Leveraging Networks & Epidemic Modeling: Creative Approaches for HIV Elimination

Specific Aims

Great strides have been made in combatting HIV in the United States (U.S.), with new HIV infections beginning to decline overall. However, certain subpopulations continue to be impacted. Between 2011 and 2015, HIV diagnoses increased by 14% among Hispanic/Latino men who have sex with men (MSM) and 4% among African American MSM.[1] As we move toward HIV elimination, our response requires increasingly creative approaches to meet the needs of historically marginalized, key populations. Individuals with acute and early HIV (AEH) and those who are HIV infected and aware, but out of care, are key drivers of ongoing HIV transmission.[2-4] Advancements such as pre-exposure prophylaxis (PrEP) and treatment as prevention (TasP) can curtail transmission from those with AEH and who are out of care,[6-9] but key populations who need them most must utilize them. Social network factors have been noted as contributing to the difference in rates of HIV acquisition among subpopulations.[10-12] Contact tracing (asking newly HIV diagnosed clients to identify their sex or drug contacts) is a basic form of sexual network elicitation that is the standard of care employed by public health departments across the U.S. to identify individuals who are unaware of their HIV infection.[13] Public health departments are now turning toward using molecular network data (individuals linked by similar HIV-1 *pol* sequences) in conjunction with contact tracing information for HIV epidemic response. While informative, sampling challenges limit the reliance on these sources alone for making inferences about HIV transmission, and many lack the expertise to do so. For instance, traditional contact tracing has produced a relatively low yield of identifying sexual contacts of newly HIV diagnosed clients,[14] and due to the nature of molecular networks, information is not provided on HIV-negative individuals that would assist with preventing onward transmission. Social network data, in contrast, are more complete than sexual contact data and often include sexual partners in the networks of MSM.[15] Despite indication of the benefits of combining the molecular and social network data, little research has been conducted on how they can be integrated for HIV care.[16]

The overall goal of this project is to better understand the complex and overlapping social and molecular network dynamics involved in HIV transmission in order to more effectively prioritize interventions to reduce HIV incidence. This project will use data from the Urban Networks Interaction (UNI) Study, a cross-sectional study that uses a social network recruitment strategy to characterize the structure of the social network of HIV-infected and at-risk persons in San Diego, as well as data from the San Diego Primary Infection Resource Consortium (PIRC), the largest, most intensively studied and well-characterized cohort of acute and early HIV infected (AEH) individuals in the United States.

Research Aims (RA):

1. **To reconstruct HIV-1 transmission networks among MSM and Transgender populations in San Diego and compare the relationship between these networks to social network data obtained on the same individuals (maps on to TA 1).**
   H1. Individuals who cluster in the HIV-1 transmission network will be indirectly connected by HIV negative individuals in the social network.
2. **To characterize HIV acquisition defined by having acute or early HIV infection (i.e. incident cases) based on an individuals' position in the combined social-molecular network (maps on to TA 1).**
   H2. Individuals who connect otherwise unconnected network clusters will be more likely to have AEH.
3. **To estimate the percent of new infections that could be averted if PrEP delivery was prioritized based on an individual's position in the combined social-molecular network versus delivery in a network-agnostic manner (maps on to TA 2).**
   H3. More HIV infections will be averted by prioritizing PrEP based on network position.

These research aims are consistent with the Office of AIDS Research (OAR) priorities and the Joint United Nations Programme on HIV/AIDS (UNAIDS) global 90-90-90 strategies to reduce HIV incidence through having 90% of those infected be aware that they are infected; 90% of those aware of their status receive treatment; and 90% of those in treatment achieve undetectable viral loads. My advanced training in the use of HIV genetic transmission network reconstruction and epidemic modeling will allow me to more effectively prioritize interventions that limit HIV transmission. Findings from this study can be applied to epidemics where ongoing transmission has been difficult to control. These models can help to identify the sources of greatest ongoing transmission and the most efficient means of interrupting ongoing transmission in the community. As incidence declines, it may become more important to better understand the residual sources of ongoing transmission.

Community (Lay) Summary- 250 words max

Much progress has been made in combatting HIV/AIDS in the United States (U.S.) since the start of the epidemic in the 1980s; with new HIV infections starting to decline overall. However, certain historically marginalized groups of people are still being impacted, preventing the elimination of HIV. Young (under 30) Latino and African American men who have sex with men (MSM) are still experiencing new HIV diagnoses in the U.S. This lifelong disease can be prevented by a medication called pre-exposure prophylaxis (PrEP) if taken by people who don't have HIV. Likewise, antiretroviral medication can prevent the spread of HIV if those who are infected take it regularly. However, it is very difficult to find and engage the populations most impacted by HIV in health care due to their marginalization. A promising strategy to finding them is the use of networks. Public health departments are turning toward molecular network data (individuals linked by similar HIV-1 *pol* sequences) to identify groups of people who are infected with a similar strain of HIV that could lead to more infections, but molecular data does not provide any information on HIV uninfected people who are at risk of contracting HIV. Therefore, we also need data on social networks (i.e. friends and sex partners). The goal of this study is to put molecular and social network data together, and then use this information to mathematically model who in the network we should focus on to make PrEP and antiretroviral medications most impactful for eliminating HIV.

Abstract- 250 words max

New HIV infections in the U.S. are beginning to decline, but marginalized groups such as Latino and African American men who have sex with men (MSM) continue to experience new infections. Individuals with acute and early HIV (AEH) and those who are HIV infected, but out of care, are key drivers of ongoing transmission. Advancements such as pre-exposure prophylaxis and treatment as prevention can curtail transmission, but populations who need them most must utilize them. Social network factors have been noted as contributing to the difference in rates of HIV acquisition. Public health departments traditionally used contact tracing (asking newly HIV diagnosed clients to identify their sex or drug contacts) to identify individuals who are unaware of their HIV infection, but this information is often incomplete due to underreporting. They are now turning toward molecular network data (individuals linked by similar HIV-1 *pol* sequences) in conjunction with contact tracing information for HIV epidemic response. While informative, sampling challenges limit the reliance on these sources alone for making inferences about HIV transmission. Social network data, in contrast, are more complete than sexual contact data and often include sexual partners in the networks of MSM. Despite indication of the benefits of combining these data, little research has been conducted on how they can be integrated for HIV care. The overall goal of this project is to better understand the complex and overlapping social and molecular network dynamics involved in HIV transmission in order to more effectively prioritize interventions to reduce HIV incidence.

CANDIDATE'S BACKGROUND

2.1 Introduction to the candidate: My first exposure to HIV prevention was through volunteer work with Chicago's National HIV Behavioral Surveillance (NHBS) system, a CDC-funded assessment of behavioral risks for HIV infection, the summer after finishing my undergraduate degree in 2006. My efforts resulted in the successful administration of over 500 surveys and HIV tests within key populations. At the end of one evening, a participant handed me a letter and asked if I could read it to her. The letter was from the Circuit Court of Cook County and stated that a man whose DNA matched that of the man who had raped her was in custody and would likely be convicted if she made an appearance in court. After hearing what I read, and as I anticipated a completely different response, she grabbed the letter, tore it up, and stormed away railing about all of the other things in her life that were of greater immediate concern, none of which were learning her HIV status. This shocking experience revealed the critical need to better understand and address factors extrinsic to the individual that influence engagement with HIV prevention and care. Thus, I cemented my goal to pursue an academic research career focused on reducing social, environmental barriers to HIV prevention and care, which remain poorly understood despite their global prevalence. Support from the Altman Clinical and Translational Research Institute KL2 award will allow me to develop skills to evaluate HIV prevention and care interventions that ultimately lead to reduced HIV transmission.

2.2 Master's training and professional experience: My interest in an academic career focused on HIV grew as I completed a Master of Public Health degree in epidemiology at the University of Illinois at Chicago (UIC), and concomitantly continued working with the NHBS as an epidemiologist. My research revealed stark disparities in HIV prevalence between Black men who have sex with men (MSM) and MSM of other race/ethnicities, despite similar levels of HIV risk. My master's thesis on this topic led me to understand that HIV risk stems not only from the behavior of the individual, but largely from the behaviors, status, and conditions of the group to which they belong.[17,18] After completing my MPH, I became the Clinical Core Epidemiologist for the Chicago Center for AIDS Research (CFAR), a collaboration between Rush University, UIC, and Cook County Health & Hospitals System. I advised clinicians on all aspects of research (study design to statistical analysis) which resulted in eight co-authored manuscripts assessing racial/ethnic disparities in HIV care, and hepatitis C co-infection and vitamin D deficiency as they relate to HIV clinical outcomes.[19-26]

2.3 Doctoral studies: In September of 2012, I entered the doctoral program in epidemiology at the University of Chicago where I studied under Dr. John A. Schneider. During this time, I was a Program Manager on two Chicago-based cohort studies of young Black MSM that I used for my dissertation research (R01 DA039934, R01 DA033875), the group with the highest rate of new HIV infections in the U.S. Given the findings of my MPH thesis, the focus of my dissertation was on utilizing social networks to inform HIV preventive care. In my first aim, I developed a social network based metric, the Network Viral Load (NVL), to measure the composite viral load within an HIV negative individual's risk network and found a positive association between NVL and HIV seroprevalence. The findings were presented at the International AIDS Conference (AIDS 2016) and the Conference on Retroviruses and Opportunistic Infections (CROI 2017) and published in *JAIDS*. Another project used logistic regression and conditional logit models to assess the impact of resiliency factors (such as social support) and adverse social-environment factors (such as exposure to violence) on network stability and HIV risk over time. I found that network instability was positively associated with both, indicating that it may be on the explanatory pathway between social-environment factors and HIV risk. The results were published in *AIDS and Behavior* and presented at the Conference of the International Network of Social Network Analysis (INSNA 2016). My experience with the challenges of implementing interventions in HIV-positive populations led me to apply for and obtain a competitive pre-doctoral fellowship in Health Services Research (T32 HS000084). Through this initial health economics exposure, I developed a project comparing the cost per HIV diagnosis of two HIV case-finding strategies. I found that the cost per diagnosis was lower using a social network-based recruitment strategy targeting direct HIV risk partners compared to a strategy recruiting social ties. Aside from dissertation research, I was first author on 2 methods-related manuscripts[27,28] and co-author on 8 manuscripts [29-35] pertaining to young MSM, the networks of those recently HIV infected, and social-environment factors.

2.4 Postdoctoral training and experience: In January of 2017, I accepted my current NIAID postdoctoral fellowship (T32 AI007384) in the Division of Infectious Diseases and Global Public Health (IDGPH) in the Department of Medicine at the University of California, San Diego (UCSD). My experience conducting social network analyses made me aware of the growing necessity of combining social network data with molecular transmission network data in identifying potential sources of HIV transmission, and the importance of

incorporating this combined network information into HIV epidemic models. Therefore, my objective for the postdoc was to combine the tools of epidemiology, public health, and social network analysis with molecular transmission network analysis and epidemic modeling to inform health policy decisions in the field of HIV. During the postdoctoral fellowship, I have worked with Dr. Susan Little (primary mentor), an expert in using molecular epidemiologic methods to infer and characterize HIV transmission networks, and Dr. Natasha Martin (secondary mentor), an experienced infectious disease epidemic modeler, to gain exposure to these fields. Through this, I have gained some preliminary exposure to epidemic modeling through developing a simple model of HIV transmission among people who inject drugs (PWID) that was presented at the International Liver Congress 2018 and co-authoring a review of modeling HCV prevention among MSM and PWID.[36] I was also awarded CFAR funding (P30 AI036214, PI: Skaathun) to estimate HIV incidence among a cohort of MSM in Tijuana (R01DA037811; PI Dr. Patterson) and determine characteristics associated with incident infections including whether they are linked within clusters. The support of this KL2 award will allow me to obtain formal training in reconstructing HIV molecular transmission networks and epidemic modeling. Acquiring this expertise will augment my previous skill-set to create population-level change in reducing HIV incidence through informing policy. Based on my research experience and scholarship (>25 peer-reviewed manuscripts), Dr. David Smith (IDGPH Division Chief) and Dr. Dillmann (Department of Medicine Chair) have proposed me for an Assistant Professor position in UCSD's Department of Medicine, which is independent of the funding of this KL2 award (see Letter of Institutional Commitment).

3. CAREER GOALS AND OBJECTIVES

My **Long Term** career goal is to conduct independent research that leverages creative approaches, such as networks & epidemic modeling, for HIV elimination. To accomplish this, my **immediate goal is to develop expertise in reconstructing HIV molecular transmission networks and HIV epidemic modeling** among MSM and Transgender populations in San Diego**.** My previous training in epidemiology, social network analysis, and sociology provides a solid understanding of the context, implications, and empirical data necessary for both HIV molecular transmission network analysis and epidemic modeling. However, I require training in both through the KL2 as they are distinct skills that differ from the classical statistical techniques applied by epidemiologists, and are not taught as a part of epidemiology or public health curriculum.

Public health departments are increasingly adapting molecular transmission networks, yet questions remain on their functionality due to limited insight on their interpretation.[16] Several methods are used to represent closely related strains of HIV. Phylogenetic analyses are used to represent the shared ancestral lineage of related strains of virus. Alternatively, transmission network maps calculate the pairwise genetic distance between sequences and infer connections between these nodes (i.e., individuals) if the corresponding distance is below a specified threshold. The latter method is faster and thus more readily scaled to large surveillance databases (>10,000 sequences) which can be analyzed within minutes to hours using software tools such as HIV-TRACE (developed by secondary mentor, Dr. Wertheim).[37] The Centers for Disease Control now routinely provides molecular HIV surveillance data and guidance on the use of these data to regional health departments. As a result, network metrics designed for social network analyses are being applied to genetic networks,[38] but there has been no formal theory as to whether they are applicable, and how the interpretation may differ. For instance, an inferred edge in transmission network maps does not prove transmission. My expertise in social network analysis combined the mentorship of Drs. Wertheim and Little on the reconstruction and interpretation of HIV genetic transmission networks will provide insight on this matter. In addition, the training will provide me with the ability to combine social and genetic network data to help better identify the source of HIV transmission.

I would like to expand my epidemic modeling experience to use the structure of the combined social and transmission network to simulate where prevention interventions such as PrEP should be prioritized. Mathematical modeling of HIV transmission networks has previously been beneficial for guiding the initiation of PrEP, but most models focus on targeting demographic and behavioral characteristics and ignore the underlying network structure.[39] The few studies that incorporate network factors use only sexual network data, which is often limited due to non-disclosure of sexual partners.[39-41] This training, coupled with the grant writing and responsible conduct of research training that I will receive through the KL2, will prepare me for a successful career as an independent researcher in HIV preventive care. I will use the results of my KL2 to submit an R01 that uses the acquired methods to develop real-time HIV interventions that harness the integration of diverse data sources (e.g. PA-17-182).

Little, Susan 10/24/2018 6:40 PM

Comment [1]: This section is a little vague.

BRITT: I added more detail and made a separate paragraph.

K01 Training Aims (TA)

1. Acquire skills in **reconstructing HIV molecular transmission networks** from HIV sequences in order to identify HIV transmission clusters.
2. Develop methodological expertise in **HIV epidemic modeling** among MSM and transgender populations.
3. Gain expertise in the **ethical conduct of research** pertaining to network analyses among MSM and Transgender populations **(Responsible Conduct of Research).**.
4. Strengthen **professional skills for a successful academic career**, including grant writing, dissemination of research findings, and the development of collaborative scientific relationships.

To accomplish the training aims, I will receive mentorship from: Dr. Susan Little (primary mentor), an infectious disease clinician with expertise in using molecular epidemiologic methods to infer and characterize HIV transmission networks; Dr. Joel Wertheim (secondary mentor), a virologist with expertise in genetic sequence analysis methods to identify HIV transmission clusters; and Dr. Natasha Martin (secondary mentor), an expert infectious disease epidemic modeler. The proposed research will be integrated within Dr. Little's ongoing Urban Network Interactions study (UNI), a cross-sectional study that characterizes the structure of the social network of HIV-infected and at-risk persons in San Diego and identifies predictors of HIV transmission and medication non-adherence.

Little, Susan 10/23/2018 7:41 PM
Comment [2]: Is this Beiwe or UNI? Just want to make sure we are really doing this in UNI – since I did not think UNI really did this.

BRITT: Not directly, but we can see if social network and social-demographic factors are associated with ever seeing a health care provider after testing positive, seeing a HCP in the past 12 months and viral load.

4. CAREER DEVELOPMENT TRAINING AND MENTORING ACTIVITIES UNDER AWARD PERIOD

The proposed KL2 award will guarantee that I can devote 75% of my full-time effort as an Assistant Professor in the Division of IDGPH at UCSD to the proposed training and research goals. **Table 1** displays the percent effort assigned to these activities over 3 years. Below, the specific courses, interactions with mentors, and professional development activities are described that will advance my training and career development (**Table 3**).

Table 1: Percent effort devoted to activities over award period

Activity	Y1	Y2	Y3
Courses, workshops, independent study	50%	20%	5%
Meeting with mentors	10%	10%	10%
Data analysis and modeling	20%	35%	35%
Manuscript and grant writing	20%	35%	50%

4.1. Training and Development with Mentors and Contributors

Susan Little, MD (Primary Mentor) is a Professor of Medicine in the Division of IDGPH, at the University of California, San Diego. She serves as the Co-Director of the Antiviral Research Center (AVRC), the major site of UCSD clinical and translational research trials related to HIV/AIDS, hepatitis, influenza, tuberculosis, and other infectious diseases of global impact, and the PI of the San Diego PIRC (AI106039), a highly collaborative research program that has been tackling the evolving challenges in the field of primary/acute HIV infection for over 20 years and has >180 peer reviewed publications. Her current research is focused on the use of molecular epidemiologic methods to infer and characterize HIV transmission networks, and the use of targeted prevention and treatment interventions to reduce HIV incidence. I will meet with Dr. Little weekly in Years 1-3; she will attend annual meetings with my co-mentors to monitor progress and ensure I have 75% protected time for my research and career development activities. Dr. Little will offer mentorship in academic career development and guide me to a goal of completing of 3-4 (1-2 first author) manuscripts per year and grant submissions to the UCSD CFAR and NIH.

Joel Wertheim, PhD (Secondary Mentor) is an Assistant Professor of Medicine in the Division of IDGPH, at the University of California, San Diego. His work focuses on the molecular evolution and phylogenetic of RNA viruses, with special attention to HIV. Recently he has focused on HIV transmission networks, both their construction and dynamics. Dr. Wertheim has >50 peer-reviewed publications. He is a previous recipient of an NIH-NIAID K01 Career Development Award (K01AI110181) to study HIV molecular transmission networks and is currently funded by an NIH-NIAID R01 (AI135992) to continue this work. I will meet with Dr. Wertheim bi-weekly to discuss the modeling aim; he will attend annual meetings with my co-mentors to monitor progress.

Natasha K. Martin, D.Phil. (Secondary Mentor) is an Associate Professor in the Division of IDGPH in the Department of Medicine at the UCSD. She is also the co-director of the Biostatistics and Modeling Core of the UCSD Center for AIDS Research. Dr. Martin is a leading infectious disease epidemic modeler, with over 15 years of experience and >60 peer reviewed publications. Her research focuses on the impact and cost-effectiveness of HIV and other blood-borne virus prevention interventions among high-risk groups, such as PWID and MSM. She is a PI of a NIDA funded modeling study (R01DA037773) assessing the epidemic and economic impact of combination and structural HIV interventions among high-risk groups in Tijuana. She has

also successfully mentored 9 pre- and postdoctoral fellows, and has provided primary mentorship during my postdoc at UCSD. I will meet with Dr. Martin bi-weekly to discuss the modeling aim; she will attend annual meetings with my co-mentors to monitor progress.
Nicole Bohme Carnegie, PhD (Contributor) is an Assistant Professor of Statistics in the Department of Mathematical Sciences at Montana State University. Her research focuses on network models, epidemic modeling, causal inference, and HIV prevention. Her work on statistical models for networks includes both theoretical developments and work as a member of the development team for *statnet*, the preeminent suite of network modeling and simulation tools. She has extensive experience building network-based epidemic models of HIV prevention and transmission, including as a primary modeler on the PUMA MP3 project. I will meet with Dr. Carnegie quarterly to discuss how we can best leverage individual-based network epidemic modeling techniques to augment Dr. Martin's expertise as it is primarily in compartmental modeling.

4.2. Specific Courses and Training

Training Aim 1: Acquire skills in reconstructing HIV molecular transmission networks from HIV sequences in order to identify HIV transmission clusters.
International Virus Evolution and Molecular Epidemiology (VEME) Workshop (Year 1): The 5-day Phylogenetic Inference module within the VEME workshop provides an introduction to theoretical background and hands-on experience in sequence analysis using phylogenetic and bioinformatics methods.
Molecular Sequence Analysis (UCSD BIMM 181) (Year 1): This Semester-long class covers sequence alignments, database searching, comparative genomics, & clustering analyses.
Structured readings & bi-weekly meetings with Drs. Little and Wertheim: I will meet weekly with Drs. Little and Wertheim to discuss molecular network methods most germane to my KL2 research, with an emphasis on the following text, "The Phylogenetic Handbook A Practical Approach to Phylogenetic Analysis and Hypothesis Testing".[42] They will guide me through the technical aspects of using HIV TRACE software to reconstruct molecular networks.

Training Aim 2: Develop methodological expertise in HIV epidemic modeling among MSM.
University of Washington Network Modeling for Epidemics workshop (Year 1): This 5-day course provides an introduction to stochastic network models for infectious disease transmission dynamics, with a focus on empirically based modeling of HIV transmission.
University of Washington Summer Institute in Statistics and Modeling in Infectious Diseases (SISMID) (Year 1): Participants choose from a series of two-and-a-half day modules and design a program best-suited to their interests. I will attend the Contact Network Epidemiology Module that introduces network concepts (e.g., nodes, degree, clustering, and modularity), and analytical and simulation-based approaches to contact network epidemiology. It will discuss both idealized and empirical networks and how modeling assumptions affect the tractability of different methods.
Directed readings and training with Drs. Martin & Carnegie: I will meet weekly with Dr. Martin to discuss modeling methods relevant to my KL2 research, with an emphasis on two textbooks: "An Introduction to Infectious Disease Modeling"[43] and "Infectious Diseases of Humans: Dynamics and Control"[44]. She will guide me through the technical aspects of epidemic modeling development, coding, and analysis using MATLAB. I will meet with Dr. Carnegie quarterly for guidance on how to implement the individual-based network epidemic modeling techniques.

Training Aim 3: Gain expertise in the ethical conduct of research pertaining to network analyses among MSM and Transgender populations (Responsible Conduct of Research).
Despite the considerable potential for social and molecular networks to reduce HIV incidence, a range of ethical, legal and social implications, limits these efforts. For example, 30 U.S. states currently have HIV specific laws criminalizing HIV transmission and non-disclosure of HIV status.[45,46] Importantly, none of these states include provisions for mitigating legal consequences through the protective use of ART, PrEP or condoms, which markedly limit the risk of HIV transmission. The same evolutionary principles that are used to identify genetically linked clusters in the population have also been used to prosecute individuals where the transmission of HIV is criminalized.[47] Molecular networks may also result in loss of individual or group privacy related to the unintentional disclosure of potential transmission between two or more individuals belonging to the same cluster.[48-50] Additionally, attributes of a particular cluster, such as behavioral or demographic

characteristics (e.g., MSM, African-American race, etc.), could conceivably expose entire groups to political, legal, and social consequences, including stigma. Furthermore, as the accuracy of transmission direction inference improves, so too may the legal and social risks to persons involved in a putative transmission. As a part of this KL2, I will learn how to consider these issues with the following **Responsible Conduct of Research Training Activities:**

Ethics at UCSD: The UCSD Research Ethics Program (REP), founded in 1997, ensures that instruction in the responsible conduct of research is available for all UCSD trainees on NIH training grants. Additionally, reflecting UCSD's commitment to providing ethics training for academics at all career stages, the REP offers courses, seminar series, workshops, and individual seminars or lectures tailored to meet the needs of programs throughout the University.

Ethics and Survival Skills in Academia at UCSD (Interdisciplinary Sciences 241): This 10-week course (25 contact hours) is designed to fulfill training requirements in the responsible conduct of research for NIH and NSF trainees. Course topics are covered through a combination of class discussions, assigned readings, and written assignments, and include: ethical conduct of research involving human subjects, responsible conduct of international research, authorship and collaboration, bias and conflicts of interest, and data management.

Directed Readings: Dr. Little will guide me through readings on the ethical conduct of HIV prevention research with vulnerable populations, including MSM and Transgender persons. Sample readings: *Ethical considerations in global HIV phylogenetic research*[51] and *Ensuring privacy in the study of pathogen genetics*.[52]

Fordham University Center for Ethics Education, HIV Prevention Research Ethics Training Institute (RETI): This NIDA-funded institute offers a 10-day workshop on research ethics. RETI fellows develop proposals to conduct mentored research investigating ethical issues in HIV-related research. During Year 1, I will prepare a RETI application proposal to supplement my KL2 research to investigate, *The Ethics of Disclosing Public Health Information among Social Network Members to Improve HIV Care.* My participation in RETI will augment my training in research ethics, support the development of a collaborative research network, and provide preliminary data for future grant proposals.

Training Aim 4. Strengthen professional skills for a successful academic career, including grant writing, the dissemination of research findings, and the development of collaborative scientific relationships.

Clinical Research Enhancement through Supplemental Training (CREST) Coursework: Due to my doctoral and masters studies in epidemiology, I have had extensive coursework in epidemiology, biostatistics, research methods, and health economics. However, I would benefit greatly from taking the *Personal Development Skills* course which provides assessment, calibration, and strengthening of one's workplace communication abilities as well as the *Research Budgeting and the Project Management* course which provides an understanding of Study Set Up and Management, Effective Study Budget Preparation and Negotiation, Billing and Financial Management, Auditing, Research Compliance and Ethical Considerations.

UCSD Division of IDGPH Trainee Sessions: These bi-weekly sessions involve presentations from IDGPH pre- and post-doctoral fellows and faculty on HIV and substance use research. Faculty also offer seminars on academic career development (grant writing, manuscript preparation, and research ethics). I will present my research annually and my proposed R01 in Year 2.

IDGPH Work In Progress: This weekly session allows speakers to present their research for discussion and constructive evaluation. I will present my KL2 results as I develop related manuscripts and grant proposals.

IDGPH Journal Club: This biweekly journal club focuses on current topics in HIV among key populations. I will present one paper per year on MSM & HIV to hone my critical analysis and presentation skills.

UCSD Department of Medicine Faculty Mentoring Program: I will participate in seminars, networking events, and meetings with my program mentor, Dr. Susan Little, who is senior faculty with substantial experience mentoring trainees and junior investigators. In the past 10 years, Dr. Little has mentored 4 infectious diseases fellows, 5 post-doctoral fellows, 3 graduate students, 1 medical resident, and 8 junior faculty members. Dr. Little is also a member of the Department of Medicine (DOM) Faculty Mentoring Program and provides regular mentoring to junior faculty members at UCSD throughout the DOM. Her advice will facilitate my advancement to independence.

CFAR Department of Medicine "My First R01" Review: The UCSD CFAR offers mock study sections providing junior investigators with a critical review of their HIV-related NIH grant applications before submission. I will submit my R01 proposal, and any other NIH grants, for review.

CFAR quantitative working group: This group meets monthly to bring novel ideas and methods to advance HIV research and to use the developing projects with the CFAR as a spur for methodological innovation. They discuss current methodological challenges in ongoing research projects and grant preparation as well as topics of interest across grants, e.g. causal mediation, mathematical modeling of epidemics, network modeling, and analytical methods for evaluation of evolving HIV genetic clusters--of relevance for the study of HIV prevention research. I will attend these meetings for the duration of the KL2 and present proposals related to my findings.
Manuscript Preparation: During biannual meetings, my mentoring team will monitor progress and ensure that I am satisfying my benchmark of 1-2 first-authored publications on the findings from my research proposal per year, in addition to 1-2 co-authored publications per year with my mentoring team (**table 2**).

Table 2: Proposed Manuscripts

Title	**Year:**	1	2	3
"Identifying missing links: How social network data contributes to HIV transmission networks" (TA 1, RA 1)		X		
"Characterizing the network position of incident HIV infections" (TA 1, RA 2)			X	
"Using combined social and molecular networks to prioritize pre-exposure prophylaxis" (TA 1 & 2, RA 3)				X

Scientific Meetings: I will attend one domestic and one international conference per year to disseminate my research findings, gain exposure to HIV modeling research (e.g. International Conference on Infectious Disease Dynamics [EPIDEMICS]), network with leaders in HIV prevention research (e.g. Conference on Retroviruses and Opportunistic Infections [CROI], International AIDS Society [IAS] Conference, and establish myself as an independent investigator in HIV Dynamics and Evolution, HIV Research for Prevention [HIVR4P].
National Center of Leadership in Academic Medicine (NCLAM) Program: Health Sciences professional development program with a mentoring component for junior faculty at UC San Diego. NCLAM helps junior faculty develop skills appropriate for their academic career, implement a personal strategic plan and expand their network of colleagues within Health Sciences and University. Junior faculty attend a series of 16 workshops with topics ranging from UC San Diego expectations for academic promotion, to skill development in teaching and research, to professional development and leadership training. During the second half of the program, junior faculty choose a professional development project and are matched with a senior faculty mentor who can facilitate their progress.
Biannual Progress Reports: I will meet with my mentor committee in person annually to discuss progress on: 1) desired skills/competencies and plans to obtain them, 2) completed and planned coursework, 3) current projects, outcomes, and barriers to completion, 4) publications in progress and under review 5) conferences planned and attended, and 6) grants applied for and received.

Table 3: Timeline of training activities under the award period

Training Aim	**Y1**	**Y2**	**Y3**
1. Acquire skills in reconstructing HIV genetic transmission networks			
Virus Evolution & Molecular Epidemiology workshop	X		
Structured readings & bi-weekly meetings with Drs. Little and Wertheim	X	X	X
Molecular Sequence Analysis (UCSD BIMM 181)	X		
Analysis of HIV-1 *pol* sequence data from UNI study		X	X
2. Develop expertise in epidemic HIV transmission modeling			
University of Washington Network Modeling for Epidemics workshop	X		
University of Washington SISMID		X	
Directed readings, weekly meetings with Dr. Martin, and quarterly meetings with Dr. Carnegie	X	X	X
Modeling of percent of new infections averted due to network based PrEP prioritization on HIV incidence among MSM		X	X
4. Training in the ethical conduct of research			
Directed readings with Drs. Little and Wertheim	X	X	X
Fordham University Research Ethics Training Institute (upon acceptance)		X	
Ethics and Survival Skills in Academia at UCSD	X		
UCSD monthly Biomedical Ethics seminar	X	X	X
5. Professional development for a successful academic career			
Meeting with Dr. Little (weekly), Drs. Wertheim & Martin (biweekly) and all mentors (annually)	X	X	X
UCSD Department of Medicine faculty mentoring program	X	X	X
CREST Personal development skills course	X		
CREST Research budgeting and project management		X	
NCLAM Program (upon acceptance)	X		
UCSD IDGPH trainee meetings, journal club, and work in progress	X	X	X

Presentations at 1 domestic and 1 international conference per year	X	X	X
Preparation and submission of manuscripts	X	X	X
Preparation and submission of CFAR pilot and R01 proposal		X	X

Research Strategy
A. Significance

A1. Epidemiology of HIV in the United States

Although HIV infections overall are beginning to decline in the U.S., certain subpopulations continue to be impacted. Between 2011 and 2015, HIV diagnoses increased by 14% among Hispanic/Latino MSM and 4% among Black men who have sex with men (MSM).[1] Reducing incidence in the remaining groups may be more challenging because these groups are historically disenfranchised, with higher rates of HIV being linked to social and economic environments and stigma.[53-56] The persistent new HIV infections are being driven by individuals with acute and early HIV (AEH) and those or who are HIV infected and aware, but out of care or non adherent to antiretroviral therapy (ART) and viremic. Those who have AEH are more likely to transmit HIV due to a transient period of high titer viremia coupled with elevated rates of risk behaviors due to being unaware of one's infection.[2-4] Phylogenetic studies suggest that up to half of all transmission events occur within the AEH phase of infection.[57,58] Pre-exposure prophylaxis (PrEP) and treatment as prevention (TasP), offer the greatest potential for reducing HIV transmission,[6-9] but need to be utilized by those who have the largest impact on curtailing transmission. Molecular epidemiology has been beneficial for characterizing transmission dynamics and identifying demographic and behavioral characteristics associated with HIV transmission. However, it does not provide a full picture of the transmission dynamics due to the exclusion of HIV uninfected individuals and HIV infected individuals who are unaware of their infection.[59] Therefore, network models that incorporate both the social network (HIV infected and HIV uninfected) and molecular network (HIV infected only) are needed to evaluate the existing and potential relative contribution of ART and PrEP in populations experiencing the highest rates of ongoing transmission.

A2. Challenges identifying AEH individuals and those at highest risk for HIV infection

One of the obstacles in identifying young Latino and Black MSM who have AEH or are not engaged in HIV care is the lack of lesbian, gay, bisexual, and transgender (LGBT) oriented venues where Latino and Black MSM reside, making the dissemination of prevention messages and delivery of services difficult.[60] Contact tracing (eliciting names of sexual and injection-drug use contacts from people newly diagnosed with HIV) is the standard of care employed by Public Health Departments across the across the United States to identify individuals who are unaware of their HIV infection.[13,61] However, this approach produces a low yield of sexual contacts of newly HIV diagnosed clients. In a review of 51 public health jurisdictions, only 0.9 contacts were identified per index.[14] A contributing factor to the low yield of sexual contacts identified is the increasing use of mobile dating applications to find partners.[62] In addition, reaching at-risk populations prioritized for HIV prevention is not straightforward because such populations do not acquire information about new strategies from public media; instead at-risk individuals often obtain and transmit information primarily through their informal social networks, especially their friends.

A3. HIV molecular network inference and use for public health

HIV phylogenetics relies on drawing inferences from the similarity between viral genetic sequences, to reconstruct transmission histories and estimate epidemiologic parameters. The high mutation rate associated with HIV replication[63] results in a nearly unique genetic sequence of HIV (i.e., a fingerprint equivalent) in each infected individual. Software such as HIV TRACE[37] is used to infer linkage between individuals with genetically similar HIV sequences and identify putative transmission clusters (i.e., individuals with closely related viruses). The HIV sequence data needed for these analyses are widely available from drug resistance tests routinely performed in clinical care settings to guide the selection of ART. Using these consensus *pol* sequence data, one can reconstruct an approximation of the sampled transmission network. Research groups have taken numerous approaches to reconstructing HIV transmission networks: phylogenetic[64,65], genetic distance[66-69], and combination methods[65,70-79].

Sequences (i.e., individuals) are indicated as linked if the pairwise genetic distance between sequences is below a specified threshold (often ≤1.5%). Genetically linked sequences represent putative transmission

events, though do not prove transmission between the source and recipient node (i.e., individuals) since unsampled intermediate nodes may be present. Identification of linked putative transmission events are critical for identifying transmission correlates or designing and evaluating prevention strategies. Wertheim (secondary mentor) *et al.*'s single linkage approach links sequences to each other based solely on their pairwise genetic distance, without the need for a tree.[80] This approach has allowed the reconstruction of HIV genetic transmission networks to be more accessible to a public health audience, with the goal of it being used for real-time HIV prevention.[81] However, without information about sexual and social network connections it is difficult to infer direct transmission links. In addition, molecular networks do not provide information on HIV negative individuals connected to the clusters who could benefit from this information the most.

Little, Susan 10/23/2018 7:44 PM
Comment [3]: At some point much earlier on – we need to introduce the term node for individual – sequence=node=individual.

BRITT: Added to career goals section, but I included it here as well.

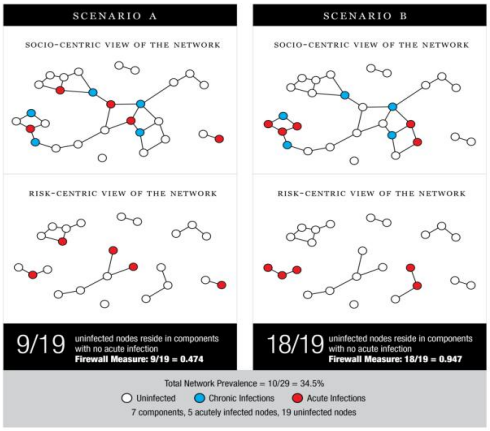
A4. Social network data

Traditional epidemiologic methods have focused on attributes of the individual as a means to assess correlates of health status. The goal of social network analysis is to explain the behavior of individuals within a network and of the system as a whole by focusing on specific features of the interconnections among individuals.[82] Relationships influence a person's behavior beyond the influence of his or her individual attributes.[83] The role of linkages in a social setting is therefore a critical feature of health and the spread of behavior. In the context of HIV, reaching an at-risk population prioritized for HIV prevention is not straightforward due to the influence of peers. At-risk individuals often obtain and transmit information primarily through their informal social networks, especially their friends, making the examination of social networks necessary for HIV risk reduction.[84] Among MSM, capturing social network data is particularly important because the networks of MSM are dynamic, with social connections becoming sexual connections and vice versa at a high frequency over time.[31] Capturing social network data helps mitigate missing sexual partner information when trying to explicitly elicit sexual partners, as is the procedure with contact tracing. Therefore, overlaying molecular data with social network data may enhance the information provided by either source alone. This study will achieve this by collecting social, sexual, and molecular network data on the same group of individuals.

A5. Modeling HIV network dynamics

Epidemic modeling is an effective methodology that can be used to inform HIV prevention policymakers and public health officials, as it evaluates the potential or observed long-term and population level impact of HIV prevention and care interventions when resources or feasibility do not permit empirical study.[85] Many epidemic models simulating the impact of PrEP implementation on HIV incidence currently exist, but most use a compartmental design[39] where only rates of movement between disease states in the population are considered rather than individual dyadic relationships and network structure.[39] However, these individual partnerships and the underlying network structure have been shown to play key roles in HIV transmission and prevention efficacy.[82] For example, a network structure that contains small sub-networks of linked HIV negative individuals within a larger network of individuals with mixed HIV serostatuses limits outbreaks, as the small size of the HIV negative sub-network serves as a structural form of herd immunity.[86] In addition to these sub-networks, the presence of individuals in the larger network who have controlled long-term HIV infection, "firewalls", also help limit outbreaks due to their lower potential of transmitting disease (as a result of a lower viral load at their stage of infection) and their insusceptibility to primary infection[86] (as demonstrated in **Figure 1** by Dombroski et al.[5]). For example, in **figure 1**, the red nodes represent acutely (infectious) HIV infected individuals, the blue represent chronically (non-infectious) HIV infected individuals, and the white represent HIV uninfected individuals. The socio-centric view depicts the entire network, and the risk-centric view removes the chronically infected individuals to show only the

Figure 1. Network Firewall Example[5]



connections between individuals who can potentially transmit to one another. Both scenario A and B have the same HIV prevalence, but the network position of the individuals in scenario B limits the spread of HIV because HIV uninfected individuals are "protected" from acquiring HIV from acute infections due to chronically infected intermediaries. The same protection could occur if enough HIV uninfected individuals are taking PrEP.

B. INNOVATION

Epidemic modeling studies have demonstrated some potential benefits of combining molecular and social network data with regard to characterizing HIV transmission networks, yet little research has been conducted on how they can best be integrated for HIV prevention and care.[16] This study is innovative in that it will be the first in San Diego to combine molecular and social network sources to provide validation of data obtained from either source. For instance, knowing the social network position of phylogenetically sampled individuals may help establish the reliability of the transmission pathways estimated in the molecular network, and conversely, molecular data can help infer potential missing social ties that existed prior to the window of time that social network data were collected.[16] Few epidemic modeling studies have taken advantage of this combined social molecular network structure to inform transmission modeling and guide interventions. Existing epidemic models that aim to optimize PrEP initiation have largely ignored the underlying social and molecular network structure and instead have focused on prioritizing PrEP to individuals based on their demographic and behavioral risk characteristics.[39] Sexual network structure (as opposed to social) has been accounted for in a handful of modeling studies,[39-41] but sexual network data are often limited due to non-disclosure of partners.

The low yield of identifying new HIV infections via contact tracing has also demonstrated that finding individuals from sexual networks to initiate into care is not feasible.[14] Rather, interventions that recruit the social network have been more effective at locating those with undiagnosed HIV infection.[87] The reason they are more effective has not been well elucidated, but may be due to high HIV prevalence combined with a significant overlap between the social and sexual networks of young MSM and transgender women. This study will help disentangle whether social network data provide a stronger 'signal' of the true transmission network than sexual network data due to fewer disclosure concerns, or if social network recruitment identifies undiagnosed but molecularly unlinked HIV infections. In addition, the social and molecular network data will provide information on HIV uninfected individuals at highest risk of HIV acquisition based on their position in the combined network. This study will provide improved insights on the prioritization of HIV prevention and care strategies as a result of modeling the unique combination of social and molecular network data.

C. APPROACH

C.1. Data Sources: Data will come from the following three studies, which are detailed below: the Urban Networks Interaction (UNI), the San Diego Primary Infection Resource Consortium (PIRC), and the Early Test (and soon the Good to Go) HIV screening program. The variables obtained from each can be found in **table 4**.

Table 4. Data sources and variables by research aims

Data Source	Year	Variables	Research Aim
Urban Network Interactions	2018-2019	Demographics, behavioral risk behaviors, social network data, molecular network data, HIV NAT, HIV VL, CD4	1,2,3
PIRC	2008-2019	Molecular network data	1,2,3
*Early Test/Good to Go**	2008-2019	HIV incidence estimates	3

** Some participants from Early Test/Good to Go also feed into UNI*

Overview of *Urban Network Interactions (UNI)* - Parent Study: UNI is a cross-sectional study that uses a social network recruitment strategy (SNS) to characterize the structure of the social networks of HIV-infected and at-risk persons in San Diego.

Description of UNI Study Process:

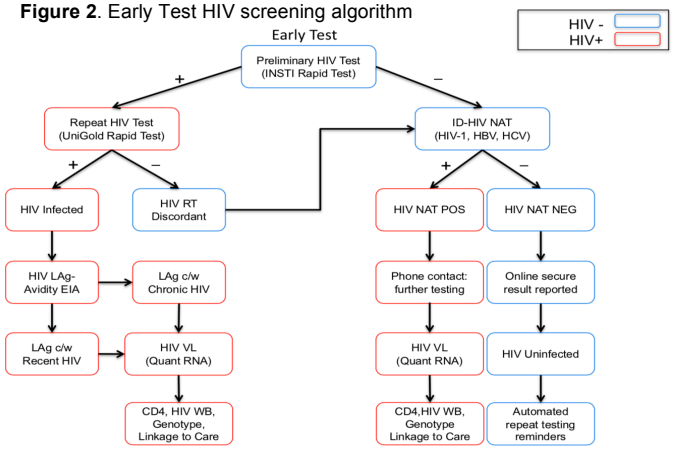
Recruitment: There are three main activities that make up the SNS recruitment: 1) recruiting, screening and interviewing "seeds", or initial recruits; 2) screening and interviewing persons who present a valid recruitment coupon to project staff; and 3) training eligible participants to recruit others.

The SNS is used to find HIV infected persons who are either unaware of their status or HIV infected, aware and out of care, or at high risk for HIV infection. The objective of SNS for this study is not to generate a generalizable sample; rather, it is to take advantage of the trust generated through the peer recruitment.

Ten to thirty participants will be recruited from the ongoing PIRC (HIV infected persons), Early Test HIV screening program (HIV uninfected persons), and from the community to serve as "seeds". These seed participants will serve as the starting point for the proposed social network chain-referral recruitment process. At study enrollment, participants will be administered a survey that records basic demographic information including: age, marital status, race/ethnicity, education, household structure, income, employment, HIV testing history, sexually transmitted infection (STI) history, PrEP use and adherence, sexual behaviors, and substance use. Brief information on participants' social networks will also be collected. HIV uninfected seeds will also undergo HIV screening with the Early Test protocol detailed in **Figure 2**. All HIV infected participants will undergo HIV pol sequencing (as part of routine drug resistance screening) to construct the molecular network. Each seed participant is asked to recruit up to 5 persons in their social network within 30 days of enrollment. The first 400 persons meeting study inclusion criteria and providing informed consent will be enrolled (including seeds).

Laboratory Testing: The Early Test screening algorithm includes an HIV antibody rapid test (RT) with reflex to individual donation NAT (ID-NAT, i.e., not pooled) in persons who are RT negative. To differentiate early HIV infection from established infection, all dual HIV RT+ persons undergo a limiting-antigen (LAg) avidity enzyme immunoassay[88] to detect recent infection. Negative HIV NAT results are provided online[89] and thus do not require a follow up visit[89]. Persons with positive HIV RT or HIV NAT results receive standard of care HIV confirmatory testing and clinical care labs (CD4, viral load and an HIV genotype).

Figure 2. Early Test HIV screening algorithm



Ability to recruit the HIV risk network through UNI:
UNI recruitment began in August of 2018. Thus far, we have enrolled 37 participants; 16 seeds and 28 recruits. We expect this number to increase significantly as a result of a new marketing campaign being rolled out called Good to Go (GoodToGoSD.com). The Good to Go campaign represents an expansion of the previous Early Test program and is a sex-positive, HIV status-neutral sexual health program providing HIV and STI screenings for those who do not know their HIV status. This program will specifically focus on recruiting MSM of color, populations in which rates of new infections are increasing both nationally and in San Diego. The new Good to Go program will open in early December after a 2 month closure, during which UNI and Early Test recruitment were significantly reduced.
We are confident in our ability to successfully recruit the network using SNS due to our prior success using a social network recruitment strategy to recruit a HIV infected and unaware persons to the PIRC program (in 2011). This previous PIRC SNS effort resulted in the recruitment of 312 participants over 10 sequential waves of data. In addition, the PI (Dr. Skaathun) will be overseeing UNI and has extensive experience with respondent driven sampling recruitment, including 5 years working with the Centers for Disease Control (CDC) sponsored National HIV Behavioral Surveillance study, and 5 years managing two cohort studies of predominantly young MSM and transgender persons in Chicago.

Overview of the San Diego Primary Infection Resource Consortium (PIRC)

The proposed KL2 will be situated in the San Diego PIRC in the Department of Medicine at UCSD. PIRC is the largest, most intensively studied and well-characterized cohort of acute and early HIV (AEH) infected

individuals in the United States. The current goals of the PIRC are community HIV testing, AEH infection staging, improving the continuum of HIV prevention and treatment, and developing a shared clinical and specimen resource for qualified investigators interested in research related to acute HIV infection and transmission. The PIRC was first started in 1996 and has been continuously supported by research grant funding since that time. The Early Test (and soon the Good to Go) HIV screening program is supported by PIRC and all newly HIV diagnosed participants are referred to the PIRC longitudinal, observational cohort – where they are provided access to immediate antiretroviral treatment without charge. In the last 5 years, the Early Test has screened over 20,745 individuals at risk for HIV infection and identified 494 newly diagnosed HIV infected individuals (62 acute, 189 early and 334 chronically HIV infected). The Early Test has documented an HIV incidence of 1.78 per 100 person years among repeat MSM testers (2.03 per 100 person-years among Hispanic MSM, and 1.86 per 100 person-years among Black MSM)[90]. The highest HIV rates in the Early Test were observed among young MSM (<24 years of age) with an HIV prevalence of 5.5% and an HIV incidence of 3.40 per 100 person-years.[90,91]

C.2. Research Aims

The research aims and their associated methods and deliverables are summarized in **table 5** below.

Table 5. Research aims, methods, and deliverables.

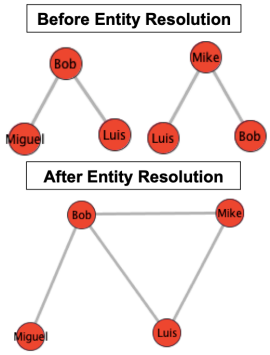
Research Aim	Method	Deliverable
Reconstruct molecular network and compare to social network	HIV-TRACE used to reconstruct molecular network, entity resolution algorithm used to construct social network on the same individuals. Effective size bridging network will be calculated on combined network.	Data for aims 2 & 3, Manuscript
Characterize HIV acquisition based on an individuals' position in the combined social and molecular network	Demographics, prevalence of STIs, select behaviors and network characteristics among persons with AEH will be compared to those who are suppressed with long-term infection using log-linear binomial regression.	Data for aim 3, manuscript
Model the percent of new infections that could be averted if PrEP delivery was prioritized based on an individual's network position	A dynamic, stochastic social network model (based on exponential-family random graph models (ERGM)) of sexual HIV transmission among MSM and transgender women in San Diego will be developed.	Manuscript, intervention guidance

C.3. Aim 1: To reconstruct HIV-1 transmission networks among MSM and Transgender populations in San Diego and compare the relationship between these networks to social network data obtained on the same individuals (maps on to TA 1)

Methods: Reconstruction of HIV genetic transmission network:
The HIV-TRACE (available at www.hivtrace.org)[92] program will be used to construct the HIV-1 transmission network with a genetic distance threshold of 0.015 substitutions/site across the prot/RT region of the HIV pol gene. This genetic distance threshold has been validated for identifying partners with direct or indirect epidemiological links[93] and is used for molecular HIV surveillance in U.S. public health.[94]

Methods: Construction of matched social network (Entity Resolution)
A multiple step process combining computerized scoring and manual verification developed by PI Skaathun,[95] will be used to construct a de-duplicated network of all respondents and social network partners (known as "entity resolution", **Figure 3**). The first step is to run a computer program (using R software)[96] on the initial list described in all surveys to create a file of information on and a "matched score" for pairs of nodes. The score will be based on and ordered by information on the following: phoneticized last name, phoneticized first name, phoneticized nickname, age, gender, and race. The file produced at this step will contain all pairs with scores that meet a threshold, which will allow us to consider them potential matches, as well as their demographic information. Two independent coders will review and score the composite list of paired nodes and manually scored each pair on a 4-point scale from 3 indicating that they are "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 will review the file with the manual scores to resolve any discrepancies. After an initial pass to resolve coder differences, a computer program will be run to verify that matched pairs are transitive and to add missing

Figure 3. Entity Resolution Example



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 will be generated, etc.) Comparisons with a score of 3 will be considered to be a "match" (the same person). A new set of unique IDs will be created for all nodes with matched nodes receiving the same the ID. An edge (tie) list will be created for all Egos (respondents) and Alters (social network partners) based on the new unique IDs. The complete network will be generated and checked for coherence (e.g., respondents being matched). Incorrect matches will be removed prior to analyses and the renumbering with unique IDs will be redone.

Methods: Bridge Identification: After the construction of both the molecular and social network, the two networks will be overlaid (via having both social network and molecular data on the HIV infected individuals), visualized, and analyzed using Visone and R software. This will allow us to identify whether HIV transmission clusters are connected by members of the social network who are not members of the HIV transmission clusters (i.e. they are either HIV negative, HIV positive but are not connected to the molecular network, or they are named social contacts in the UNI study, but did not participate in the study so do not have lab data). These individuals who connect otherwise unconnected groups are known as "bridges" and have implications for HIV interventions. Being in the bridge position has been independently associated with HIV seropositivity.[95,97] Consequently, bridges serve as essential targets for reducing transmission because they potentially transmit infection from an infected cluster to an uninfected cluster. Research has shown that immunization based on bridging is more effective than immunization based on number of contacts alone.[12] We will calculate the effective size bridging metric developed by Burt[98] (n-2t/n), where n= the number of network members and t= the number of ties between network members.[99] For instance, if an individual has a network of 8 people and there are four ties between the network members, the effective size would be 8−(8/8) = 7.[99] Higher effective size indicates more bridging. The proportion of bridges in the network will be accounted for in RA 3.

NM 11/6/2018 7:57 PM

Comment [4]: This is a great start but I think is missing the critical final analysis, which in my mind would compare the utility and the value of the sexual vs social network data and how it maps to the molecular network data?

BRITT: I agree that this would be an interesting analysis, but we aren't explicitly collecting sexual network data as far as I know.
Susan, do we collect sexual contacts in Early Test or PIRC?

The construction of this combined network will provide an estimate of the underlying HIV risk network structure, which will aid in the identification of those at highest risk for HIV acquisition. We hypothesize that individuals who cluster in the HIV-1 transmission network will be indirectly connected by HIV negative individuals in the social network. These results will be used to model PrEP prioritization in aim 3.

C.4. Aim 2: To characterize HIV acquisition defined by having acute or early HIV infection (i.e. incident infection) based on an individuals' position in the combined social and molecular network (maps on to TA 1).

Method Overview: Persons with AEH (who are viremic and highly infectious) will be located in the combined social and molecular network from RA 1 and compared to those who have long-term infection with undetectable viral load in terms of their behavioral and network characteristics (for example, the structural properties of their social network such as degree and the proportion of their network that exhibits risk behaviors, and whether or not they are members of molecular clusters). Characterizing individuals with AEH is of interest because due to their recent acquisition of HIV, it can be assumed that those who are HIV uninfected who share these characteristics are at high risk of acquiring HIV.

Statistical Analysis: The outcome of interest will be either being HIV infected with AEH (persons presenting with negative HIV-1/2 serologies and virus detected via individual donation (i.e., not pooled) HIV nucleic acid testing (NAT)) or having long-term HIV infection and viral suppression (<50 copies/mL). Bivariate associations between characteristics of interest including demographics, prevalence of STIs, selected behaviors, and network characteristics among persons with AEH compared to those who are suppressed with long-term infection will be obtained using chi-squared for categorical variables and Kruskal-Wallis for continuous variables. Independent predictors of AEH will be assessed using logistic regression. The following network metrics will be calculated and compared: degree, density, and bridging. The results of this analysis will allow us to identify HIV uninfected individuals at highest risk for HIV acquisition who would benefit most from HIV prevention interventions, such as PrEP.

Britt Skaathun 11/5/2018 3:47 PM

Comment [5]: Victor-is there a more exciting analysis we could do that won't confuse the reviewers (most won't have stats backgrounds)?
Do I need a power calculation?

C.5. Aim 3: To model the percent of new infections that could be averted if PrEP delivery was prioritized based on an individual's network position versus delivery in a network-agnostic manner (maps on to TA 2).

Method Overview: A dynamic, individual-based stochastic network model of HIV transmission among MSM and transgender women in San Diego will be developed to determine the future impact of PrEP prioritization strategies on HIV incidence among MSM/TW. The model will incorporate behavioral, molecular, and network features, and will be parameterized with results obtained from Aim 2 as well as with data from the PIRC and Early Test programs.

Epidemic model structure: The model will be a dynamic, individual-based stochastic network model (based on Exponential-family random graph models (ERGM[100])) of sexual HIV transmission among MSM and transgender women in San Diego. We include transgender women due to their high susceptibility to high HIV infection and their social and sexual network connection to MSM. The CDC estimates approximately one-quarter of all transgender individuals in the United States are infected with HIV, and transgender women of color have the highest prevalence with a more than 50% infection rate.[101] Thus far in the UNI study, 4% of the population are transgender, 25% of whom are HIV infected. Transmission due to injection will be ignored due to the low prevalence (1%) of injection drug use among MSM in San Diego.[90] ERGMs are an exponential-family model that account for dyadic dependence and model network structure. They treat nodes (individuals) as fixed and model the process that creates the observed network structure.[100] The *dynamic* HIV transmission model will mechanistically simulate the HIV epidemic across this network, with a susceptible individual's risk of acquiring HIV changing over time depending on their risk behaviors, PrEP status, and HIV infection status/stage and intervention status (e.g. higher infectivity in the acute HIV stage, and lower infectivity on ART compared to latent untreated HIV) of their sexual partners. We will model relationship formation and dissolution as well as sexual behavior within relationships (casual vs. main partnerships, anal sex acts, condom use, and insertive, receptive or versatile role selection).[40]

Data requirements: The model will be parameterized with demographic, behavioral, and network data from the UNI study, and HIV care data from PIRC. Additional data on sexual HIV transmission probabilities by stage of HIV infection (acutely infected, chronically infected with virus present, and virally suppressed), and natural history of HIV infection by stage will be obtained from the literature.[102] ART will be assumed to reduce transmissibility by 96%[6] and mortality by 70%.[103] As implemented by Carnegie et al. (Contributor), PrEP uptake will be defined as accepting at least one prescription and considered at rates 20%, 40%, and 60%, and adherence will be considered as negligible (zero doses/week), low (two doses/week), and high (four or more doses/week).[39] Per contact risk will be reduced by 0%, 75%, and 90% respectively.[8,39]

Model calibration and uncertainty analysis: The model will be calibrated to 3 HIV prevalence[90,91,104] and 1 HIV incidence rate estimates among MSM in San Diego between 2008 and 2014.[90] Findings from **RA 1** and estimates from the literature will be used to assign prior distributions for all model parameters. For each individual, parameters will be randomly sampled from prior distribution ranges. We will simulate ten model trajectories to assess stochastic variations; model simulations falling within the confidence intervals of the epidemiological calibration data will be accepted

Representation of Social, Molecular and Sexual Networks:[105]
Our modeling methods aim to preserve certain features of the cross-sectional and network structure as reported in UNI, PIRC, and Early Test. We will model dynamic HIV transmission on a dynamic network structure. Our methods do so all within the context of changing population size (due to births, deaths, arrivals and departures from the population) and changing composition by attributes such as age.
The network features that we aim to preserve are as follows, with the parameters for each described in turn:

- The proportion of persons in bridge positions (obtained from **RA 1**)
- The proportion of persons in any given combination of main and casual partnerships (obtained from PIRC and Early Test)
- The expected number of one-time contacts per time step had by persons in each main-casual combination (obtained from the literature)
- Variation across persons in the numbers of one-time contacts (obtained from the literature)
- Race mixing within each of the different relational types (obtained from PIRC and Early Test)
- Age mixing within each of the different relational types (obtained from PIRC and Early Test)

Model scenarios & outputs: We consider several hypothetical scenarios for annual provision of PrEP. We

model the percent of new infections averted over the next ten years due prioritizing PrEP based off of different positions within the network (results obtained from **RA 1** and **RA 2**) versus the same number of randomly selected people and person-years within the network receiving PrEP. For instance, we will model PrEP prioritization among those in bridge positions (obtained from **RA 1**) as well as the network metrics that are found to be significant in **RA 2**. These models perform day-by-day simulations of network and disease dynamics on populations of initial size 10,000 MSM over 10 years. In general, to assess stochastic variation, we repeat the simulation for each set of inputs twenty times.[39] Five outcomes will be generated for each scenario: HIV incidence; HIV prevalence; the number of new HIV infections averted (NIA) and percent of infections averted (PIA) across the next 10 years relative to no PrEP; and the number of person-years on PrEP per infection averted (number needed to treat [NNT]).[40]

C.6. Limitations, Strengths and feasibility: Completeness of network data: Much of the data are self-report, including the elicited network members. Thus, there could be concern about missing data within the network. Network data, however, are rarely complete,[106] and our rigorous entity resolution methodology will allow us to link individuals who did not name one another, increasing the completeness of the network. Cross-sectional data: The proposed social network analyses will be based on cross-sectional data, which will prohibit us from making conclusions about the directionality of observed associations. Epidemic model parameter uncertainty: Uncertainty will be addressed through detailed univariate sensitivity analyses to assess the impact of changing a single variable or assumption on the model projections. Despite these limitations, this study will provide useful elucidation of how social network data can enhance molecular network data for future HIV prevention efforts.

C.7. Potential implications and future direction: This proposal optimizes interdisciplinary, state of the art methods that will prepare me to address the OAR priority of reducing HIV incidence. Specifically, training in reconstructing HIV molecular networks and molecular epidemic modeling will inform how to effectively stop HIV transmission given available resources. This new skillset coupled with my extensive experience in public health, epidemiology, and social network analysis will ensure that I will produce impactful independent research in the field of HIV prevention.

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