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ORIGINAL PAPER

A Network Approach to Determine Optimization of PrEP Uptake in Athens, Greece

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Abstract
Although the HIV epidemic in Athens, Greece has reemerged and spread in men who have sex with men (MSM), state-supported PrEP programs have not been instituted. A PrEP intervention was implemented building upon an existing network cohort of MSM (308 participants; 1212 network members). A PrEP intervention cohort of 106 participants was selected based upon sex behaviors. Individual, partner, and network characteristics were compared between the cohorts. The PrEP cohort members were more highly connected and in more influential positions in the network than their peers. Further, their sexual network connections' behaviors increased their vulnerability to HIV infection relative to the rest of the network's sex partners. This included greater stimulant use (24.2% vs 7.0%; $\chi^2 = 28.2$; $p < 0.001$), greater rates of at least weekly condomless sex (OR = 2.7; 95% CI 2.1–3.5; $\chi^2 = 59.2$; $p < 0.001$) and at least weekly use of drugs or alcohol during sex (OR = 3.4; 95% CI 2.6–4.3; $\chi^2 = 89.7$; $p < 0.001$). Finally the PrEP cohort's social networks showed similarly increased vulnerability to seroconversion, including greater rates of injection drug use (4.1% vs 0.5%; $\chi^2 = 3.9$; $p = 0.04$), greater stimulant use (33.6% vs 14.6%; $\chi^2 = 16.9$, $p < 0.001$), and higher rates of recent STIs (21.6% vs 13.1%; $\chi^2 = 4.4$; $p = 0.04$). Thus, this PrEP intervention engaged individuals in vulnerable positions with vulnerable connections within an MSM community.

Keywords MSM · PrEP · HIV · Athens · Greece

Introduction

One of the many impacts of the 2009 economic crisis in Greece was a rise in HIV incidence in Athens, notably including men who have sex with men (MSM) [1]. In 2019, MSM accounted for approximately half of new HIV infections in Greece, bringing the HIV-positive rate in Athenian MSM to roughly 13% [2–4]. Several interventions, including rapid testing screening and treatment, have been implemented among MSM, but the utility of integrating other biomedical prevention such as pre-exposure prophylaxis (PrEP) has yet to be examined in this context [5–7].

PrEP is shown to be effective when used as directed [8]. Among MSM living in Greece, however, only 53.2% of

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HIV-negative individuals had heard of PrEP and only 6.5% had ever used PrEP on their own [9], likely due the absence of an official PrEP program in Greece.

The PrEP For Greece (P4G) intervention was recently completed in Greece and examined the feasibility of PrEP among HIV-negative MSM [10]. At the outset, P4G aimed to engage individuals considered most vulnerable for seroconversion, including individuals who practiced condomless anal sex and had sex with HIV-positive partners [11]. Recent sexually transmitted infections (STIs) were also used as a screening factor as this has been shown to correlate with HIV status [12–14]. The study also enrolled only MSM from ages 18–39, an age group that, in Greece, has been shown to be more vulnerable to HIV seroconversion [2].

There has not previously been an analysis to determine whether the particular individuals engaged in PrEP are indeed the most vulnerable to HIV infection and the most likely to transmit HIV onwards based upon their network position and connections. This analysis seeks to determine whether individuals enrolled in the P4G project were, in fact, those who would most impact onward transmission based upon their network position, network characteristics and individual level attributes. We hypothesize that this is indeed the case. That is, that P4G successfully engaged vulnerable and centrally located individuals in the network. Such an analysis would guide the development of programmatic approaches to PrEP implementation and highlight a network-informed PrEP engagement strategy that could be utilized for disease transmission interruption in emerging and re-emerging epidemics.

Materials and Methods

Recruitment

PrEP for Greece (P4G) is an intervention that utilized the infrastructure from the SOPHOCLES cohort study of men who have sex with men (MSM) in Athens, Greece from 2016 to 2018 [15]. SOPHOCLES recruited MSM in the Athens metropolitan area using respondent-driven sampling (RDS), resulting in 308 participants and 1212 named network members. Participants were remunerated 20 euros for survey completion and 5 euros for each successful referral.

Eligibility criteria for referred participants in SOPHOCLES required that all participants: (1) identified as male; (2) were between the ages of 18–39; and (3) reported oral or anal sex with a man in the previous 12 months. Computer-assisted interviews were conducted by a certified nurse at Checkpoint Athens' LGBTQ health center, gathering network data on participants' five most recent sex partners along with various other demographic and behavioral characteristics detailed below. Together, participants and their referrals comprised the SOPHOCLES network.

P4G identified 132 potential candidates for PrEP based on HIV-negative serostatus and HIV risk factors such as alcohol or drug use during sex. These candidates were invited to screen for eligibility based on the following criteria: (1) assigned male sex at birth; (2) age 18 or older; (3) documented HIV-negative via antibody test using the Genscreen™ ULTRA HIV Ag-Ab or ARCHITECT HIV Ag/Ab Combo immediately prior to beginning PrEP; (4) were screened for other STIs; (5) had adequate renal function; and 6) were at increased risk for HIV infection. Increased risk was defined as any of the following in the previous 6 months: (6a) condomless anal sex with ≥ 2 cisgender male or transgender female partners, (6b) ≥ 2 episodes of anal sex with at least one HIV-positive partner, or (6c) sex with a cisgender male or transgender female partner along with self-reported history of syphilis, rectal gonorrhea, or rectal chlamydia in the previous six months [16]. 106 MSM completed and met eligibility screening and were enrolled in the P4G cohort.

Survey Instruments

All participants were asked to provide demographic characteristics, sex practices, and substance use behaviors. Demographic questions included age, nationality, education, housing status, health insurance status, and sexual orientation. Participants were then asked in detail about their five most recent sex partners. Information was gathered on each named partner, as well as participants' sexual practices with each partner. This included types of sex behaviors, condom and drug or alcohol use during sex, and group sex due to their importance in sexual network mixing and transmission [17]. Participants were also asked for their self-reported history of testing and diagnosis of HIV and other STIs.

The WHO ASSIST survey was used to evaluate substance use among participants. This assessed for a wide variety (10) of substances and the individual's practices for each. Participants were also asked to rate the frequency with which they had felt certain emotions in the past week to assess their current mental health status using an abbreviated version of the Brief Symptom Inventory (BSI), validated for the Greek context [18].

The HIV Incidence Risk Index for men who have sex with men (HIRI-MSM) is a clinical formula that assigns different weights to various individual-level behaviors to determine if that individual is at risk for HIV seroconversion and thus an optimal candidate for PrEP [19]. It uses seven questions which assess age, sexual behavior, and methamphetamine and/or popper use. Inhaled nitrate and methamphetamine use was assessed in the prior three months to interview instead of six months. The number of times a participant

had receptive anal sex with a man, number of HIV-positive partners, and instances of insertive anal sex with an HIV-positive partner in the past six months were estimated using the information collected via named partners.

Entity Resolution

Given that the identity of network members cannot be easily verified, an "entity resolution" process was implemented to match identical individuals nominated by separate study participants. This process followed previously utilized algorithms [20, 21]. Matches were made based upon age (5 years younger or older), first names within two characters, and last names and/or initials. In addition, network members lacking name data were matched on nationality (Greek versus non-Greek) and residence region. All other potential matches were rejected.

Analytic Plan

Descriptive Characteristics

Univariable logistic regressions were used to compare demographics, behavior, and HIRI-MSM risk score components between the P4G and non-P4G participants. Odds ratios and their 95% confidence intervals were calculated to determine effect size of the variables.

A multivariable model predicting P4G membership using the component variables of the HIRI-MSM score was constructed to assess which variables remained significant when controlling for the others. Lastly, Receiver Operation Characteristics (ROC) curves were generated based on the univariable models predicting P4G membership with the dichotomized HIRI-MSM score (using cutoff scores of both 20 and 25) as the predictor. These curves were used in conjunction with other analyses to confirm that those placed on PrEP were appropriate targets for intervention. These analyses were performed using Stata 14.2. The ROC curves were generated using R statistical software version 3.6.2

Network Connectivity Parameters

Degree and eigenvector centrality for combined social (RDS) and sex networks were calculated to evaluate P4G participants' network connectivity and potential for transmission. Degree centrality measures the number of connections a particular participant has to other network members; eigenvector centrality is a measure of the influence of a participant. Participants with high eigenvector centrality are themselves connected to *other* highly connected participants. These centrality measures were computed using the igraph package in R and t-tests were subsequently performed to examine the differences in the centrality between the two groups.

Estimated Risk of Seroconversion

The HIRI-MSM [19] along with self-reported sex behaviors were used to estimate the number of seroconversions avoided by this PrEP intervention. First, the HIRI-MSM was used to calculate a risk value for each participant. To calculate the number of condomless anal sex events within a one-year period, the self-reported number of anal sex events with a named partner was multiplied by the reported frequency of condomless sex, with "always" counting as 1, "frequently" as 0.75, "sometimes" as 0.5, "rarely" as 0.25, and "never" as 0.

Transmission rates from one condomless receptive and insertive anal sex event was assumed to be 1.38% and 1.1%, respectively [11]. Transmission was assumed to be distributed binomially for each type of anal sex, and insertive and receptive anal sex were assumed to be mutually exclusive. The probability of transmission during at least one condomless anal sex event for both insertive and receptive sex was computed and the results summed to estimate the cumulative probability of transmission for a participant. Participants with an overall transmission probability of 50% or greater were treated as seroconversions.

To estimate the number of network seroconversions avoided by this PrEP intervention, the P4G cohort was divided into those with a HIRI-MSM score of 10–24 and of 25 or greater, assigning 2.0% and 7.0% probability of seroconversion in the next year, respectively, based on the incidence rate calculated by Lachowsky et al. [19, 22]. Using these incidence rates yielded six potential seroconversions avoided due to PrEP use in the P4G group during a one-year period. A random sample of six was then taken from the P4G participants and any sexual ties who were HIV-negative and had a transmission probability over 50% were identified as at risk of seroconversion. This process was repeated for 10,000 samples to generate a 95% confidence interval of the number of network seroconversions. These estimates were generated using R statistical software version 3.6.2.

Results

The SOPHOCLES network was assembled from a total of 62 initial individuals, resulting in 308 participants and 1212 named network members. P4G enrolled 106 (34.4%) participants from the SOPHOCLES cohort. Six of these participants were lost to follow-up before the first treatment appointment and, throughout the first year, 74% of participants demonstrated perfect adherence to their PrEP regimen [10]. Table 1 presents descriptive characteristics, comparing

Table 1 Demographics of an MSM cohort in Athens, Greece by PrEP uptake subgroup

Characteristics	PrEP uptake subgroup[a], n = 106 n (%)	MSM network[b], n = 202 n (%)	OR (95% CI)	Wald χ^2	p-value
Age—mean (sd)	33.5 (9.3)	27.5 (7.3)	1.1 (1.1–1.1)	31.1	< 0.001
Age				32.6	< 0.001
18–28	38 (35.9%)	138 (68.3%)	REF		
29–49	41 (38.7%)	50 (24.8%)	3.0 (1.7–5.15)		
41–48	22 (20.8%)	10 (5.0%)	8.0 (3.5–18.3)		
49 +	5 (4.7%)	4 (2.0%)	4.5 (1.2–17.7)		
Sexual orientation				0.0	0.955
Gay	90 (84.9)	172 (85.2)	REF		
Bisexual/other	16 (15.1)	30 (14.9)	1.0 (0.5–2.0)		
Nationality				0.9	0.353
Greek	90 (84.9)	179 (88.6)	REF		
Other	16 (15.1)	23 (11.4)	0.7 (0.4–1.4)		
Education				8.1	0.017
High school or less	20 (18.9)	55 (27.2)	REF		
Tertiary school[c]	60 (56.6)	122 (60.4)	1.4 (0.7–2.5)		
Masters or greater	26 (24.5)	25 (12.4)	2.9 (1.4–6.1)		
Employment				12.9	0.005
Full-time	59 (55.7)	71 (35.2)	REF		
Part-time	16 (15.1)	39 (19.3)	0.5 (0.3–1.0)		
Student/other	13 (12.3)	49 (24.3)	0.3 (0.2–0.6)		
Unemployed	18 (16.7)	43 (21.3)	0.5 (0.3–1.0)		

[a]P4G

[b]Non-P4G (SOPHOCLES with the P4G subgroup removed)

[c]Secondary school: Vocational schools, private colleges, technologic institutes, universities, military academies

non-P4G (SOPHOCLES with the P4G subset removed) to the P4G participants. The two groups' demographics differed in several ways.

First, P4G and non-P4G members' social (referral) network showed differences. As shown in Table 2, P4G participants' referral networks showed more injection drug use (4.1% vs 0.5%; $\chi^2 = 3.9$; $p = 0.049$) and stimulant use (43.5% vs 31.7%; $\chi^2 = 16.9$; $p < 0.001$) on average than did non-P4G members' referral networks. P4G's referral networks were also more likely to include other P4G members (55.8% vs 11.7%; $\chi^2 = 62.5$; $p < 0.001$). The P4G referral networks also tended to be older (32.0 years vs 26.9 years; $\chi^2 = 23.6$; $p < 0.001$) and reported a higher rate of STIs in the past twelve months (21.6% vs 13.1%; $\chi^2 = 4.4$; $p = 0.037$) on average.

Additionally, P4G members' five most recent sex partners were on average more than three years older ($\chi^2 = 22.1$; $p < 0.001$) and more likely to have used PrEP (4.2% vs 1.2%; $\chi^2 = 7.8$; $p = 0.005$). Their sex partners were also more likely to use stimulants on average (24.2% vs 7.0%; $\chi^2 = 28.2$; $p < 0.001$) than non-P4G's partners. Moreover, P4G's five most recent sex partners also practiced greater rates of at least weekly condomless sex (OR = 2.7; 95% CI 2.1–3.5; $\chi^2 = 59.2$; $p < 0.001$) and at least weekly use of drugs or alcohol during sex (OR = 3.4; 95% CI 2.6–4.3; $\chi^2 = 89.7$; $p < 0.001$) versus never.

Whole network-level connection characteristics showed a higher number of average connections (degree centrality) (4.75 versus 3.51; $z = -7.1$; $p < 0.001$) and eigenvector centrality (0.01 versus $3.8e^{-17}$; $p < 0.001$) in P4G than non-P4G.

All P4G participants were HIV-negative to be eligible for PrEP, whereas the HIV seroprevalence of the non-P4G cohort was 12.9%. The self-reported HIV prevalence of participants' sex partners in the non-P4G network was 5.5%. Among non-P4G seronegative respondents, an average of 3.9% of named partners were HIV-positive. This is in contrast to the exclusively HIV-negative P4G cohort which reported, on average, 11.9% of partners as HIV-positive ($\chi^2 = 10.8$; $p < 0.001$). P4G participants were also, on average, 6 years older ($\chi^2 = 42.9$; $p < 0.001$).

Study participants' self-reported substance use is described in Table 3. Alcohol use did not differ significantly

Table 2 Attributes and behaviors of social and sex network members of an MSM cohort in Athens, Greece by PrEP uptake subgroup

Attributes	PrEP uptake subgroup[a] mean (sd)	MSM network[b] mean (sd)	OR (95% CI)	Wald χ^2	p-value
Social network characteristics[c]					
Age	32.0 (8.8)	26.9 (6.2)	1.09 (1.06–1.13)	23.6	< 0.001
% living w/ HIV	4.1 (15.4)	4.3 (17.2)	1.00 (0.98–1.01)	0.0	0.899
% w/ injection drug use	4.1 (19.4)	0.5 (4.4)	1.03 (1.00–1.06)	3.9	0.049
% in P4G	55.8 (47.8)	11.7 (29.9)	1.03 (1.02–1.03)	62.5	< 0.001
% w/ stimulant use[d]	33.6 (43.5)	14.6 (31.7)	1.01 (1.01, 1.02)	16.9	< 0.001
% w/ STI past 12 mos	21.6 (38.9)	13.1 (30.6)	1.01 (1.00–1.01)	4.4	0.037
Sex network characteristics					
Age	32.8 (6.0)	29.1 (6.0)	1.10 (1.06–1.15)	22.1	< 0.001
% living w/ HIV	11.9 (20.8)	5.5 (17.7)	1.02 (1.00–1.03)	7.2	0.007
% w/ injection drug use	3.2 (12.6)	0.9 (5.7)	1.03 (1.00–1.06)	3.7	0.054
% used PrEP	4.2 (9.8)	1.2 (6.7)	1.04 (1.01–1.08)	7.8	0.005
% w/ stimulant use[d]	24.2 (29.3)	7.0 (18.5)	1.03 (1.02–1.04)	28.2	< 0.001
Weekly or more condomless anal sex—n (%)	212 (42.2)	151 (21.3)	2.7 (2.1–3.5)	59.2	< 0.001
Weekly or more sex drug use[e]—n (%)	237 (47.1)	148 (20.9)	3.4 (2.6–4.3)	89.7	< 0.001

[a]P4G

[b]Non-P4G (SOPHOCLES with the P4G subgroup removed)

[c]Indicates network of referrer of participant and who the participant referred

[d]Stimulants: cocaine and/or methamphetamines

[e]Sex drug: alcohol or drug use during sex

between the two groups, although stimulant use (cocaine or methamphetamines) was more likely in the P4G subset (OR = 4.8; 95% CI 2.7–8.4; $\chi^2 = 29.7$; $p < 0.001$). P4G participants also had higher odds of reporting a recent STI (OR = 4.2; 95% CI 2.1–8.1; $\chi^2 = 17.5$; $p < 0.001$).

Self-reported sex behaviors are reported in Table 3. P4G participants had a median of 30 sex partners in the preceding six months versus four for non-P4G ($\chi^2 = 35.0$; $p < 0.001$) and were more likely to report group sex at least once per month (OR = 36.7; 95% CI 15.0–89.6; $\chi^2 = 63.7$; $p < 0.001$) compared to never. They were also more likely to report at least one recent instance of condomless anal sex (OR = 5.0; 95% CI 2.7–9.2; $\chi^2 = 26.4$; $p < 0.001$) and drug or alcohol use during sex with their five most recent partners (53.3% of partners vs 25.5% of partners, $\chi^2 = 37.0$; $p < 0.001$).

The CDC's HIV Incidence Risk Index for MSM (HIRI-MSM) components are shown in Table 4. A score of ten indicates "substantial risk" of seroconversion. Both non-P4G and P4G members' mean scores fall well above this threshold, and only one member of the P4G cohort had a score below ten. In contrast, nearly 10% of non-P4G members had a score of less than ten, indicating low risk. The average risk score for P4G was 27.6 (sd = 7.8), whereas the non-P4G mean was 21.5 (sd = 8.2) ($\chi^2 = 31.2$; $p < 0.001$). Notable contributors to this elevated score among P4G participants included more P4G participants with at least one partner living with HIV (33.0% vs 12.4%; $\chi^2 = 17.6$; $p = 0.001$), and greater inhaled nitrate use (44.3% vs 13.0%; $\chi^2 = 21.6$; $p < 0.001$) and stimulant use (41.5% vs 12.9%; $\chi^2 = 29.7$; $p < 0.001$). P4G participants also referred seronegative individuals with higher average HIRI-MSM scores as compared to referrals from non-P4G (28.3 vs 21.2; $\chi^2 = 27.3$; $p < 0.001$). When controlling for P4G membership, centrality measures were still associated with HIRI-MSM scores. The average HIRI-MSM score increased by 2.3 points ($\beta = 2.3$, $t = 7.59$, $p < 0.001$) for every additional sexual partner, and increased by an average of 18.2 ($\beta = 18.2$, $t = 2.22$, $p = 0.027$) for every one-unit increase in eigenvector centrality when controlling for group membership.

The mean P4G participant HIRI-MSM score corresponds to a 92.8–94.8% specificity for predicting seroconversion in the next six months. That is, 92.8–94.8% of individuals who did *not* seroconvert in six months had a score *less* than the P4G average. The mean non-P4G score corresponded to a specificity of 80.2–84.8%. Sensitivity was 31.5–37.5% for P4G and 50.6–54.1% for non-P4G, indicating the percentage of those who *did* seroconvert in six months who had a HIRI-MSM score at least as high as the cohort averages [19].

Multivariable analysis of variables used to calculate the HIRI-MSM score found age and number of recent male partners remained significant when controlling for other variables. These results are found in Table 5. The area

Table 3 Drug and sex behaviors of an MSM cohort in Athens, Greece by PrEP uptake subgroup

Characteristics	PrEP uptake subgroup[a], n = 106 n (%)	MSM network[b], n = 202 n (%)	OR (95% CI)	Wald χ^2	p-value
Drug use					
Injection drug use[c]	6 (5.7)	7 (3.5)	1.7 (0.5–5.1)	0.8	0.367
Stimulant use[d,e]	44 (41.5)	26 (12.9)	4.8 (2.7–8.4)	29.7	< 0.001
Alcohol use[d]				1.5	0.216
Monthly or less	23 (21.7)	57 (28.22)	REF		
Once/week or more	83 (78.3)	145 (71.8)	1.42 (0.8–2.5)		
Inhaled nitrates use[d]	47 (44.3)	38 (13.0)	3.4 (2.0–5.8)	21.6	< 0.001
Sex behaviors					
Sex drug use w/recent partners[f]—% of partners (sd)	53.3 (36.0)	25.5 (32.7)	1.0 (1.0–1.0)	37.0	< 0.001
# Sex partners past 6 mo	30 (45)[f]	4 (10)[f]	1.0 (1.0–1.0)	35.0	< 0.001
Group sex in past 6 mo				63.7	< 0.001
Monthly or more	50 (47.2)	15 (7.43)	36.7 (15.0–89.6)		
Less than monthly	47 (44.3)	88 (43.6)	5.9 (2.7–12.7)		
Never	9 (8.5)	99 (49.0)	REF		
STI[h] past 12 mos	28 (26.4)	16 (7.9)	4.2 (2.1–8.1)	17.5	< 0.001
Condomless anal sex ≥ 1 times[i]	91 (85.9)	111 (55.0)	5.0 (2.7–9.2)	26.4	< 0.001
Insertive partner ≥ 5 times[i]	79 (74.5)	104 (51.5)	2.8 (1.6–4.7)	14.8	< 0.001
Receptive partner ≥ 1 time[i]	80 (75.5)	154 (76.2)	0.9 (0.6–1.7)	0.0	0.881

[a]P4G

[b]Non-P4G (SOPHOCLES with the P4G subgroup removed)

[c]Lifetime use

[d]Past 3 monthsuse

[e]Stimulants: cocaine and/or methamphetamines

[f]Sex drug: alcohol or drugs during sex

[g]Median (IQR)

[h]STI: syphilis, chlamydia, and/or gonorrhea

[i]With 5 most recent partners in any time frame

Table 4 HIRI-MSM risk score components of members of an MSM cohort in Athens, Greece by PrEP uptake subgroup

HIRI-MSM Question	PrEP uptake subgroup[a] score mean (sd)	MSM network[b] score mean (sd)	Wald χ^2	p-value
Age	5.2 (2.5)	6.8 (2.0)	29.8	< 0.001
Number of male partners[c]	5.9 (2.4)	2.4 (3.0)	62.0	< 0.001
Number of times receptive anal sex[c]	7.5 (4.3)	7.6 (4.3)	0.0	0.881
Number of times insertive anal sex[c]	4.5 (2.6)	3.1 (3.0)	14.8	< 0.001
Number of HIV-positive partners[c]	1.9 (3.0)	0.7 (1.9)	17.6	< 0.001
Methamphetamine use[d]	1.2 (2.2)	0.3 (1.2)	19.2	< 0.001
Inhaled nitrate use[d]	1.3 (1.5)	0.6 (1.2)	21.6	< 0.001
Total score	27.6 (7.8)	21.5 (8.2)	31.2	< 0.001

[a]P4G

[b]Non-P4G (SOPHOCLES with the P4G subgroup removed)

[c]In the past 6 months

[d]In the past 3 months

Table 5 Multivariable logistic model predicting P4G membership by HIRI-MSM score components

HIRI-MSM question	OR (95% CI)	Wald χ^2	p-value
Age category			
18–28	REF	12.1	0.007
29–49	2.4 (1.2–4.6)		
41–48	4.3 (1.6–11.2)		
49 +	2.4 (0.5–11.6)		
Number of male partners[a]			
0–4	REF	42.9	< 0.001
6–10	2.3 (0.9–6.0)		
> 10	10.4 (5.0–21.8)		
Receptive anal sex ≥ 1 time[a]	0.7 (0.3–1.4)	1.24	0.266
Insertive anal sex ≥ 5 times[a]	1.8 (1.0–3.4)	3.5	0.062
Number of HIV-positive partners[a]			
0	REF	1.8	0.413
1	1.7 (0.7–3.9)		
> 1	1.6 (0.5–4.5)		
Methamphetamine use[a]	1.8 (0.7–4.8)	1.6	0.210
Inhaled nitrate use[a]	1.2 (0.6–2.4)	0.3	0.557

[a]In the past 6 months

under the curve (AUC) for this analysis was 85%, indicating a participants' HIRI-MSM score could be accurately used to predict enrollment in P4G 85% of the time. When using only the HIRI score itself, dichotomized by a cutoff of 20 and 25, the AUC is 62.6% and 66.9%, respectively (Fig. 1).

Based upon HIRI-MSM scores, approximately six P4G members avoided seroconversion due to PrEP use. Furthermore, approximately one network member avoided seroconversion due to an adjacent member's use of PrEP. Thus, assuming perfect PrEP adherence, an estimated seven (95% CI 6–8) total HIV infections were likely prevented by 12 months of the P4G intervention as compared to no PrEP at all.

Discussion

There were several notable findings from this analysis. First, as expected based on the eligibility criteria, P4G participants were more likely to report greater individual-level vulnerability. Second, we found increased network-level vulnerability factors among P4G participants. In addition, P4G members had more average connections and were situated at influential points in the social network. Cumulatively, then, P4G participants were themselves more vulnerable to HIV infection and transmission and were also connected to more vulnerable individuals.

Aside from general health criteria, P4G participants were selected only based on reported practice of at least one behavior associated with HIV transmission (including condomless anal sex with ≥ 2 cisgender male or transgender female partners, ≥ 2 episodes of anal sex with at least

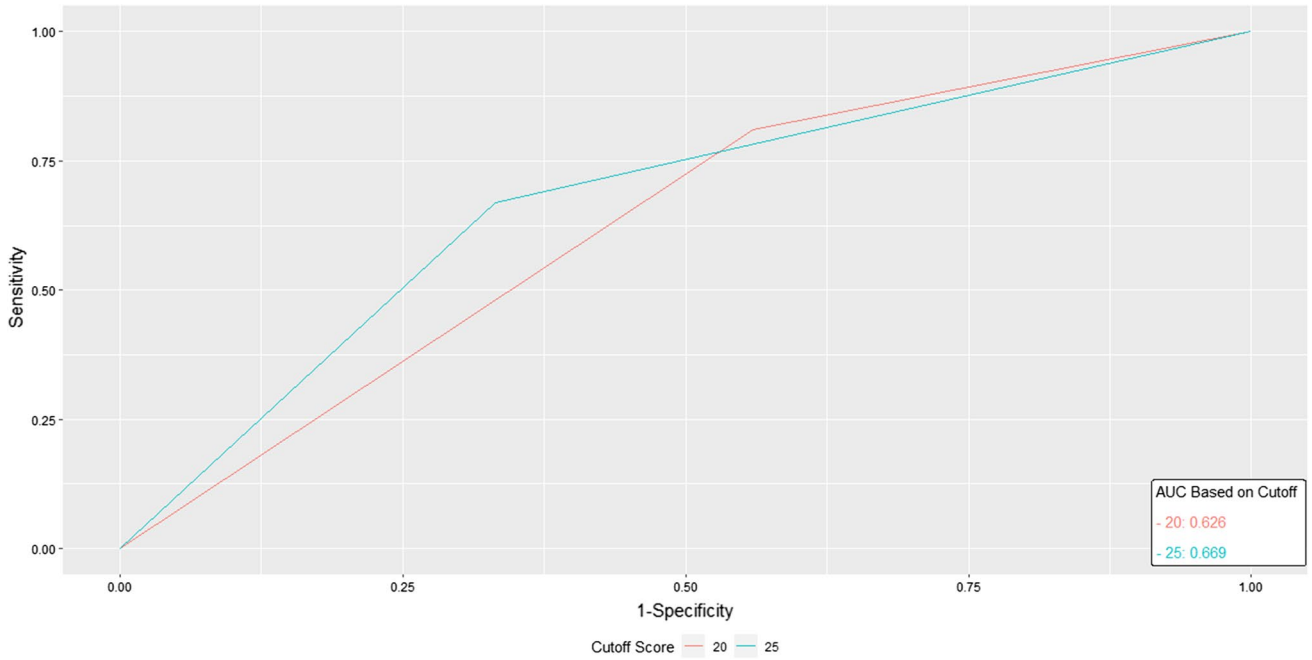

Fig. 1 ROC curves of logistic model predicting P4G membership by dichotomized HIRI-MSM score

one HIV-positive partner, or sex with a cisgender male or transgender female partner along with self-reported history of STI in the previous six months). Unsurprisingly, then, when compared to the non-P4G group, P4G members were more likely to report all of these behaviors. However, they were also more likely to report other vulnerability factors, as were their partners. As a whole, both the P4G cohort and their network were at increased vulnerability for HIV infection in multiple ways.

P4G members were also more likely to report behaviors not specifically identified as inclusion criteria. This included greater incidence of group sex, more sex partners, and greater use of drugs or alcohol during sex. These have all been linked to greater vulnerability to HIV infection [23, 24]. Thus, it appears that the relatively limited inclusion criteria, requiring self-report of just one of three named risk factors, was associated with multiple additional risk factors. This resulted in a P4G cohort that was more vulnerable to HIV infection than the broader non-P4G network.

The P4G cohort's sex partners and social networks similarly showed increased rates of seroconversion vulnerability factors. For example, P4G's sex partners had greater rates of sex drug use and condomless sex, and their social networks had higher rates of injection drug use. This indicates that P4G members were also surrounded by more vulnerable network subsets where HIV is more likely to be transmitted. Thus, targeting individuals in these clusters for PrEP intervention reduced not only the individual's risk of seroconversion, but may have also helped protect the entire vulnerable cluster. Moreover, as evidenced by their elevated average eigenvector centrality, P4G participants had more influential positions and transmission potential in their social (RDS) and sexual networks. This puts both them and their surrounding network at increased vulnerability for rapid HIV transmission. They are thus primary targets for interventions.

The HIRI-MSM score provides a useful summative perspective of these data. P4G participants had a higher average score, indicating greater vulnerability. This was also true for P4G's referrals, suggesting that their social networks are also more vulnerable on average to seroconversion according to the HIRI-MSM index. This is in keeping with other findings indicating P4G participants' social and sex networks are more likely to report a number of vulnerability factors. Further, the HIRI-MSM score appears to have inadvertently identified influential network members as shown by the positive association between centrality measures and HIRI scores when controlling for group membership, furthering its value for interventions to mitigate HIV transmissions.

A negative interpretation of P4G's elevated average risk score, however, is decreased sensitivity; P4G captured fewer potential seroconversions at the expense of excluding more low-risk individuals. One model has suggested, however, that increasing a HIRI-MSM cutoff for PrEP eligibility of 25 can result in a more cost-effective intervention [25]. This may therefore be an appropriate tradeoff in a low-resource setting.

A strategy that thus includes network information may be useful in similar HIV epidemics in MSM populations. Targeting vulnerable, highly connected individuals in an RDS-derived MSM social network for PrEP intervention may simplify the process of recruitment by (1) identifying vulnerable, influential individuals within vulnerable sex network clusters and (2) reducing the number of necessary inclusion criteria. This may be due in part to RDS's efficacy in recruiting vulnerable and otherwise hard-to-reach MSM social networks [26–28]. In addition, because just one of three risk factors was needed to correlate with elevated HIRI-MSM scores, this method avoided the need to administer the full HIRI-MSM panel of questions while still successfully targeting vulnerable network members (high HIRI-MSM scores) in vulnerable positions (elevated eigenvector centrality). Thus, this study demonstrates the efficacy of combining methods of identifying vulnerable, hard-to-reach MSM individuals (RDS) with an abbreviated risk factor assessment as a method of network-level PrEP intervention.

Further research should seek to follow cohorts over time to determine the scale of reduction of HIV infections for this method of PrEP intervention. In addition, we found group sex and self-report of STI (chlamydia, gonorrhea, syphilis) in the past 12 months were both associated with higher HIRI-MSM scores. A larger, longitudinal study could elucidate the predictive power of incorporating these variables into the index.

Limitations of this study are similar to other network studies. The network was not a random sample of the population. Further, the actual number of network members interviewed was relatively small (n = 308) compared to contacts reported by these network members (n = 1212), and the data is participant perception of network members' behaviors which may not reflect actual behaviors. Moreover, network measures of centrality should be carefully interpreted; there are unknown individuals and connections in the network that were not captured. However, simulations have shown eigenvector centrality in particular is stable when a network is sampled, and a sampled network's centrality measures have high correlation with the true values in the presence of missing individuals [29, 30]. Additionally, non-P4G participants' HIV status was self-reported. There may also be a self-selection bias in the group who ultimately enrolled in P4G compared to the 26 individuals who were potentially eligible but did not enroll. Moreover, adherence to PrEP was not perfect among the P4G participants. Calculations of avoided HIV infections by the intervention are thus only approximate. Finally, the HIRI-MSM was developed in an

American context and thus may not be suitable to evaluate the risk of a Greek MSM population.

Conclusion

Beginning with a highly connected network as a pool of eligible participants for PrEP intervention appears to have been a successful method to engage not only network members but also network clusters most vulnerable to HIV infection. The three screened vulnerability factors were associated with behaviors that increased not only the individuals' vulnerability to HIV infection, but also their social and sexual partners' vulnerability. They also identified highly connected individuals within the network. Thus, P4G's strategy of using a vulnerable RDS network as the basis for a PrEP intervention successfully engaged extremely vulnerable individuals who were well-positioned in the network (i.e. highly connected, with HIV-positive and HIV-negative partners) to slow the spread of HIV across the entire network.

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