-22.02	4.96*	1.33-18.54	

Abbreviations: OR = odds ratio; CI = confidence interval; PrEP = pre-exposure prophylaxis;

¹Defined as HIV seropositive with previous HIV seronegative in a prior wave.

²In the past 12 months

³Intermittent use is defined as less than and including weekly use; heavy use is defined as at least once daily.

⁴Includes the use of ecstasy/molly/E, marijuana, cocaine/crack, heroin, psychedelics, methamphetamines, prescription drugs

^{*}p <0.05; **p <0.001

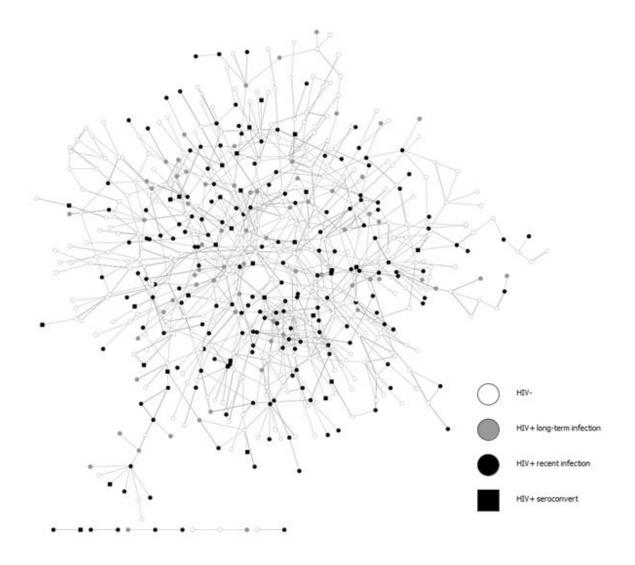


Figure 6. Total network, including social and sexual ties, among participants who were HIV seronegative- at baseline (n = 606).

¹A recent HIV infection at baseline was defined as either: 1) a new diagnosis ≤9 months prior to interview date or 2) a laboratory confirmed acute infection at baseline.

²Long-term HIV infected individuals at baseline were defined as those who were HIV-positive with a diagnosis date ≥9 months prior to interview date

DISCUSSION

To date, little research has characterized the relative contributions of network members with recent and long term HIV infection on seroconversion. In this study, we present new findings regarding the role of both recent and long-term HIV infected network members. First, we found that 10% of our population-based sample of YBMSM who were negative at baseline seroconverted during the 18 month study period and none of the individual level behaviors or demographics were associated with this seroconversion. Second, we found that an increase in the number of recently HIV infected individuals in a participant's network significantly increased the rate of seroconversion. Finally, we found that for each additional member of a participant's network who is using PrEP there was a significant decrease in the odds of seroconverting.

Network composition plays a key role in predicting HIV risk among young black men who have sex with men. While past research has shown that members of the same network typically share HIV risk behaviors, 54,98 our study demonstrates that the timing of HIV infection among network members itself, either recent or long-term, may also play a role in risk of HIV acquisition. These findings are similar to past research which utilized both the Duke-UNC-Emory Acute HIV Consortium data as well as data available on long-term HIV infections from previously published studies. Study findings have demonstrated that men are hyperinfectious during acute HIV infection, and that there is a decreased odds of transmission per coital act among those with long-term HIV infection, likely due to an increased probability of antiretroviral use. 94 Further, past research has shown that probability of transmission of HIV among long-term HIV infected is insufficient to sustain an epidemic. 103 Currently, there is no research examining the probability of HIV transmission among recent or long-term HIV infected BMSM. Our findings suggest that, in this young population, recent infection seems to be playing

a larger role in the risk of HIV transmission. We also observed that differences in network composition may alter an individual's risk of HIV acquisition and may be key in targeting future interventions, particularly among those who have a recent HIV infection. 104

Prior work has demonstrated that many MSM spend a significant amount of time using multiple mobile apps such as Grindr© and Jack'd© and that the age at which respondents first used these apps was significantly associated with age at the first instance of either insertive or receptive anal intercourse. The New York Community Healthcare Network reported that, among users of hook-up apps, 80.9% of users knew that HIV was transmitted through "unprotected anal sex, vaginal sex, and – less frequently – oral sex", yet almost half of the respondents (46.6%) reported condomless anal intercourse, 106 a finding also found among MSM in Los Angeles. The While past research has demonstrated that hook-up sites significantly increase the risk of HIV acquisition, we did not find this to be a significant predictor of seroconversion in this study. However, one recent study found that young MSM express a willingness to participate in HIV prevention programs via these platforms 108, particularly among non-White MSM, 109 making them a potential key source for HIV prevention given the high rate of use observed in this cohort. Further research is necessary to investigate whether HIV prevention programs administered via these platforms can reduce the risk of HIV infection.

The role of marijuana use in risk of HIV acquisition may depend, in part, on network typology. Past research has shown that those who use marijuana use as a sex-drug – that is a drug used to make sex easier, better, or last longer –are more likely to participate in HIV risk behaviors, such as group sex and condomless sex. Additionally, other research has shown that heavy marijuana users are more likely to be unaware of their HIV-positive status. Our findings suggest that the role of heavy marijuana use may be more complicated than previously thought,

we found that heavy marijuana users were less likely to seroconvert during the study period, compared to those who never use marijuana. This finding suggests that the network context in which an individual uses marijuana may play a key role risk of HIV acquisition. Further research should be conducted to address this finding.

We observed that network-level use of PrEP significantly reduced individual-level HIV acquisition risk, supporting the findings of past research. Khan et al. (2013) tested a "firewall effect" theory, suggesting that HIV infected individuals with low infectivity may prevent the spread of the virus through the network, a theory confirmed by later work. 111 Our findings also support this theory and suggest that one's risk environment plays an important role in individual risk of HIV acquisition; in this study, an increase in the network-level use of PrEP may establish a firewall, essentially shielding segments of the network from onwards transmission.

Encouragingly, recent work utilizing data from the National HIV Behavioral Surveillance study has found overall knowledge regarding PrEP and PEP to be on the rise between 2011 to 2014. 112

Further, recent increases in PrEP interest and knowledge have been found among MSM using a sexual networking site, however, uptake of PrEP use among those who would benefit most was not observed. 113

While we found several important factors associated with HIV seroconversion, there are some important limitations to our study. First, our study utilizes baseline characteristics to predict future HIV seroconversion and thus does not allow for causal inference. While we were able to utilize interval censored survival analyses, our study would have benefited from a more accurate date of diagnosis, as opposed to relying on the midpoint between interview dates or on archived department of public health surveillance data. We also aimed to collect as much network data as possible, however, as with many network studies we are not observing the

complete network of individuals nor were we able to determine HIV serostatus of unobserved network members. Finally, we were only able to infer potential relationships between risk of seroconversion and recent or long-term infection among network members based upon network proximity and were not able to determine whether a transmission occurred or the direction of transmission utilizing our data.

In the context of our study limitations, we have shown that an increase in the number of acute/recent HIV infected individuals in one's network is associated with an increased rate of seroconversion. We also demonstrated that the odds of seroconversion are significantly reduced by an increase in the number of network members who use PrEP and marijuana use. Early diagnosis and treatment is a critical first step in the HIV care continuum and together with PrEP awareness and use are critical targets for disrupting the transmission of HIV through high risk networks.

SUMMARY

Objectives

This project had three primary aims: 1) to describe and examine local, inferred HIV molecular networks among YBMSM, 2) to examine the interrelation of molecular and social networks while presenting novel methods for the expansion of partner services, and 3) to investigate characteristics of persons who become HIV-positive.

Summary

In chapter 3 we utilized phylogenetic methods to infer HIV molecular networks among YBMSM, finding that those who self-reported symptoms of depression and those who had a strong support network were significantly less likely to be members of molecular clusters. We found that those who had unstable housing and who reported lower marijuana use had significantly more ties to other individuals within molecular clusters, while those identifying as bisexual, those participating in group sex and those with higher numbers of sexual partners had significantly fewer ties. Finding that those who use marijuana heavily was a bit of a unique finding, especially given past research I have conducted. In this case, it means that those who never use marijuana are at significantly greater risk of entering HIV molecular clusters. ^{40,110} It was also surprising that depressed individuals are less likely to be in molecular transmission clusters, given that past research has shown they are more likely to participate in risk-associated behaviors. In both of these cases, these findings need to be analyzed further, however both may be unique to our risk population.

In Chapter 4, we combined social and molecular networks in order to examine their interrelation and how they can be utilized in a public health setting. We found no overlap in first, second, or third degree networks between the social and molecular networks. We did find, however, that approximately half of the ties in the molecular network were also present in the participants' Facebook® network. Further, we found a consistent 45-50% overlap of ties between the social, sexual, and Facebook® networks. In addition, we presented a novel method of enhancing current partner tracing efforts with molecular network data. Here, too, we were surprised in that we did not find any overlap between the social and molecular networks. We had expected similar overlap to past studies, ⁸⁹ however, the source of our social ties were quite different from past work and may be the source of our differing results. In contrast, it was encouraging to see that approximately half of other network ties (RDS, social, sexual, and Facebook®) overlapped suggesting that social networks may be a good proxy for other risk networks in the future, although this has to be studied in more detail.

Finally, in Chapter 5 we assessed the role of network composition, specifically among recent and long-term HIV-infected individuals, on odds of HIV seroconversion. We found that the odds of seroconversion increased significantly with each additional recent HIV infected individual in one's network. The number of long-term infected individuals in one's network did not significantly alter odds of seroconversion. We also found that for each additional member of one's network who used PrEP, the odds of seroconversion decreased significantly, adjusting for overall network size as well as the number of HIV-negative individuals in one's network. This work was particularly exciting since it produced novel findings around network-level PrEP use and argues for a stronger push in PrEP use. These results also suggest that a "network-level"

immunity", similar to herd immunity, may be able to be achieved in networks similar to those observed here.

Taken together, these results enhance and inform one another. We found differing risk behaviors associated with both molecular and social networks. These two studies then merged into a larger analysis allowing for the presentation of methods of combining the two to enhance current partner tracing efforts. For example, departments of public health may, in the future, be able to incorporate phylogenetic data into their current methodology to stem the transmission of HIV through high-risk networks. By incorporating the methods suggested in these analyses, they may then be able to prevent large transmission clusters from growing or forming in the first place. While this would certainly be a boon to HIV prevention in general, this type of enhancement to current HIV prevention would particularly benefit young black MSM, those who are at highest risk of becoming HIV-positive and are also who are the most likely to be in larger molecular transmission clusters. These studies also provide the research community with further insight into the risk factors associated with both seroconversion and the growth of molecular transmission clusters and hopefully guiding future research in HIV prevention. Overall, the work presented in this dissertation has the potential to inform public health prevention towards a goal of reversing the tide of new HIV diagnoses among all individuals, but particularly among young Black men who have sex with men.

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