



Network Modeling of PrEP Uptake on Referral Networks and Health Venue Utilization Among Young Men Who Have Sex with Men

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Abstract

The objective of this study is to identify individual-level factors and health venue utilization patterns associated with uptake of pre-exposure prophylaxis (PrEP) and to evaluate whether PrEP uptake behavior is further diffused among young men who have sex with men (YMSM) through health venue referral networks. A sample of 543 HIV-seronegative YMSM aged 16–29 were recruited in 2014–2016 in Chicago, IL, and Houston, TX. Stochastic social network models were estimated to model PrEP uptake. PrEP uptake was associated with more utilization of health venues in Houston and higher levels of sexual risk behavior in Chicago. In Houston, both Hispanic and Black YMSM compared to White YMSM were less likely to take PrEP. No evidence was found to support the spread of PrEP uptake via referral networks, which highlights the need for more effective PrEP referral network systems to scale up PrEP implementation among at-risk YMSM.

Keywords Social network analysis · PrEP · Health care delivery system · Young men who have sex with men · Systems science methodology · Exponential random graph models · Auto-logistic actor attribute models

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Introduction

In the United States, young men who have sex with men (MSM) have an elevated rate of HIV infection. Both Texas and Illinois bear an excess burden of new HIV infections in the United States (U.S.) [1]. Houston accounted for 29.3% of the new infections in Texas, 78.3% were men, approximately 85.8% were among MSM [2]. Chicago accounted for 55.7% of the new infections in Illinois [3], 83.2% were men, of whom 92.1% were among MSM [4].

Tenofovir disoproxil fumarate with emtricitabine as pre-exposure prophylaxis (PrEP) was approved by the U.S. Food and Drug Administration (FDA) in 2012 to reduce the number of new HIV infections. Several randomized clinical trials have demonstrated safety, efficacy, and effectiveness of PrEP to prevent HIV acquisition [5–8]. According to the latest report, 98,732 individuals have started PrEP since 2012, and 36,732 individuals were estimated to start PrEP in 2016. Men and individuals aged 25 years old or older are estimated to have the highest rates of PrEP use, and African Americans and Hispanics are estimated to have low PrEP use relative to their rates of new HIV infections [9]. These numbers indicate a lag in PrEP uptake, especially among young racial/ethnic minority men, and this is of concern given the CDC estimate that one in four, or 492,000 MSM, have indications for PrEP [10].

PrEP uptake among the highest risk groups in the U.S. faces implementation challenges [11] and lack of financial coverage [12]. These barriers are exemplified in cities such as Atlanta, where few MSM (estimated to be 15%) achieve HIV protection via PrEP, given barriers within multiple stages of the PrEP care continuum [13]. This study employs stochastic social network models [14, 15] to estimate PrEP uptake and referral patterns among YMSM, and their utilization patterns of health centers to guide future implementation efforts.

Background

PrEP implementation among the highest risk sub-populations of MSM, such as young MSM (YMSM) and racial/ethnic minority MSM, is challenged by the need for sustained engagement of at-risk communities and health care providers [16, 17]. Structural barriers, such as stigma and discrimination that impede access to HIV health services [18], also may contribute to disparities in PrEP awareness and create age and race/ethnicity-specific barriers to PrEP uptake [13, 17, 19, 20]. Although younger Black MSM have a higher intention to adopt PrEP than older Black MSM [21], they tend to have lower PrEP awareness and

uptake [17, 22]. Younger or Black MSM are less likely to be aware of the availability of PrEP [20, 23], and MSM of color tend to perceive barriers to PrEP uptake [19]. Lack of awareness limits self-referral, and limited health care insurance coverage serves as a barrier to clinical care access, including obtaining PrEP for Black YMSM [20], which may restrict PrEP access for this at-risk population in some jurisdictions [16].

PrEP awareness among YMSM may be enhanced by participation in other health services, including HIV prevention programs [17]. However, a mismatch between prevention services and the needs of this population may impede PrEP implementation, given evidence that HIV uninfected Black MSM tend not to affiliate with health centers that provide HIV-prevention services [24]. To optimize PrEP implementation among YMSM, a traditional approach would include focus on individual-level interventions, such as increased PrEP awareness, knowledge of accessibility, and uptake among providers and patients. Although this level of intervention is underway, we posit that important system-level organizational promotion, such as active involvement and coordination between health providers and health organizations in both public and private sectors, also is important.

Social Network Approaches to Health Systems Research

Social network analysis has been applied to health systems research, as it offers powerful methodological tools to examine complex collaborative networks of organizations [25] to define the boundaries of health systems and the structural embeddedness of networks, thus allowing researchers to examine their impacts on diffusion of knowledge and, ultimately, health outcomes [26]. Public health delivery systems operate through coordination of partnerships between multiple public and private health organizations, without which delivery systems may perpetuate inequalities in the availability of health care [27]. Our study regards health delivery systems as being formed by inter-organizational partnerships or collaborative networks of health organizations [27–30] that, in the HIV prevention context, range from community-based organizations that provide health services to clinics that are both publicly and privately funded.

Existing network studies in health services research, however, have been limited to descriptions of network characteristics, usually within one type of network [27–30]. Few network health systems studies include (a) a holistic approach to model and test specific network structures, i.e., density, (b) examination of multiple networks concurrently,

or (c) identification of local network patterns in relation to the outcomes [30, 31].

Systems Science Perspective of Health Delivery System

Systems science allows us to examine complex and embedded characteristics of PrEP care delivery systems that engage YMSM. It also provides insight into the entire system that comprises connections among different components and their interactions to form a coherent whole [32]. In the context of network analysis, a health system is regarded as comprising various interconnected networks that form sub-systems that are interdependent and nested and, thus, affect each other and the behavior of network members [26, 30]. We build on systems science to examine complex PrEP delivery systems that are composed of multiple networked components that reflect YMSM's health center utilization and their referral patterns.

This study examines health service networks, including both service and care providers that engage YMSM in Houston and Chicago. Both cities were selected as our study sites that highlight important similarities and differences. First, according to the 2010 US census, the cities are similar in population size (with a ranking of third and fourth largest for Chicago and Houston, respectively). Second, the political culture in regard to same-sex laws is different in the two states. Illinois was the first US state to repeal its same-sex criminalization laws and same-sex sexual activity has been legal since 1962, while in Texas, such a repeal occurred over 40 years later. Third, the health care systems between the two states are different. Illinois adopted Medicaid expansion but Texas opted out. This circumstance provides different insurance coverage contexts, which may pose different challenges in linking YMSM to PrEP care.

System-level factors, such as PrEP referral patterns generated by community-based organizations (CBOs) and agencies, funding sources, and relationships with the referral site, may help to overcome or mitigate uptake barriers, resulting in PrEP diffusion and accessibility, especially for those without insurance [20]. We refer to these health organizations (i.e., CBOs and PrEP providers that form referral relationships with each other) as “health venues” and to YMSM health venue utilization as “affiliation networks” between YMSM and health venues. We operationalize a PrEP delivery system as being formed by multiple networks that comprise two integrated network levels: (1) referral relationships between CBOs and PrEP providers and (2) utilization patterns of YMSM to these health venues. This multilevel referral-affiliation network consists of client-referral ties from CBOs to PrEP providers and

utilization by YMSM of both CBOs and PrEP providers. We view these networks by looking both inward (within network ties) and outward (between-network ties) to form a complex, nested networked system of PrEP care delivery that engages YMSM in Houston and Chicago.

Aims of the Current Study

There are two objectives in our study. Our primary objective is to identify potential individual and other network factors associated with PrEP uptake among YMSM. These factors include individual-level characteristics, e.g., socioeconomic characteristics, behaviors, and utilization patterns of health centers, i.e., propensity of attending health venues. Our secondary objective is to determine whether naturally occurring PrEP referral networks diffuse PrEP uptake behavior among YMSM by estimating PrEP uptake and referral patterns among YMSM.

Data and Methods

Study Setting and Data Collection

Data for this analysis come from a multi-site, longitudinal network study, Young Men's Affiliation Project (YMAP). YMAP consists of two Phases. In Phase I, we collected data on a sample of YMSM-serving venues of various types. Semi-structured interviews were conducted at three waves with venue representatives (mostly interviewing one representative per venue, but for large venues that consist of multiple departments, more than one representatives were interviewed). The baseline survey was conducted in 2013–2014 from 58 venues in Chicago and 80 venues in Houston using computer-assisted personal interviewing via Qualtrics software [33]. These venues were selected based on informant-driven sampling reflecting perceived importance and/or frequency of attendance by YMSM. Inclusion criteria for venue representatives included having affiliation with the venue for at least 6 months, not planning to leave the venue within the next 2 years, and having legal ability to access the venue (age; e.g., bars, clubs serving alcohol). More detailed descriptions of Phase I procedures and survey items are available elsewhere [34].

In Phase II, we collected individual-level survey data at baseline and follow-up. At baseline, YMSM aged 16–29 in Houston ($N=378$) and Chicago ($N=377$) were recruited, using respondent-driven sampling (RDS) [35] between 2014 and 2016. Eligibility criteria included male birth sex and identity, engaging in oral or anal sex with another male in the prior year, and residing in and planning to remain in Chicago or Houston for the following year. We collected

both survey data and blood samples for HIV/STD testing, processed according to site-specific algorithms using HIV-1/HIV-2 multi-spot differentiation and HIV RNA (viral load) tests. More detailed descriptions of Phase II procedures and survey items are available elsewhere [36, 37]. We obtained assent/consent from all participants; parental consent was waived for minors (under 18 years of age). All three institutions that participate in YMAP received approval from their respective institutional review boards (HSC-SPH-12-0830).

This study used both venue and YMSM-specific data from baseline Phase I and Phase II, but we restricted our sample to 49 sites characterized as “health venues” ($N=25$ for Houston, and $N=24$ for Chicago) by excluding other types of social venues where YMSM interact with peers such as bars, sporting organizations, etc., and to HIV-seronegative YMSM ($N=259$ for Houston and $N=284$ for Chicago).

Measures

Behavioral Outcome

PrEP uptake behavior was treated as a binary outcome variable, where 1 indicates that YMSM have ever taken PrEP, and 0 otherwise.

Characteristics of YMSM

We included the following covariates related to YMSM: race/ethnicity (Hispanic, White, Black, other), education (from 1 for grade \leq high school, to 7 for doctorate), lifetime housing instability (yes or no), insurance type (“not insured,” “privately insured,” or “publicly insured such as Medicaid CountyCare or Medicare”). In addition, we included syphilis infection with RPR titers $\geq 1:2$ (yes or no) and measured risk behavior by the number of sex partners in the prior six months, and the number of illicit drugs ever used (continuous, with the maximum of 10 types of illicit drugs).

Characteristics of Health Venues

We included the following covariates related to venues: HIV service providers (yes or no), PrEP provider (yes or no), percentage of Black clientele (continuous).

Affiliation Network Between YMSM and Health Venues

Study participants were provided with city-specific lists for health venues, including clinics and other spaces where health services are provided. Participants identified health venues attended in the last 12 months.

Referral Network Among Health Venues

Venue representatives were provided with a roster of health venues and asked to identify those to which referrals are made (of clients or members) for goods or services in the past 24 months. These referrals include referrals of not only YMSM but also any clients, and referrals for any health services, not specifically for PrEP services.

Analytical Methods

Network Visualization

We visualized our combined affiliation network data between YMSM and health venues, and referral networks between health venues, using the igraph network visualization [38].

Social Influence Analysis

Auto-logistic actor attribute models (ALAAMs) as used to test how YMSM’s PrEP uptake behavior may be affected by their own demographics (e.g., race/ethnicity, age), their behaviors (e.g., number of sex partners), their health venue utilization patterns, the characteristics of utilized health venues, and the referral patterns among these health venues. The various attributes, behavior and associations with network structures are represented by network configurations, and each configuration is assigned a parameter in ALAAMs. All models presented in this study are fitted using the PNet software [39], and provides adequate fit to the data. A positive and significant ALAAM parameter estimate indicates the corresponding effect, whether it represents attributes or behavior of YMSM or their network positions, are positivity associated with PrEP uptake. More detailed information on ALAAMs, model formulations, estimation procedure, model assessment, and specifications are found in the online supplemental information.

Table 2 presents the configurations we included in our ALAAMs together with the estimated parameter values and their standard errors.

Our primary research question on whether PrEP uptake may be influenced through venue referrals is tested by the “Influence through venue referral” effect representing YMSM who attended health venues that referred patients to one another. The other configurations that focus on our secondary objects are, PrEP density effect for the baseline propensity for YMSM to take PrEP; affiliation activity effect to test how venue attendance activities may encourage or discourage PrEP uptake; affiliation YMSM two-star effect to test how attendance at multiple health venues may affect

the uptake of PrEP; affiliated venue attribute effects to test whether venues of specific types or with particular profiles are more likely to be affiliated with YMSM who take PrEP; and YMSM's own attributes to test how YMSM demographics may predict their PrEP uptake.

Results

Descriptive Statistics

Table 1 shows descriptive statistics for characteristics of YMSM in both Houston ($N=259$) and Chicago ($N=284$).

Fifty-five (21%) participants in Houston and fifty (18%) participants in Chicago reported to have ever taken PrEP. For both cities, nearly half of the participants were Black, and a majority had at least a high school education, stable housing, and insurance of some kind and reported inconsistent condom use, were syphilis uninfected, and reported

Table 1 HIV-seronegative YMSM descriptive statistics, from the YMAP Study, Houston ($N=259$) and Chicago ($N=284$), 2014–2016

Variable	Houston	Chicago
Ever taken PrEP		
Yes	55 (21.2%)	50 (17.6%)
No	175 (67.6%)	197 (69.4%)
Race/ethnicity ^a		
Hispanic	60 (23.2%)	36 (12.7%)
White	52 (20.1%)	72 (25.4%)
Black	124 (47.9%)	158 (55.6%)
Other	23 (8.9%)	17 (6.0%)
Education		
High school or less	84 (32.4%)	97 (34.2%)
More than high school	171 (66.0%)	182 (64.1%)
Lifetime housing instability ^a		
No	213 (82.2%)	199 (70.1)
Yes	41 (15.8%)	81 (28.5%)
Insurance type ^a		
Not insured	90 (34.8%)	54 (19.0%)
Privately insured	142 (54.8%)	101 (35.6%)
Publicly insured (e.g., Medicaid, CountyCare)	21 (8.1%)	122 (43.0%)
Condom use behaviour		
Consistent use	67 (25.9%)	70 (24.7%)
Inconsistent use	168 (64.8%)	197 (69.4%)
Syphilis infection status		
Negative	214 (82.6%)	200 (70.4%)
Positive	30 (11.6%)	30 (10.6%)
Number of sex partners	5.41 (6.37; 0, 30)	7.53 (14.31; 0, 150)
Number of illicit drugs ever used ^a	2.46 (2.14; 0, 9)	2.63 (2.21; 0, 9)
Health venue attendance ^a	1.4 (1.7; 0, 12)	2.0 (2.3; 0, 11)
1st quarter percentile	0 health venue 95 (36.7%)	0 health venue 78 (27.5%)
2nd quarter percentile	1 health venue 68 (26.3%)	1 health venue 87 (30.6%)
3rd quarter percentile	2 health venues 50 (19.3%)	3 health venues 67 (23.6%)
4th quarter percentile	12 health venues 46 (17.8%)	11 health venues 52 (18.3%)

List of drugs: cannabis, cocaine, meth, inhalant, sedative, hallucinogens, opioid, pain killer, steroids, and ecstasy

^aHouston and Chicago are statistically different in terms of race/ethnicity ($p<0.001$), lifetime housing instability ($p<0.001$), insurance type ($p<0.001$), and number of health venues attended ($p<0.05$). Either mean (SD; min, max) or n (percentage); percentage computation includes missing values

an average of 5–7 sex partners during the prior 6 months. As for health venue characteristics, both in Houston and Chicago, about twenty percents of health venues provided PrEP and HIV services, and another 44% in Houston and another 75% in Chicago provided only HIV services. In Houston, a total of 19 (76%) venues are referral sites, and 24 (96%) venues received referrals; in Chicago, 17 (71%) venues are referral sites, and 23 (96%) venues received referrals. The average percentage of clientele who were Black was 28% for Houston and 65% for Chicago.

Network Visualization

Figure 1 shows referral networks among health venues in combination with the pattern of health venue utilization by YMSM (line of dots at the bottom) for Houston (left) and for Chicago (right).

YMSM in Houston have few affiliation ties to health venues in general (i.e., blue ties are sparse in Houston). In Houston, all of the five PrEP provider venues (green star nodes) also provide HIV service. Out of the other 20 non-PrEP-providing health venues, there are another six venues that provide only HIV service (green square nodes). In addition, 97 (37%) YMSM are affiliated with at least one of five of both PrEP and HIV service providers (green star nodes), while 125 (48%) YMSM are affiliated with at least one of 20 non-PrEP-providing health venues. In Chicago, 51 (18%) YMSM affiliated with at least one of 19 PrEP providers, while 193 (68%) YMSM affiliated with

at least one of five non-PrEP-providing health venues. In both cities, more YMSM affiliate with the non-PrEP-providing health venues as compared to PrEP providers, but the percentage of the Houston YMSM who affiliate with PrEP providers is more than twice that of the YMSM in Chicago (37% vs. 18%). Referral ties (yellow) among health venues (regardless of PrEP-offering status) are similar in density for both Houston and Chicago (0.18 in Houston and 0.20 in Chicago).

Auto-Logistic Actor Attribute Models (ALAAMs)

Table 2 presents the predictors of PrEP uptake as estimated parameter values and their standard errors from our regression analysis. In Chicago, the relationships between network activity and PrEP uptake are not significant for “affiliation activity,” “affiliation YMSM two-star,” or “influence through venue referral.” These indicate that the uptake of PrEP is not dependent on the ties to other YMSM and health venues. In other words, there is no evidence that attendance at health venues, in general, encourages PrEP uptake. YMSM who attend health venues with a greater percentage of Black clientele, however, tend to take PrEP, as suggested by the positive and significant “affiliated venue Black clientele percentage” parameter. In addition, YMSM’s own attributes are more relevant in predicting their PrEP behavior in Chicago; i.e., YMSM who are White, have a lifetime history of housing instability, report inconsistent condom use, or who have more sex partners are more likely to take PrEP.

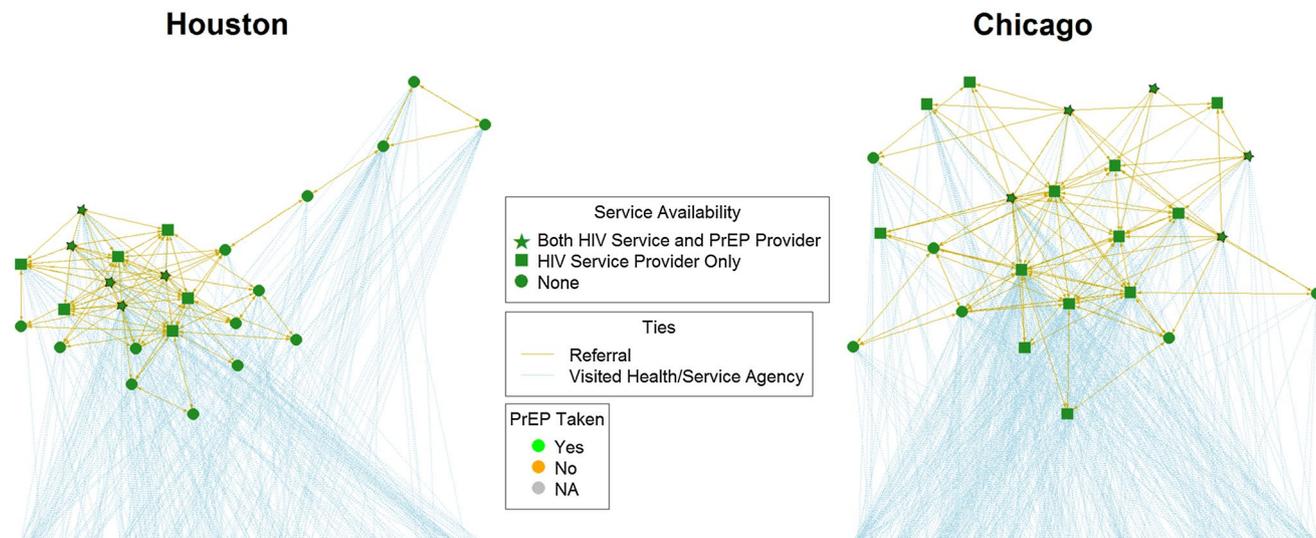
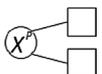
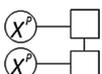
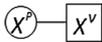


Fig. 1 Multilevel network comprising referral ties between health service venues and affiliation ties between HIV-seronegative YMSM and health venues for Houston (25 venues and 259 YMSM) and Chicago (24 venues and 284 YMSM), 2014–2016. Yellow lines represent referral ties, venue shapes represent service availability (both

HIV service and PrEP provider, HIV service provider only, neither), YMSM color represents status of PrEP use, and affiliation ties from YMSM to health venues is shown in light blue. The graphs demonstrate different utilization patterns (light blue) by YMSM across cities

Table 2 Auto-logistic actor attribute models (ALAAMs) effects, configuration, parameter and standard error estimates to predict PrEP uptake among young men who have sex with men (YMSM), from the YMAP Study, Houston ($N=259$) and Chicago ($N=284$), 2014–2016

Effects	Configuration	Houston		Chicago	
		Est.	SE	Est.	SE
Network position					
PrEP density (test baseline propensity for YMSM to take PrEP)		- 0.52	0.75	- 3.91	1.17
Affiliation activity (test how venue attendance activities may encourage (+) or discourage (-) PrEP uptake)		- 0.55	0.36	- 1.47	0.81
Affiliation YMSM two-star (test how attendance of multiple health venues may affect the uptake of PrEP)		0.15	0.07	0.03	0.05
Influence through venue referral (test whether YMSM who attend health venues that are referring clients to one another are more or less likely to take PrEP)		- 0.01	0.01	0.00+	0.00+
Venue attributes					
Affiliated with HIV service providers (test whether HIV providers are more likely to be affiliated with YMSM who take PrEP)		0.42	0.39	0.70	0.47
Affiliated venue Black clientele percentage (test whether venues with more Black clientele percentage are more likely to be affiliated with YMSM who take PrEP)		0.00+	0.01	0.02	0.01
YMSM attributes					
Hispanic		- 1.34	0.65	1.15	0.92
White		- 0.24	0.55	1.83	0.90
Black		- 1.34	0.58	- 0.51	0.88
Lifetime housing instability		0.29	0.49	1.01	0.47
Privately insured		- 0.36	0.42	0.83	0.64
Publicly insured		0.69	0.61	0.57	0.60
Inconsistent condom use		0.57	0.39	1.45	0.62
Syphilis infection		- 0.62	0.70	- 0.39	0.82
Education		0.01	0.13	- 0.06	0.15
Number of sex partners		0.02	0.03	0.03	0.01
Number of illicit drugs ever used		0.05	0.08	- 0.06	0.09

Circle indicates YMSM, and square indicates health venues. YMSM’s PrEP uptake behavior, as the dependent variable in our ALAAMs, is denoted by binary random variable X^p . Other attributes of YMSM as covariates are denoted by X^p . Venue attributes are denoted by X^v . Significant parameter estimates are listed in bold font, and 0.00+ indicates that the estimate or standard error is greater than 0.00 rather than 0. The effects involving YMSM attributes (X^p) test whether other attributes of YMSM such as race/ethnicity, insurance types, or levels of education, etc. may predict their PrEP uptake, similar to traditional logistic regression models

In Houston, however, YMSM’s race/ethnicity rather than risk behavior plays an important role, whereby both Hispanic and Black YMSM are less likely to take PrEP, even after taking into account insurance status. The positive and significant “affiliation YMSM two-star” effect shows that YMSM are more likely to take PrEP if they have attended multiple health venues; i.e., more health venue utilization encourages PrEP uptake. We did not find a significant effect of “influence through venue referral” on PrEP uptake, which suggests that there was no evidence to support the spread of PrEP uptake driven by the health venue referral networks.

Conclusions

This is the first study to utilize a systems science conceptual framework to define complex PrEP delivery systems that engage YMSM as a multiplex referral-affiliation network by triangulating CBOs, PrEP providers, and YMSM and by using social network models to identify the building blocks of the complex structures to predict PrEP uptake behavior among YMSM. Our study analyzed empirical network data that represent a naturally occurring structural pattern of linkage to PrEP care for YMSM in the community by modeling PrEP uptake behavior. We have identified some patterns of

referral and health venue utilization in relation to individuals' characteristics or behavior. Based on the models presented, we can conclude that health venue referral networks do not drive the diffusion of PrEP uptake among YMSM. Existing referral networks might not operate well for achieving effective PrEP delivery among YMSM.

It remains unclear why referral network forces did not drive PrEP uptake in samples of YMSM in Chicago and Houston. One consideration is that specific PrEP referral networks may not have been mature enough to play a role. PrEP referral networks may not have been mature because the baseline venue sample was collected very soon after FDA approval and right at the time of CDC recommendations released in 2014 for daily oral PrEP with TDF/FTC as one prevention option for sexually-active adult MSM at substantial risk of HIV acquisition [40]. In addition, unmeasured social constructs such as medical mistrust and institutional bias may have outweighed referral network forces. Other possibilities might be that the effects were more at the individual level, i.e., patients were either self-referring or were at sites that offered primary prescriptions. This calls for attention to system features of referring health venues to ensure that they are both accessing the highest risk population and referring effectively. We suggest that future analyses will be key to better understanding how more mature PrEP referral networks vary in their effect across YMSM with a distribution of health venue utilization.

Our results also indicate that in Houston, utilization of multiple health venues encouraged PrEP uptake, whereas, in Chicago, this was not the case. As for PrEP uptake, in Houston, YMSM's race/ethnicity, but not their sexual risk behavior, plays an important role: Both Hispanic and Black YMSM were less likely to take PrEP compared to White YMSM. This is consistent with a prior study that reports lower PrEP uptake among Black versus White and Black versus White MSM in particular [41, 42]. Our results may inform our understanding of why such profound disparities in new infections with HIV exist, despite their network involvement. Addressing the efficacy with which health venues where at-risk individuals participate in risk assessment, HIV testing, and PrEP referral, where appropriate, may improve PrEP access for these populations. In contrast, in Chicago, YMSM who engage in sexual risk behaviors, such as having inconsistent condom use and having more sex partners, predicted PrEP uptake. These findings also may be due to different health insurance systems in Houston and Chicago. Coverage for PrEP is available and accessible in Chicago and may even be more accessible to YMSM of color who make up the majority of Medicaid expansion recipients of PrEP care (data not shown). In Houston, it may be that YMSM who are more connected to health venues are able to obtain PrEP and that a connection to multiple venues increases the likelihood of getting a match between client

insurance eligibility and PrEP provision. Alternatively, connection to multiple venues may be a proxy for having adequate transportation. In addition, there may be a lack of PrEP awareness among potential PrEP users and the information gap may differ geographically. Optimized referral networks would likely enhance PrEP uptake patterns in both cities.

Considering the failures of the existing naturally occurring PrEP referral system, our study implies the need for multiple points of contact within the healthcare system where PrEP education and prescription can occur. This is especially true given the "purview paradox," whereby primary care providers and HIV specialists may not consider PrEP implementation to fall within their personal clinical domain and instead see "others" as responsible for prescribing PrEP rather than themselves [43].

Although our study takes a structural perspective to address complex PrEP delivery systems and an advanced network methodology, it has limitations in terms of the generalizability of our findings and potentially unmeasured variables, including qualitative information. Additionally, our data may have limitations in providing sufficient information to determine the recent PrEP uptake and the timing of YMSM's health venue utilization that then could lead to PrEP provider referral. However, we believe that our PrEP uptake measure (ever versus never) is a valid reflection of recent PrEP uptake among our participants considering limited PrEP uptake by 2014 when CDC guideline was released for the MSM population [44] and our baseline data collection period.

Implementation research from various disciplinary perspectives to optimize PrEP uptake [45] is important for optimization of PrEP engagement among the most-at-risk populations of YMSM. Effective PrEP uptake likely requires models and approaches that move beyond traditional primary care provision for patients as is implemented in prevention of other chronic disease conditions. For example, cardiovascular disease prevention includes routinized assessments in clinical settings of non-stigmatized behaviors in mostly older populations and acts on objective clinical findings for certain conditions (i.e., hypertension and hypercholesterolemia). In contrast, assessment for PrEP eligibility occurs before entry into clinical care settings among younger populations with often-stigmatized behaviors. Based on our data, it appears that the connections between these pre-clinical health venues and clinical contexts are not driving PrEP uptake. As with other prevention efforts, individuals at risk may not perceive themselves as such or may face barriers to access. Therefore, additional intervention and action are needed from multiple sources [46].

From a public health perspective, we suggest systematic optimization of referral patterns and structures that identify those at risk and that drive client linkage to appropriate PrEP-providing clinics. We also recommend feedback

loops that link clients on PrEP back to pre-clinical contexts, where their continued engagement and adherence can be supported outside of clinical settings. This suggests an integrated public health systems approach to clinically-oriented, community-supported HIV prevention in at-risk populations.

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Compliance with Ethical Standards

Conflicts of interest K. Fujimoto, L. Kuhns, and J. Schneider have received research grants from Gilead Sciences, Inc. C. Flash serves on the scientific advisory board of Gilead Sciences, Inc.

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