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ORIGINAL PAPER

Characterizing the Role of Neighborhood Disadvantage in a Digital PrEP Intervention for Young Sexual and Gender Minority Men

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Abstract

While digital health interventions (DHIs) have become an increasingly common approach to address HIV vulnerability among young sexual and gender minority men who have sex with men (YSGMMSM), few studies consider the role of neighborhood disadvantage in DHI efficacy and engagement. The present study is a secondary data analysis of 212 YSGMMSM aged 16–24 that combined biological and clinical survey data from the primary efficacy randomized controlled trial (RCT) of P3, a PrEP adherence DHI, with a measure of neighborhood disadvantage to characterize P3 engagement and efficacy among high and low disadvantage neighborhoods. We found that participants residing in high disadvantage neighborhoods engaged with P3 a median of 63 days (IQR = 39–76), compared to 77 days (IQR = 51–82) in low disadvantage neighborhoods. Among those who received the P3 intervention, participants residing in high disadvantage neighborhoods had higher odds of PrEP non-adherence (OR = 3.6, CI = 1.2, 10.4). Further, we found that there was minimal difference in PrEP non-adherence rates among those residing high disadvantage neighborhoods between intervention and control groups (28% vs. 25%) compared to 9% in the intervention condition and 18% in the control condition among those residing in low disadvantage neighborhoods. Despite this, receiving the P3 intervention did not moderate the relationship between neighborhood disadvantage and PrEP non-adherence. These findings suggest that neighborhood disadvantage may play a role in PrEP adherence DHI efficacy and engagement among YSGMMSM. Further research is needed to quantify the role of neighborhood disadvantage in YSGMMSM using HIV DHIs.

Keywords HIV prevention · PrEP adherence · Syndemics · Neighborhood effects · Structural disparities · Digital health interventions · MHealth

Introduction

Digital health interventions (DHIs) have become an increasingly common approach to address the disproportionate HIV vulnerability among young sexual and gender minority men who have sex with men (YSGMMSM) [1–16]. Several factors contribute to the growing trend of addressing HIV vulnerability with DHIs, including cost-effectiveness, the ability to deliver dynamic, real-time interventions, and the high adoption and utilization of smartphones among YSGMMSM [17–24]. However, sufficiently engaging participants with DHI interventions to achieve the intended outcome is an ongoing problem [25–27]. For example, a pilot study of AllyQuest, an anti-retroviral therapy (ART) adherence DHI for YSGMMSM who are HIV positive, found that, on average, participants used the DHI for 21 of the 28-day pilot period and that higher levels of daily usage

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were correlated with better HIV self-management outcomes [28]. However, there is significant variance in daily logins between users, with some users logging in almost every day throughout the trial period and others logging in less than five days total. Collectively, this suggests that effectively engaging YSGMMSM in DHIs is related to DHI efficacy.

Past work has utilized DHIs to improve pre-exposure prophylaxis (PrEP) adherence among YSGMMSM, as PrEP has been shown in clinical trials to be safe, efficacious, and could reduce the likelihood of HIV acquisition by 99% when taken as prescribed [29–33]. Past PrEP adherence DHIs have mostly taken the form of text messaging systems or digital pill monitoring systems and have had mixed results [34–39]. For example, one study found no significant differences in minimally acceptable PrEP adherence, measured through dried blood spot (DBS) derived tenofovir diphosphate (TFV-DP) concentrations, between a text-messaging intervention and the standard of care in adult men who have sex with men [37]. Further, digital pill systems have documented barriers to engagement (e.g., managing physical components of the pill system was cumbersome) and digital pill systems have not been shown to independently improve PrEP adherence compared to a standard of care [34, 35]. Finally, one study of a bi-directional text messaging system (PrEPmate) demonstrated that the intervention condition was significantly correlated with higher retention in clinical care and TFV-DP concentrations. However, this study notes that despite enrolling an adult population (mean age 35), many of whom were early PrEP adopters, retention and adherence dropped by roughly half between week 4 and week 36 of the trial [38]. This suggests that further research is needed to characterize engagement in PrEP DHIs.

There are numerous, multilevel barriers to real-world PrEP adherence and medication adherence among youth ranging from individual-level (e.g., medication adherence self-efficacy) to structural (e.g., healthcare access) [40–57]. Due to this, non-adherence to PrEP can be conceived as a form of HIV vulnerability in YSGMMSM, as this increases the likelihood of HIV infection. The syndemic (synergistic epidemics) model has been used to unpack the multifactorial nature of HIV vulnerability among YSGMMSM [58–72]. These works have highlighted how simultaneous exposure to co-occurring health conditions (e.g., polysubstance use and depression) can result in disproportionate increases in HIV vulnerability [61–70]. Notably, two studies found that the count of co-occurring syndemic health conditions was associated with lower ART adherence [40, 73] and another study found that co-occuring syndemic health conditions was associated with lower PrEP adherence [74]. Additionally, the syndemic model emphasizes the role that structural and social contextual factors (e.g., neighborhood disadvantage) play in the development of co-occurring syndemic conditions and HIV vulnerability. Neighborhood disadvantage has been found to be associated with several forms of HIV vulnerability, including ART and PrEP adherence [74–82]. Systematic reviews of DHI design, engagement, and evaluation paradigms have suggested that structural and social contextual factors are potential influences on effective engagement in DHIs and note that this is a broadly understudied area [83, 84]. Due to the potential simultaneous influence of structural and social contextual factors on HIV vulnerability and effective engagement, DHIs aimed to reduce HIV vulnerability should characterize engagement and DHI efficacy among varying structural and social contextual conditions (such as neighborhood disadvantage).

The present study is a secondary analysis of a RCT testing the efficacy of P3, a PrEP adherence DHI for YSGMMSM. We aim to characterize P3 efficacy and engagement among P3 participants residing in high and low disadvantage neighborhoods. Further, we aim to identify if and to what extent P3 moderates the relationship between neighborhood and syndemic conditions and PrEP adherence in YSGMMSM.

Methods

Parent Study

P3 is a user-centered, multimedia PrEP adherence phone application that includes text, videos, quizzes, and a social wall in which participants can share experiences from successes to challenges with PrEP adherence. An extended version of P3 (named P3+) includes the aforementioned multimedia phone application with the addition of adherence counselors trained on the Next Step Counseling (NSC) adherence counseling curriculum through the P3 phone application [16, 85–87]. Participants were recruited from 9 study sites: Tampa, Florida; Boston, Massachusetts; Chicago, Illinois; Houston, Texas; Philadelphia, Pennsylvania; Chapel Hill, North Carolina; Atlanta, Georgia; Bronx, New York; Charlotte, North Carolina. A mix of in-person, venue-based, and web-based recruitment methods were utilized. Residential zip code was collected from each participant. After providing informed consent either in-person or electronically, participants were randomized to one of three treatment arms (standard of care, P3, or P3+) using a 1:1:1 randomization scheme. Standard of care was defined according to Centers for Disease Control and Prevention guidelines, which includes medication adherence counseling at PrEP initiation and at 3-month intervals, PrEP education, adherent support, and monitoring of medication adherence (see cited protocol for further details) [16]. The study took place from March 2019 to September 2021. Clinical survey assessments and laboratory specimens were

collected at baseline and 3 months over the 3-month study duration. Study visits were initially planned to be conducted in-person at the same study site where participants enrolled. All study sites stopped in-person study activities on March 17, 2020 to reduce the transmission of COVID-19. Virtual recruitment and virtual study activities began in June 2020. Additionally, some study sites were able to conduct limited in-person activities based on local regulations and COVID-19 restrictions. The parent study was reviewed and approved by the Institutional Review Board of the University of North Carolina at Chapel Hill, USA (17-9551). A Certificate of Confidentiality was obtained from the National Institute of Child Health and Human Development. For participants between the ages of 15 and 17, a waiver of parental consent was obtained. The parent trial is registered at ClinicalTrials.gov (NCT03320512).

Parent Study Eligibility

Inclusion criteria were as follows for the parent study: (1) 16–24 years of age; (2) assigned male sex at birth; (3) report sex with or intentions to have sex with men or transwomen; (4) have reliable daily access to an Android or iOS smartphone with a data plan; (5) are able to speak and read English; (6) are HIV-uninfected (confirmed by self-report at enrollment visit); and (7) are not currently on PrEP but plan to initiate in the next 7 days and have an active PrEP prescription (prescription confirmed by study staff) or currently on PrEP and have an active PrEP prescription (prescription confirmed by study staff).

Secondary Analysis

The present study aims to characterize P3 engagement and efficacy among participants residing in high and low disadvantage neighborhoods by combining a measure of neighborhood disadvantage with the clinical survey and biological data collected from the primary P3 RCT [88]. Further, we quantified if and to what extent P3 moderated the effect of neighborhood disadvantage on P3 efficacy among YSGMMSM enrolled in the study aged 16–24. The present study was reviewed by the Northeastern University Institutional Review Board and determined to be exempt. We utilized a de-identified analytic dataset curated by the parent study's staff and the secondary analysis principal investigator had no contact with participants and made no attempts to re-identify participants post hoc.

Secondary Analysis Eligibility

Participants from all three trial arms of the primary study were eligible for inclusion in this secondary data analysis ($n=246$). Participants who were lost to follow-up (LTFU, defined as participants who did not begin the month 3 survey) were excluded ($n=34$). This resulted in a dataset of 212 participants.

Measures

PrEP Non-adherence

We defined PrEP non-adherence at 3 months as a binary measure. Due to study operation interruptions related to the COVID-19 pandemic, PrEP non-adherence at 3 months was derived using a combination of dried blood spot (DBS)-derived estimates of tenofovir diphosphate (TFV-DP) levels and self-reported PrEP adherence in the past month. Participants were considered PrEP non-adherent if their DBS-derived TFV-DP levels were consistent with ≤4 doses per week. DBS estimates of TFV-DP were derived during the parent study using a previously defined procedure [16, 88, 89]. However, 31% (66/212) of eligible participants were unable to provide biological specimens. Where DBS-derived measures were absent, self-reported PrEP adherence in the past month was used instead. This was ascertained through the following survey question: "in the last month, what percent of the time did you take your PrEP as prescribed (once a day)". Responses could range from 0% (none of the time) to 100% (all of the time). There is mixed evidence regarding the accuracy of self-reported measures of PrEP adherence [90–92]. However, issues of over-reporting PrEP adherence in young men who have sex with men decrease significantly with age [92]. Further, we found that the area under the receiver operating characteristics curve (AUC) between self-report measures and biological measures among participants with biological and self-report PrEP non-adherence measures was high (>=0.79). Given that the AUC was high and that the median age of secondary-analysis-eligible participants is 22, supplementing the missing biological PrEP adherence measures with self-report is likely sufficiently accurate. Neighborhood disadvantage was not related to the likelihood of participants submitting DBS data (OR=1.4, CI=0.6, 3.5, $p=0.5$).

Neighborhood Disadvantage

We defined neighborhood disadvantage as a binary measure. We cross-walked each participant's self-reported residential zip code to a Zip Code Tabulation Area (ZCTA), which is used as a proxy for the participant's neighborhood. ZCTAs are a geographic unit described by the US census based on US zip codes and are a suitable proxy for a participant's residential neighborhood [93, 94]. The social vulnerability

index (SVI) was used to describe neighborhood disadvantage at the ZCTA level. This index is comprised of 15 factors across 4 themes derived from American Community Survey measures (1: socioeconomic status, 2; household composition, 3: disability, minority status, and language, and 4: housing type and transportation). This index was created to describe neighborhood vulnerability to natural disasters, including health-related disasters such as epidemics. The SVI is an ordinal scale ranging from 0 to 15, where each factor is assigned a point if that item is in the 90th percentile or higher across the entire US [95]. For example, if a given neighborhood is in the 90th percentile or higher in unemployment rate, that neighborhood receives one point on the ordinal scale. We defined neighborhood disadvantage as a binary measure created from this scale, where neighborhoods in the 90th percentile across the entire US for the final SVI ordinal scale were considered disadvantaged neighborhoods. Past work has demonstrated that P3 participants who reside in high disadvantage neighborhoods are at increased vulnerability for PrEP non-adherence in the P3 sample [74]. This is consistent with other studies which found that clustering of syndemic conditions and neighborhood disadvantage are related to HIV vulnerability, notably lower rates of ART adherence [40, 64, 67–70, 73, 75–82].

P3 Intervention Condition

We constructed a binary measure to represent participants who were randomized to the standard of care condition in the P3 RCT (1 = participants who received the standard of care, 0 = participants who received the P3 or P3 + intervention). Intervention conditions (P3 and P3+) were aggregated to increase power to detect effects and the primary results manuscript found no significant difference between intervention arms in terms of PrEP adherence [88]. While unconventional, it is necessary to code participants who received the standard of care as exposed (i.e., "1") for use in effect moderation analyses, as all exposure measures need to be coded in the same direction relative to the outcome (i.e. exposures coded as all harmful or all protective), which improves interpretation [96, 97]. Since results from the primary RCT showed that participants who did not receive the intervention were more likely to be non-adherent at 3 months [88] and P3 participants who reside in high disadvantage neighborhoods are at increased vulnerability for PrEP non-adherence in the P3 sample [74], this coding direction aligns both measures for use in effect moderation analysis.

Syndemic Condition Clustering

We defined syndemic clustering as a binary measure. Similar to prior studies, we defined a cluster of syndemic conditions as having two or more of the following binary measures at baseline: depression, anxiety, polysubstance use, not employed or in school, black, indigenous, people of color (BIPOC) identity (as a proxy for experienced racism), and lifetime history of arrest [64, 66–70]. Recent work has found that syndemic condition clustering is independently associated with PrEP non-adherence among YSGMMSM after controlling for other factors, including neighborhood disadvantage [74].

Depression

We constructed a binary measure of depressive symptoms. The patient health questionnaire-8 (PHQ8) [98, 99] questionnaire was used to assess baseline depressive symptoms respectively. These inventories ask participants to rank how frequently they experience symptoms from not at all, several days, more than half the days, and nearly every day. Scores range from 0 to 24 in the PHQ-8. Lower scores represent less frequent and higher scores represent more frequent symptoms. Participants who scored 10 or more on the PHQ-8 were considered as having depressive symptoms, as this is the recommended screening cutpoint for further evaluation and represents symptoms of moderate to severe depression [99, 100]. Prior research utilizing a syndemic framework has consistently found that depression among YSGMMSM contributes to increased HIV vulnerability or other syndemic conditions that co-occur with HIV (e.g., intimate partner violence) [62–64, 66–69].

Anxiety

We constructed a binary measure of anxious symptoms. The generalized anxiety disorder-7(GAD-7) [101] questionnaire was used to assess baseline anxious symptoms. These inventories ask participants to rank how frequently they experience symptoms from not at all, several days, more than half the days, and nearly every day. Scores range from 0 to 21 in the GAD-7. Lower scores represent less frequent and higher scores represent more frequent symptoms. Participants who scored 10 or more on the GAD-7 were considered to have anxious symptoms. Like the PHQ-8, a score of 10 is the recommended screening cutpoint for further evaluation and represents anxious symptoms of moderate to severe anxiety [101]. The role of anxiety in HIV syndemics and HIV vulnerability has yet to be characterized in a syndemic analysis.

Polysubstance Use

We constructed a binary measure of polysubstance use. This measure was defined as use of two or more substances reported at baseline consistent with a brief or intensive

intervention using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) [102]. Substances considered fall into the following categories: Opioids, stimulants, inhalants, hallucinogens, and sedatives. This is consistent with prior research into HIV vulnerability in YSGMMSM examining HIV vulnerability with the exception that we did not include cannabis use in our measure of polysubstance use [64, 66–70] as cannabis use has consistently been shown to have no positive or negative relationship to PrEP adherence in YSGMMSM [103, 104].

Lifetime History of Arrest

We constructed a binary measure of lifetime history of arrest. P3 participants who reported any previous history of being arrested in their lifetime at baseline were considered to have a lifetime history of arrest. Past literature has identified justice system involvement as co-occurring with other syndemic measures and related to HIV vulnerability [67, 70].

Not in Education, Employment, or Training

We constructed a binary measure of educational and vocational attainment. P3 participants who reported neither currently being in some form of education (high school, college, trade school, etc.) nor employed at baseline were considered not in education, employment, or training. Unemployment has been consistently linked to HIV vulnerability [105].

BIPOC Racial Identity

We constructed a binary measure of experienced racism. Participants were considered black, indigenous, people of color (BIPOC) if they disclosed any racial or ethnic identity other than non-Hispanic ethnicity and Caucasian as their race. This measure was used as a proxy for individual health-related disadvantages experienced by BIPOC persons living in the US. The experiences of health-related disadvantage among BIPOC persons living in the US is a distinct phenomenon that exists within and across strata of socioeconomic status [106–109]. Furthermore, BIPOC racial and ethnic status has been linked to HIV vulnerability in studies without a syndemic framing [110–115].

P3 Engagement

Engagement was defined as a continuous measure. Participants started with a baseline amount of USD in a bank ($90). Participants gained $0.5 or lost $1.0 from this initial bank for each day the participant logged in and completed one of the following three tasks: (1) completing a quest, (2) post on the social wall, (3) use the medication tracker. This measure serves as a quality proxy for engagement because it correlates with the behavior pattern P3 aims to adjust (i.e. daily use of P3 mimics the daily dosing pattern of PrEP) and each task is related to putative behavior change mechanisms identified in the creation of P3 (e.g., completing a quest is related to gamification, posting on the social wall is related social engagement, utilizing the medication tracker is related to instrumental support) [16, 88]. Engagement measures derived from summarizing users' participation and navigation through a DHI are suitable measures of engagement, as these measures provide an objective view into patterns of use with high ecological validity [25–27]. Further, engagement with P3 has been shown to be associated with lower PrEP non-adherence [116].

Control Measures

Age, BIPOC racial identity, syndemic condition clustering, and PrEP non-adherence in the past 30 days at baseline were used as control variables. Several other sociodemographic characteristics were collected by the primary RCT but not utilized in this analysis due to the lack of variability (e.g., gender identity) or lack of suitability (e.g., income, as many participants are minors or are in school).

Analytic Plan

Participants eligible for the present secondary analysis are described by intervention condition. Engagement was assessed by describing dollars accrued over the 3-month trial and corresponding days in which a participant logged in to complete a daily activity stratified by those residing in high and low disadvantage neighborhoods. Descriptive statistics include measures of central tendency (e.g., mean, median) and measures of distribution (range, 25th and 75th percentile).

We used a combination of descriptive statistics, generalized linear mixed-effect models (GLMM), and model-derived data visualizations to characterize P3 efficacy among participants residing in high and low disadvantage neighborhoods. Prior to modeling any exposure measures (e.g., neighborhood disadvantage) we derived the intraclass correlation coefficient (ICC) from the two-level unconditional model (participants nested in zip codes) with PrEP non-adherence as the outcome. We constructed a GLMM model that controlled for age, race, syndemic condition clustering, and PrEP non-adherence at baseline. This model estimates relative risks of PrEP non-adherence for mutually exclusive sets of participants. These include participants who reside in high disadvantage neighborhoods

Table 1 Baseline characteristics of eligible YSGMMSM aged 16–24 ($N=212$) for secondary analysis, stratified by intervention condition[a]

	Overall	P3/P3+	SOC
Participants	212	141	71
3-Month PrEP Non-Adherent (%)	49 (23.1)	28 (19.9)	21 (29.6)
Baseline PrEP Non-Adherent (%)	71 (33.5)	46 (32.6)	25 (35.2)
BIPOC (%)	113 (53.3)	72 (51.1)	41 (57.7)
Not in Education or Employment (%)	15 (7.1)	10 (7.1)	5 (7.0)
Lifetime History of Arrest (%)	12 (5.8)	9 (6.5)	3 (4.4)
Polysubstance Use	17 (8.0)	7 (5.0)	10 (14.1)
Depressive Symptoms (%)	29 (13.7)	18 (12.8)	11 (15.5)
Anxious Symptoms (%)	36 (17.0)	21 (14.9)	15 (21.1)
Syndemic Cluster (%)	51 (24.1)	29 (20.6)	22 (31.0)
Neighborhood Disadvantage (%)[c]	50 (23.6)	29 (20.6)	21 (29.6)
Age (median [IQR])[b]	22.00 [20.00, 23.00]	22.00 [20.25, 23.00]	22.00 [21.00, 23.00]
Male Gender (%)	194 (91.5)	129 (91.5)	65 (91.5)
Trial Site (%)			
Tampa	34 (16.0)	23 (16.3)	11 (15.5)
Atlanta	16 (7.5)	10 (7.1)	6 (8.5)
Boston	33 (15.6)	22 (15.6)	11 (15.5)
Philadelphia	24 (11.3)	15 (10.6)	9 (12.7)
Chicago	31 (14.6)	23 (16.3)	8 (11.3)
Houston	29 (13.7)	18 (12.8)	11 (15.5)
Bronx	14 (6.6)	9 (6.4)	5 (7.0)
Chapel Hill	23 (10.8)	15 (10.6)	8 (11.3)
Charlotte	8 (3.8)	6 (4.3)	2 (2.8)

P3: Prepared, Protected, EmPowered. App-based mobile health intervention to improve PrEP adherence among 16–24 year old YSGMMSM

[a]Continuous measures tested with t-test, categorical measures tested with Fishers exact

[b]Nonnormal distribution, Kruskal-Wallis Rank Sum Test used

[c]Based on the Social Vulnerability Index as described by the Centers for Disease Control and Prevention

(compared to low disadvantage neighborhoods), participants who received the standard of care (as opposed to the P3/P3+intervention condition), and participants who simultaneously reside in high disadvantage neighborhoods and received the standard of care. Relative risks are reported as odds ratios with corresponding 95% confidence intervals (CIs), which were derived by exponentiating participant (i.e., level 1) beta coefficients and CIs. A parameter is considered statistically significant if the CI does not contain the null value of 1. Additionally, we derived measures of multiplicative and additive interaction (relative excess risk due to interaction [RERI]) [97]. If the CI did not contain the null value of 0, the RERI estimate was considered statistically significant. Finally, we calculated and visually compared model-derived covariate-adjusted predicted proportions of PrEP non-adherence among those living in high versus low disadvantage by intervention condition.

Table 2 Engagement with P3 among eligible secondary analysis participants (US YSGMMSM aged 16–24) stratified by neighborhood disadvantage ($n=141$)[a]

	Low Disadvantage ($n=112$)		High Disadvantage ($n=29$)	
	Dollars Accrued (USD)	Number of Daily Logins[b]	Dollars Accrued (USD)	Number of Daily Logins
Minimum	$1.5	1	$15.0	10
25th Percentile	$77.0	51	$58.5	39
Median	$115.0	77	$95.0	63
Mean (SD)	$98.7 ($35.2)	--	$85.0 ($35.0)	--
75th Percentile	$123.5	82	$114.0	76
Maximum	$135.0	90	$134.0	89

P3: Prepared, Protected, EmPowered. App-based mobile health intervention to improve PrEP adherence among 16–24 year old YSGMMSM

[a]Participants included from P3 and P3+arms only, as engagement was not measured in standard of care arm

[b]Number of days over the 90-day trial period where the participant logged in to complete one of the follow activities: (1) quest completion, (2) social wall post, (3) use the medication tracker

Results

Table 1 compares descriptive statistics for eligible participants across intervention conditions (P3/P3+and SOC). No significant differences in participant characteristics were observed among eligible participants between intervention conditions. See the primary adherence results detailed in Hightow-Weidman et al. (2024) for further details [88]. Overall, the median age of P3 RCT participants was 22 years of age (interquartile range [IQR]=20–23). Seventy-one (34%) participants were considered PrEP non-adherent at baseline and 49 (23%) participants were considered PrEP non-adherent at 3-month follow-up. Fifty (24%) participants reported a residential address in a zip code corresponding to high (>=90th percentile) neighborhood disadvantage. 40% (20/50) of P3 RCT participants living in high disadvantage neighborhoods were PrEP non-adherent compared to 18% (29/162) of P3 RCT participants living in low disadvantage neighborhoods. 38% (19/50) of P3 RCT participants residing in high disadvantage neighborhoods had a cluster of syndemic conditions compared to 20% (32/162) of P3 RCT participants living in low disadvantage neighborhoods.

Table 2 characterizes the distribution of P3 engagement among participants residing in high versus low disadvantage neighborhoods among participants in the intervention arms only, as no engagement measures were collected in the

standard of care arm. P3 participants living in high disadvantage neighborhoods earned an average of $85 (median = $95, SD = $35) compared to $99 (median = $115, SD = $35) among P3 participants living in low disadvantage neighborhoods. In high disadvantage neighborhoods, 55% (16/29) of participants earned $90 or more (logging in to the intervention for at least sixty of the ninety trial days) compared to 71% (79/112) in low disadvantage neighborhoods.

Table 3 describes the GLMM model constructed to assess the interaction between neighborhood disadvantage, intervention condition, and PrEP non-adherence among the 212 eligible participants. The unconditional model (binary PrEP non-adherence regressed against intercepts clustered within zip codes) had an ICC of 0.23. The reference category refers to participants who received P3 or P3 + and resided in a low-disadvantage neighborhood during the time of the trial. Comparatively, participants who received the standard of care and resided in low disadvantage neighborhoods were 2.0 times more likely to be PrEP non-adherent at 3 months (OR = 2.0, CI = 0.8, 5.0). This was not statistically significant as evidenced by the CI covering the null value of 1. Participants in high disadvantage neighborhoods who received P3 or P3 + were 3.6 times more likely to be PrEP non-adherent at 3 months compared to those who received the intervention but resided in low disadvantage neighborhoods (OR = 3.6, CI = 1.2, 10.4). This was statistically significant as evidenced by the CI not covering the null value of 1. Finally, participants who simultaneously resided in a high disadvantage neighborhood and received the standard of care were 3.0 times more likely to be PrEP non-adherent at 3 months (OR = 3.0, CI = 0.9, 10.2). This was not statistically significant, with the lower bound of the CI (0.9) narrowly covering the null value of 1. The multiplicative interaction term was not significant (OR = 0.4, CI = 0.8, 4.0) nor was the additive measure of effect moderation (RERI = −1.6, CI = −6.3, 3.0). Baseline PrEP non-adherence in the past 30 days was associated with PrEP non-adherence at 3 months (OR = 2.67, CI = 1.17, 6.07). Figure 1 shows that among those who received the intervention and lived in low disadvantage neighborhoods, the covariate adjusted PrEP non-adherence rate was 9% compared to 18% for those who did not receive the intervention but also lived in low disadvantage neighborhoods. For those living in high disadvantage neighborhoods, participants who received the intervention had a covariate-adjusted PrEP non-adherence rate of 28% compared to 25% among those who did not receive the intervention.

Table 3 Interaction between neighborhood disadvantage and P3 intervention condition on PrEP Non-Adherence US YSGMMSM aged 16–24 (n = 212)[g]

P3/P3 + or Standard of Care OR (95% CI) [Participant Count]	Neighborhood Disadvantage OR (95% CI) [Participant Count]	
	Low-disadvantage	High-disadvantage
P3/P3+	Reference [n = 112][a]	3.6 (1.2, 10.4)* [n = 29][b]
Standard of Care	2.0 (0.8, 5.0) [n = 50][c]	3.0 (0.9, 10.2) [n = 21][d]
Multiplicative Interaction[e]	0.4 (0.8, 4.0)	
Additive Interaction[f]	−1.6 (−6.3, 3.0)	

*Statistical significance (alpha = 0.05)

[a]Participants in the P3/P3 + intervention condition and not living in a disadvantaged neighborhood (OR_{00})

[b]Participants in the P3/P3 + intervention condition and living in a disadvantaged neighborhood (OR_{01})

[c]Participants in the standard of care condition and not living in a disadvantaged neighborhood (OR_{10})

[d]Participants in the standard of care condition and living in a disadvantaged neighborhood (OR_{11})

[e]Multiplicative interaction defined as: $OR_{11}/(OR_{10} * OR_{01})$. Null value of 1, 95% confidence interval

[f]Additive interaction defined as: $OR_{11} - OR_{10} - OR_{01} + 1$. Null value of 0, 95% confidence interval

[g]Controlled for age, BIPOC racial identity, syndemic condition clustering and baseline PrEP non-adherence

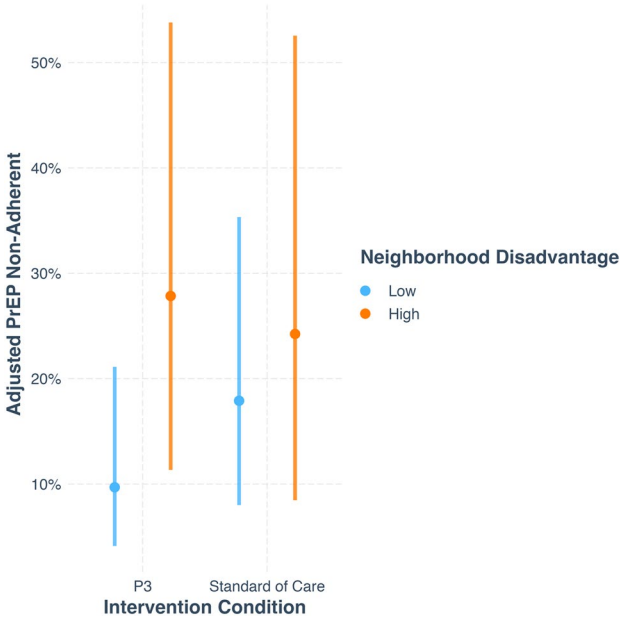

Fig. 1 Model Derived PrEP Non-adherence rates among secondary analysis eligible US YSGMMSM aged 16–24 (n = 212) participating in the P3 RCT Stratified by Neighborhood Disadvantage

Discussion

In this study, we characterized how P3 DHI engagement and efficacy varied among participant's residing in high and low disadvantage neighborhoods. Results indicate that intervention engagement was lower in high disadvantage neighborhoods. Descriptive and model-derived graphical comparisons suggest that the intervention was less efficacious among participants residing in high disadvantage neighborhoods. Further, results show that among those who received the P3 intervention, residing in a high disadvantage neighborhood was significantly related to an increased likelihood of PrEP non-adherence. Despite this, neighborhood disadvantage did not statistically significantly moderate the relationship between intervention condition and PrEP non-adherence on the multiplicative or additive scale. However, this may be due to several factors, detailed below, including low power (which is common in secondary analysis of RCTs). Finally, we found that baseline PrEP non-adherence was a significant predictor of PrEP non-adherence at 3 months. Collectively, these findings suggest that DHIs aiming to decrease HIV vulnerability among YSGMMSM may benefit from considering how to incorporate attributes of the neighborhood into DHIs.

DHIs are often highlighted for their ability to engage vulnerable populations, such as YSGMSM, in a way in which traditional interventions cannot [9]. Participants residing in high disadvantage neighborhoods engaged with P3 9 fewer days (corresponding to $14) compared to those who were not in high disadvantage neighborhoods. Past systematic reviews have highlighted how structural contextual characteristics might influence engagement with DHIs [83, 84]. For example, one study found that despite granting internet access through study procedures, households with a difficulty maintaining internet connectivity had significantly lower rates of health information seeking via the internet [117]. Further, past work has found that measures of neighborhood segregation and disadvantage are associated with worse broadband connectivity [118, 119]. However, a recent mediation secondary analysis of the P3 RCT found that participant-level internet connectivity problems were associated with a higher probability of PrEP non-adherence but *not* with lower engagement with P3 [116]. These mixed results across studies suggest that further work is needed to disentangle the multitude of neighborhood characteristics, such as broadband connectivity, which may be influencing engagement and efficacy with HIV DHIs and DHIs broadly.

We found that participants residing in high disadvantage neighborhoods were almost four times more likely to be PrEP non-adherent compared to those in low disadvantage neighborhoods among those who received the P3 intervention. Further, participants in low disadvantage neighborhoods who received the intervention were about half as likely to be PrEP non-adherent (9% PrEP non-adherence) compared to those who did not receive the intervention (18% PrEP non-adherence). However, all participants in high disadvantage neighborhoods shared a similar probability of PrEP non-adherence, despite intervention condition (roughly 25%). This suggests that the intervention had a differentially lower impact on participants residing in high disadvantage neighborhoods. However, we did not find quantitative evidence that receiving the intervention statistically significantly moderated the relationship between neighborhood disadvantage and PrEP non-adherence among eligible YSGMMSM. This is likely due to low power, which is common in secondary analyses of clinical trials examining interaction effects. However, it is possible that this may also be due to the relatively small sample of eligible participants, the specific geographic distribution (i.e., mostly urban neighborhoods with only a quarter of participants residing in high disadvantage neighborhoods), or that participants were required to have an active PrEP prescription, suggesting that participants enrolling in the trial were poised to begin or continue taking PrEP. Further, 66% of participants eligible for this secondary analysis were PrEP adherent at baseline and this was significantly related to PrEP adherence at 3 months. This suggests that the lack of an observed moderation effect may be due to a combination of low variance in neighborhood disadvantage combined with a small sample of YSGMMSM who were already adhering to PrEP. These mixed results suggest that characterizing the role of neighborhood disadvantage in PrEP adherence DHIs may be particularly suitable in a stage 4 effectiveness trial, as the goal of effectiveness trials is to examine the intervention in broader, real-world conditions [120].

In Stowell's review of DHI design and evaluation for vulnerable populations, they note possible avenues to harness physical neighborhoods in conjunction with DHIs to potentially help with structural barriers to DHI engagement and efficacy. While prior work examining how neighborhood characteristics influence DHI efficacy and engagement is incredibly sparse, this review draws on examples from healthy eating DHIs among vulnerable populations which address this topic to some degree. Stowell et al. suggest that establishing a physical presence in the neighborhood in conjunction with a DHI may provide a sense of legitimacy through a shared environment, operational support, and social accountability [83]. For example, a field trial of EatWell, a healthy eating DHI for low-income African American communities designed around creating and sharing memories of healthy eating around one's local neighborhood, found that participants shared a sense of community with their physical neighborhoods which was fostered by using EatWell in addition to virtual community created

within the DHI. A different healthy eating DHI designed for low socioeconomic status families, Snack Buddy, worked with a community outreach program to provide academic support for K-12 children prior and during field testing. This suggests that DHIs may benefit from integrating neighborhood features directly into the application (such as with EatWell) and working with neighborhood and community organizations when deploying DHIs (such as with Snack Buddy).

Strengths and Limitations

This study has several tradeoffs to consider due to its design as a secondary analysis of RCT data. The primary RCT has several strengths including clear temporality between exposure(s) and outcome (PrEP non-adherence) and strict inclusion and exclusion criteria of the RCT address several sources of confounding via restriction (age, digital literacy, rurality, sexual orientation. The measures added in this secondary data analysis are also robust. The SVI used to measure neighborhood disadvantage is a validated scale created by the Centers for Disease Control and Prevention [95] and the individual syndemic condition scale is an established measure based on several previous syndemic studies of HIV vulnerability in YSGMMSM [61–70, 74]. This combination of study characteristics provides a strong foundation to characterize how P3 intervention status modifies the relationship between neighborhood disadvantage, clustering of syndemic conditions, and PrEP non-adherence.

There are limitations to consider with this study. Firstly, 31% of eligible participants (66/212) did not have DBS derived measures of TFV-DP. This is due to study operation changes related to COVID-19 restrictions. Prior to COVID-19 restrictions, collection of biologic specimens used to measure PrEP non-adherence were completed in-person at study sites by study staff. Once COVID-19 restrictions were instantiated, several activities were shifted to be completed within participants' home. With respect to PrEP adherence measures, participants were asked to complete at-home DBS collection. This change from in-person collection via trained study staff to at-home collection likely generate much of the missingness in DBS derived PrEP adherence measures. As noted in the methods, where DBS derived measures were missing, self-reported measures of PrEP non-adherence were used. Overall evidence is mixed with respect to the validity of self-report PrEP adherence measures, with some work showing that self-report are sufficient for estimating protective serum levels of PrEP [90, 91]. Further, internal testing showed that among those with both biologic and self-report measures of PrEP adherence, the area under the receiver operating characteristics curve was high (=0.79).

The parent P3 RCT was not originally designed with the intent to examine neighborhood effects. Therefore, the sample size of participants and distribution of neighborhoods could be improved for statistical analyses examining interaction with multilevel models. Significantly more disadvantaged neighborhoods were represented in the P3 RCT study than the national average. However, the closer the ratio of high to low disadvantage neighborhoods is to 50/50, the more power these comparisons will have. Future research, particularly effectiveness and implementation studies, may consider using a sampling frame of neighborhoods to generate a sample of neighborhoods closer to a 50/50 ratio. This would improve the ability to examine the effects of neighborhood characteristics on participant-level outcomes through the DHI [121].

Conclusion

We characterized efficacy and engagement with P3, a PrEP adherence DHI for YSGMMSM, in high and low disadvantage neighborhoods. We found that participants in a digital PrEP adherence intervention (P3) in high disadvantage neighborhoods engaged comparatively less than those in low disadvantage neighborhoods. Further, we found that the intervention did not significantly moderate the relationship between neighborhood disadvantage and PrEP non-adherence among YSGMMSM in the P3 sample. This may be due to several reasons including small sample of eligible participants, overrepresentation of high disadvantage neighborhoods, and most participants being on PrEP already or about to begin. However, descriptive and graphical comparisons suggest that the intervention may be less efficacious in high disadvantage neighborhoods. Significant further work is needed to characterize the role physical neighborhoods play in DHI efficacy among YSGMMSM.

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Declarations

Competing Interests The authors do not have any conflicts of interest to report.

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