Digital intervention engagement mediates the relationship between intrapersonal measures and pre-exposure prophylaxis adherence: a secondary analysis of a randomized controlled trial of sexual orientation and gender minority youth on pre-exposure prophylaxis

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Abstract

Background: Improving adherence to Pre-Exposure Prophylaxis (PrEP) via digital health interventions (DHIs) for young sexual and gender minority men who have sex with men (YSGMMSM) is promising for reducing HIV burden among YSGMMSM. Measuring and achieving effective engagement (engagement sufficient to solicit PrEP adherence) in YSGMMSM is challenging.

Objective: The present secondary analysis of the P3 (Prepared, Protected, empowered: a digital PrEP adherence intervention) randomized controlled trial (RCT) utilized causal mediation to quantify whether and to what extent intrapersonal behavioral, mental health, and sociodemographic measures were related to effective engagement for PrEP adherence in YSGMMSM.

Methods: Of 264 YSGMMSM participants aged 16-24 in the primary RCT, 140 participants were eligible for the present secondary analysis (retained at follow up, received DHI condition in primary RCT, complete trial data). Participants earned US currency for daily usage of P3 and lost US currency for non-usage. Dollars accrued at 3-month follow-up was used to measure engagement. PrEP non-adherence was measured via blood serum levels consistent with ?4 doses weekly at 3-month follow-up. Logistic regression was used to estimate the total effect of baseline intrapersonal measures on PrEP non-adherence, represented as non-adherence odds ratios (NAR) with a null value of 1. The total NAR for each intrapersonal measure was decomposed into direct and indirect effects. Direct effects represent relationships between intrapersonal measures and PrEP non-adherence controlling for engagement with P3. Indirect effects represent relationships between intrapersonal measures and PrEP non-adherence operating through P3 engagement.

Results: For every $1 earned above the mean ($96), participants had 2% (NAR=0.98, 95% CI=0.97,0.99) lower odds of PrEP non-adherence. Frequently using phone apps to track health information was associated with a 71% (NAR=0.29, 95% CI=0.06,0.96) lower odds of PrEP non-adherence. This was overwhelmingly a direct effect, not mediated by engagement, with a percent mediated (PM) of 1%. Non-Hispanic White participants had 83% lower odds of PrEP non-adherence (NAR=0.17, 95% CI=0.05,0.48) and was a direct effect (PM=4%). Participants with depressive symptoms and anxious symptoms had 3.4 (NAR=3.42, 95% CI=0.95,12.00) and 3.5 (NAR=3.51, 95% CI=1.06,11.55) higher odds of PrEP nonadherence, respectively. Anxious symptoms largely operated through P3 engagement (PM=51%).

Conclusions: P3 engagement (dollars accrued) was strongly related to lower odds of PrEP non-adherence. Intrapersonal measures operating through P3 engagement (indirect effect, e.g., anxious symptoms) suggest possible pathways to improve PrEP adherence DHI efficacy in YSGMMSM via effective engagement. Conversely, the direct effects observed in the present study may reflect existing structural disparity (e.g., race/ethnicity) or behavioral dispositions towards technology (e.g., tracking health

via phone apps). Evaluating effective engagement in DHIs with causal mediation approaches provides a clarifying and mechanistic view of how DHIs impact health behavior.

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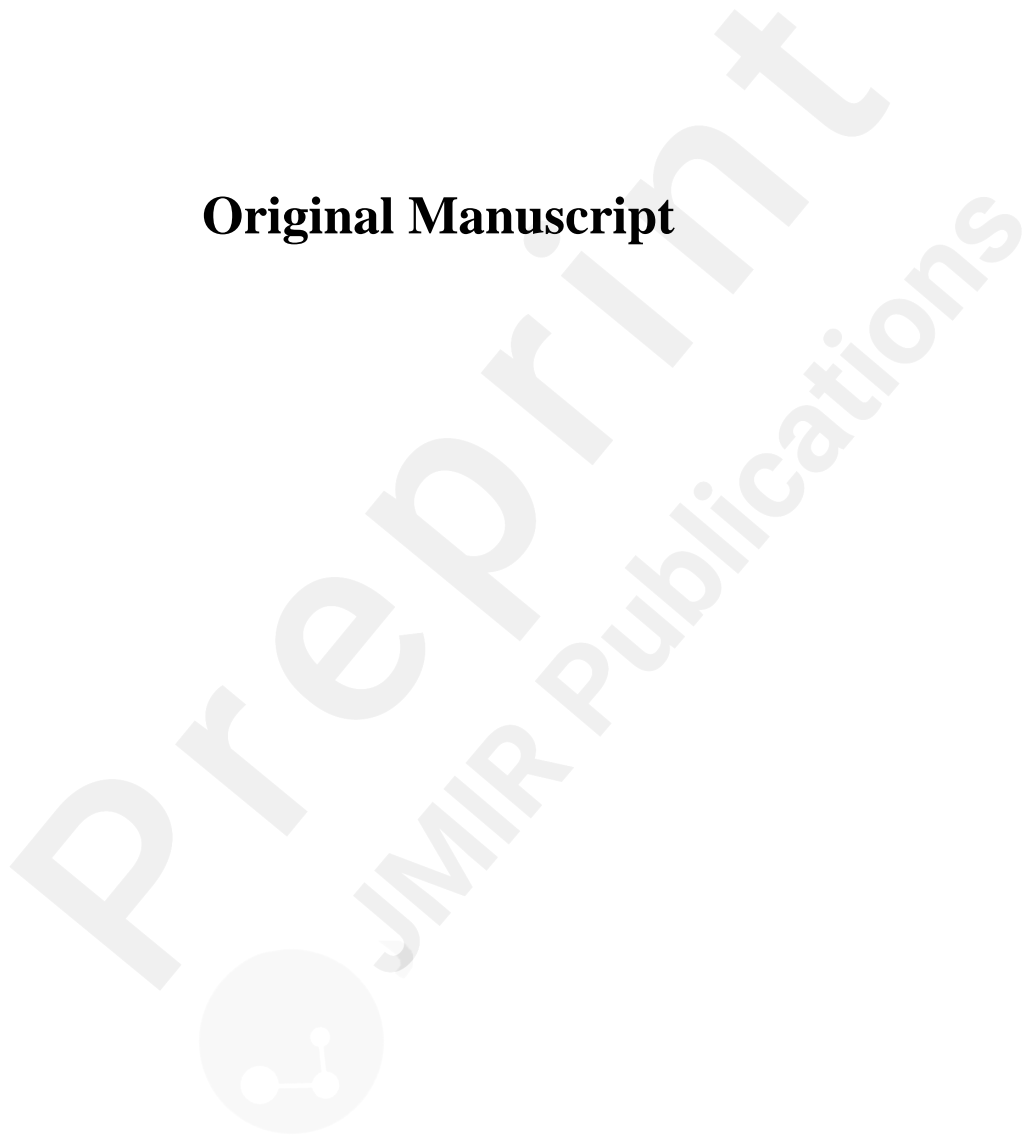
Original Paper

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provides a clarifying and mechanistic view of how DHIs impact health behavior.

Keywords: Engagement; Pre-Exposure Prophylaxis; Digital Health Intervention; Adherence; MSM;

Introduction

Young sexual and gender minority men who have sex with men (YSGMMSM) are burdened with a disproportionate and growing vulnerability to HIV in the United States (US).[1–8] Of the 30,692 incident HIV cases in 2020, 71% were among men who have sex with men (MSM) and 24% were among MSM aged 13-24.[8] Additionally, a meta-analysis of transgender women age 15 and older found they were 48 times more likely to have HIV compared to other adults of reproductive age.[1] While pre-exposure prophylaxis (PrEP) has demonstrated efficacy in reducing incidence of HIV in US YSGMMSM in randomized controlled trials (RCTs), [9,10] adherence to these medications outside of clinical trial settings has been suboptimal for reducing transmission. [9,11] Furthermore, findings from population and agent-based simulation studies demonstrate that PrEP uptake and adherence is associated with a decrease in incident HIV infections, lowering incidence by as much as 25%.[12,13] Altogether, this suggests that improving PrEP adherence is a fruitful pathway to reducing HIV incidence in YSGMMSM.[9,11–13]

Digital health interventions (DHI) are a potentially powerful and increasingly prevalent mechanism for delivering PrEP interventions to YSGMMSM.[14–20] Due to the pervasiveness of digital communication and entertainment among youth, including YSGMMSM, DHIs are a suitable delivery mechanism for HIV prevention interventions due to their potential to effectively engage participants. [21–25] However, to our knowledge, there is a paucity of clinical trials directly testing the efficacy of digital PrEP adherence interventions. Adjacent digital PrEP adherence interventions such as automated text-messaging services or digital pill systems have had mixed results in youth populations. For example, digital pill systems have documented barriers to engagement and have not shown that they independently improve PrEP adherence compared to a standard of care.[26–29] Further, DHIs implemented to address other health problems in target youth populations have encountered problems effectively engaging participants. For example, one study which developed a mobile app for self-management of Type 1 diabetes among adolescents found no association between intervention condition and primary or secondary clinical outcomes. Furthermore, this study found that only 9% of participants met the criteria for high engagement levels (measured as an individual uploading blood glucose readings 3 or more days per week).[30]

For these reasons, effectively engaging YSGMMSM in PrEP adherence DHIs is likely an essential element to achieving protective levels of PrEP adherence.[25,31,32] Yardley et al. define effective engagement as "sufficient engagement with the intervention to achieve intended outcomes." This framework describes effective engagement as a macro form of engagement, one which relates to the overarching goal of the intervention (e.g., PrEP adherence) as opposed to micro-engagement, where the focus is on the moment-to-moment user experience of the intervention. Yardley et al. and other review articles utilizing Yardley et al.'s effective engagement framework describe a plethora of issues with operationalizing and measuring effective engagement in prior research. Most notably, engagement research to date is largely correlational, relies on the assumption that engagement is intrinsically a precursor to the intended outcome, and does not account for intrapersonal measures such as motivation to use the intervention or digital literacy.[25,31–36] This highlights the need to empirically test and corroborate models of engagement, by modeling how intrapersonal measures influence engagement and then subsequently mediate behavioral outcomes (e.g., PrEP adherence). [25,33,37] These works also highlight the suitability of paradata (defined as data documenting users' access, participation, and navigation through a DHI) for constructing measures of engagement, as

these measures provide an objective view into patterns of use with high ecological validity.[25,31,32]

Causal mediation analysis is a fitting statistical framework for investigating the relationship between intrapersonal measures and effective engagement as it addresses all the aforementioned issues by Yardley et al, has been extensively explicated, [38–43] and applied in previous research in other domains.[44] This approach allows for the total effect (e.g., the effect of baseline digital literacy on PrEP adherence) to be decomposed into a direct and indirect effect. The direct effect models the effect of a given intrapersonal measure on PrEP adherence controlling for engagement with the intervention. Conversely, the indirect effect models how a given intrapersonal measure is related to PrEP adherence operating through engagement, and thus is an excellent measure of effective engagement. This approach is causal in nature (as opposed to correlational), explicitly models the relationship between engagement and outcome (as opposed to relying the assumption that engagement and the outcome are related), and incorporates intrapersonal measures (as exposures or controls).[38,39,41] The integration of the effective engagement framework with the casual mediation approach provides a combined theoretical and analytical approach for evaluating effective engagement in DHIs.

Intrapersonal measures, in addition to being a requisite component of unbiased effective engagement models, are key measures of interest themselves due to tailoring. Tailoring, defined as the use of individuals' data to customize intervention content based on their psychological, socioecological, and behavioral profile, is a property of DHIs which has demonstrated efficacy in promoting effective engagement with DHIs.[25,45–49] Several barriers and facilitators to engagement have been identified in qualitative research.[50] For example, baseline motivation to change [25,51] or baseline comfort with the intervention modality (e.g., phone/app-based intervention) may influence engagement and subsequent behavior change.[50–61] Furthermore, aspects beyond the individual's control, such as internet access, may influence engagement and therefore intervention efficacy. [50,62–64] However, there is a lack of quantitative research which aims to isolate and quantify the impact that intrapersonal psychological, sociodemographic, and behavioral measures have on engagement and subsequent behavioral outcomes of interest. Collectively, this suggests that these measures should be evaluated against measures of engagement and subsequent behavior change to isolate the effect each of these measures has and how best to utilize tailoring to promote the positive effects or mitigate any negative impacts these measures may have.

To this end, the present study collates clinical survey data, biological PrEP adherence measures, and paradata from the P3 (Prepared, Protected, emPowered) RCT[19,65] in a secondary data analysis utilizing the causal mediation framework[38–43] to quantify whether and to what degree intrapersonal behavioral, mental health, and sociodemographic measures impact effective engagement with respect to PrEP adherence in YSGMMSM.

Methods

Study Design

The present study is a secondary analysis which combined clinical survey data, biological PrEP adherence measures, and paradata collected from a three-arm RCT testing the efficacy of P3, a PrEP adherence DHI.[19,65] This secondary analysis utilized the causal mediation framework and statistical analysis procedures to characterize whether engagement with the P3 intervention mediated the relationship between baseline intrapersonal measures and PrEP adherence at 3 months. This study was reviewed by the Northeastern University Institutional Review Board and determined to be exempt determination, category 4 (secondary research for which consent is not required). This secondary analysis utilizes a de-identified analytic dataset curated by the parent study's staff. The

principal investigator had no contact with participants and made no attempts to re-identify participants post hoc.

Parent Study

Intervention

P3 is a user-centered PrEP adherence phone application which incorporates a variety of content in multiple formats to serve the diverse needs, barriers, and motivations of YSGMMSM. This phone application included text, videos, quizzes, and a social wall in which participants could share experiences, from success stories to challenges. Additionally, P3 incorporated game-like elements such as daily health-related quests, in-app rewards, unlocking character driven narratives, and social connection activities. P3 employed a financial incentive to encourage daily use in which small monetary incentives are awarded for daily use of P3 (not necessarily PrEP). Participants started with $90 USD in an initial bank, and then were awarded $0.50 USD for each day of app use or 1$ USD was deducted for each day of non-use over the 3-month intervention period. The maximum a participant could earn was $135 and the minimum is $0. P3+ is an extension of P3, in which participants were also connected with an adherence counselor trained on the Next Step Counseling (NSC) adherence counseling curriculum through the P3 phone application.[19,65–67]

Clinical Trial Eligibility and Procedures

Starting in May 2019, P3 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. Inclusion criteria were as follows: 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). 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. Clinical survey assessments and laboratory specimens were collected at baseline and 3 months in the trial period. Paradata (in the two intervention arms) was collected continuously throughout the intervention period and summarized at 3 months.[19] 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 trial concluded in September 2021.

Secondary Analysis Eligibility

Participants from the primary study who received the P3 or P3+ intervention were eligible for inclusion in this secondary data analysis (n=163). Participants in the P3 and P3+ condition who were lost to follow-up (LTFU, defined as participants who did not begin the month 3 survey) were excluded (n=22). One participant with incomplete survey information pertaining to study-relevant exposure measures was also removed. This resulted in a dataset of 140 participants (Figure 1).

Outcome

PrEP non-adherence at 3 months (binary) was the primary outcome measure used in this analysis. If

serum levels of tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP) were consistent with less than or equal to 4 doses per week, the participant was considered non-adherent. In cases where TFV-DP and FTC-TP values were missing, self-reported doses of PrEP in the last 7 days prior to the 3-month clinical survey was used. Participants who reported less than or equal to 4 self-reported doses of PrEP in the last 7 days were considered non-adherent. Prior research has found that self-report measures of PrEP adherence correlate with protective serum levels.[68,69]

Mediator

Engagement was defined as dollars accrued by 3 months. This measure was mean-centered (participant dollars accrued − mean dollars accrued) when used in modeling. As mentioned above, participants started with a baseline amount of USD in a bank, and gain or lose money from this initial bank corresponding to use and non-use, respectively. 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 is a global measure of engagement over the entire 3 months (as opposed to other measures such as click-throughs which only measure the completion of specific features).

Intrapersonal Measures

Several intrapersonal measures were constructed from the baseline survey administered in the primary RCT based on prior research.[25,50] These measures, described below, focused on patterns of phone and phone app usage, measures of mental health, and sociodemographic information.

Phone and Phone App Usage

Several binary measures describing phone and phone app usage were derived from the baseline survey. A participant was considered to have experienced disconnects if they lost access to their phone or phone service at any time in the past year prior to the baseline survey. Prior qualitative research identified poor internet access as a barrier to engagement in DHIs.[50,52–54,57,60,62–64,70] Those who averaged 7 or more hours per day on the internet outside of work or school were considered high internet users. Those who used phone apps twice or more per day were considered frequent phone app users. These measures acted as proxy variables for digital literacy and digital familiarity, which have been shown in qualitative research to act as engagement facilitators.[46,51–61,71–73] Binary measures describing participants' propensity to use phone apps for a variety of purposes were derived from questions whose answers follow a Likert scale with the following ranked choices: never, rarely, sometimes, often, decline to answer. Participants who disclosed that they "often" use phone apps for chatting with friends, chatting with family, looking for romantic dates, looking for casual sex, or for tracking their health were considered highly interested in using phone apps for those activities. Prior qualitative research has identified social support in various forms enabled through a DHI as engagement facilitators.[50,58,59,74–76] Finally, a binary measure representing intervention arm (P3 or P3+) was constructed to be used a control measure.

Mental Health

The patient health questionnaire-8 (PHQ8)[77,78] and generalized anxiety disorder-7[79] questionnaires were used to assess depressive and anxious symptoms respectively. Both scales 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 and 0 to 21 in the GAD-7, with lower scores representing less frequent experiences and higher scores representing more frequent experiences of depressive and anxious symptoms, respectively. Participants who scored 10 or more on the PHQ-8 and GAD-7 were considered as having depressive or anxious symptoms, respectively.[78–80] Prior research has identified that psychological distress from trauma

is associated with lower engagement, which suggests that other stressors on mental health may also act as barriers to engagement.[81]

Sociodemographic Measures

Sociodemographic measures captured from the baseline survey include race/ethnicity and age. Participants were considered non-Hispanic White if they disclosed non-Hispanic ethnicity and Caucasian as their race. In prior research, sociodemographic measures have mixed effects on engagement.[82–89] For example, older age has been observed as an engagement facilitator and an engagement barrier in different studies.[82,83] These measures were used to control for confounding (further specifications below) and investigated as exposures of interest for their relationship to effective engagement..

Statistical Analysis

Descriptive statistics for eligible secondary analysis participants were generated and are reported in Table 1. Table 1 also compares the 140 eligible participants to the 22 participants who were LTFU. To quantify how engagement with P3 mediates the relationship between baseline intrapersonal measures and PrEP non-adherence at 3 months, the causal mediation framework was employed. This analytic approach extends the counterfactual framework to mediation, has been extensively explicated, clarifies several confounding assumptions, accommodates exposure-mediator interaction, [38–43] has been applied in previous research,[44] and complements the effective engagement theoretical framework by explicitly decomposing the total effect of each intrapersonal measure on PrEP non-adherence into a direct and indirect effect (i.e. the effect mediated by P3 engagement). Figure 2 visually depicts the integration of effective engagement and causal mediation through a theoretical causal diagram. In this study, effect decomposition was accomplished by first fitting a linear regression for the effect of each exposure (e.g., anxious symptoms) on the mediator (mean-centered dollars accrued at 3 months), adjusting for confounding. Then, a logistic model for the relationship between each exposure (e.g., anxious symptoms) and PrEP non-adherence, adjusting for the same confounders, dollars accrued at 3 months (i.e., the mediator), and the exposure-mediator interaction was fit. The following baseline measures were used to adjust for confounding: age, race, and intervention arm. Several other critical measures were controlled through the primary study's design via the eligibility criteria. Intention to initiate PrEP, PrEP access, sexual orientation, and English literacy were verified at enrollment. The total effects estimated from these two models with corresponding confidence intervals (CI) and p-values are reported in Table 2. The total effect for each intrapersonal measure on PrEP non-adherence at 3 months is presented as a non-adherence ratio (defined as the rate of non-adherence in the exposed divided by the rate of non-adherence in the unexposed). These two regression models are then used to derive direct and indirect effects. The direct effect represents the effect of a given intrapersonal measure on PrEP non-adherence independent of P3 engagement. This effect is estimated by comparing the estimated PrEP non-adherence in the exposed to the unexposed while setting P3 engagement to the level that would have naturally occurred in the absence of the exposure. The indirect effect represents the effect of a given intrapersonal measure on PrEP non-adherence operating through the mediator. This effect is estimated by comparing the outcome for the exposed for different contrasts of the mediator (e.g., between levels of P3 engagement). Mediation results including direct effect and indirect effect with corresponding confidence intervals and percent mediated (PM) are reported in table 3. Mediation is assessed using a combination of total and indirect effect size, statistical significance, and PM. P-values are reported in tables 1 and 2 for transparency but CI's are used as the primary determinant of statistical significance for mediation analysis, determined by if the CI overlaps the null value. For the first model in Table 2 (linear regression of dollars accrued) the null value is 0 and for the second model in Table 2 (logistic regression of binary PrEP adherence) the null value is 1.

Results

Participant Characteristics

Table 1. Comparison of eligible secondary analysis sample and loss to follow up participant characteristics in a secondary analysis of PrEP adherence and DHI engagement among US YSGMMSM aged 16-24

	Eligible	LTFU	P-value[a]
Participants	140	22	
Non-adherent to PrEP at 3 months (%)	24 (17.1)	-	-
Dollars accrued at 3 months (median [IQR])	112.5 [73.25, 123.50]	-	-
High internet user (%)	29 (20.7)	3 (13.6)	0.63
Disconnect from phone in past 12 months (%)	16 (11.4)	3 (13.6)	1.0
Frequent phone app user (%)	127 (90.7)	21 (95.5)	0.74
Frequently use phone apps for:			
Chat with friends (%)	126 (90.7)	22 (100.0)	0.29
Chat with family (%)	76 (54.3)	13 (59.1)	0.85
Find romantic dates (%)	43 (30.7)	4 (18.2)	0.34
Look for casual sex (%)	38 (27.1)	5 (22.7)	0.86
Track health (%)	38 (27.1)	8 (36.4)	0.53
Depressive symptoms (%)	18 (12.9)	2 (9.1)	0.88
Anxious symptoms (%)	21 (15.0)	5 (22.7)	0.55
Non-Hispanic White (%)	69 (49.3)	9 (40.9)	0.62
Male (%)	128 (91.4)	20 (90.9)	1.0
Intervention arm: P3+ (%)	71 (50.7)	9 (40.9)	0.53
Age (median [IQR])	22.0 [20.0, 23.0]	22.0 [20.0, 23.0]	0.53[b]
Site (%)			0.12
Tampa	23 (16.4)	5 (22.7)	
Atlanta	10 (7.1)	5 (22.7)	
Boston	22 (15.7)	2 (9.1)	
Philadelphia	14 (10.0)	4 (18.2)	
Chicago	23 (16.4)	1 (4.5)	
Houston	18 (12.9)	4 (18.2)	
Bronx	9 (6.4)	1 (4.5)	
Chapel Hill	15 (10.7)	0 (0.0)	
Charlotte	6 (4.3)	0 (0.0)	

[a] Continuous measures tested with t-test, categorical measures tested with Fishers exact.
[b] Nonnormal distribution, Kruskal-Wallis Rank Sum Test used.

The average age of participants was 22 years of age. Overall, 17% were considered non-adherent to PrEP at 3 months. Participants accrued a median $112.50 (IQR= $73.25, $123.5) and a mean $96.40 (SD = $35.1). A median $112.50 accrued translates to 75 days of app use on average over the 3-month trial period. Participants were largely heterogenous with respect to phone, technology, and internet usage patterns. Notable exceptions to this pattern: 91% of participants used phone apps more than once per day and 91% of participants disclosed that they often use phone apps for chatting with

friends. No significant differences in selected baseline intrapersonal characteristics were observed between eligible and LTFU participants (Table 1).

Multivariate Analysis

Table 2. Multivariate relationships between intrapersonal measures and Engagement with P3, PrEP non-adherence among 140 US YSGMMSM youth aged 16-24

Intrapersonal Measures	Engagement[a]		PrEP Non-adherence[a]	
	Estimate (95% CI)[d]	P-value	Non-adherence Ratio[c] (95% CI)[e]	P-value
Dollars accrued at 3 months	-	-	0.98 (0.97,0.99)	0.02
High Internet User	-5.51 (-19.65,8.63)	0.45	2.31 (0.80,6.46)	0.11
Disconnect from phone in past 12 months	-6.42 (-24.00,11.16)	0.48	3.84 (1.14,12.81)	0.03
Frequent Phone App User	21.49 (2.50,40.47)	0.03	0.66 (0.17,2.88)	0.55
Frequently use phone apps for:				
Chat with friends	-1.26 (-20.36,17.85)	0.90	0.82 (0.20,4.37)	0.80
Chat with family	9.71 (-1.45,20.86)	0.09	0.99 (0.38,2.63)	0.99
Find romantic dates	1.22 (-11.14,13.57)	0.85	0.78 (0.23,2.32)	0.67
Look for casual sex	-5.06 (-17.49,7.36)	0.43	0.71 (0.21,2.08)	0.55
Track health	2.00 (-10.42,14.41)	0.75	0.29 (0.06,0.96)	0.06
Depressive Symptoms	-8.16 (-24.82,8.51)	0.34	3.42 (0.95,12.00)	0.05
Anxious Symptoms	-15.95 (-31.57,-0.32)	0.05	3.51 (1.06,11.55)	0.04
Non-Hispanic White[f]	17.02 (5.95, 28.10)	<0.01	0.17 (0.05,0.48)	<0.01
Intervention Arm: P3+[f]	12.48 (1.47,23.50)	0.03	1.05 (0.41,2.71)	0.92
Age[f]	2.55 (-0.19,5.29)	0.07	0.82 (0.65,1.02)	0.08

[a] Multivariate models are adjusted for age, race/ethnicity, and intervention arm.
[b] Multivariate models are adjusted for age, race/ethnicity, intervention arm, dollars accrued at 3 months, and dollars accrued at 3 months * intrapersonal measure.
[c] Derived by exponentiating estimated regression coefficients.
[d] Null value is 0.
[e] Null value is 1.

[f] Intrapersonal measure is also a control measure. Model constructed using age, race, and intervention arm for engagement and age, race/ethnicity, intervention arm, dollars accrued at 3 months, and dollars accrued at 3 months * intrapersonal measure for PrEP non-adherence.

Table 2 presents multivariate regression results for the effect of intrapersonal measures on engagement (dollars accrued by 3 months). Frequent phone app users earned $21.49 (CI = 2.50, 40.47) more than infrequent phone app users through the 3-month trial period. Participants who reported anxious symptoms in the past two weeks (GAD7 score >= 10) earned $15.95 (CI = -31.57, -0.32) less throughout the 3-month trial period than those with mild or no anxious symptoms in the past 2 weeks. Non-Hispanic White individuals earned $17.02 (CI = 5.95, 28.10) more on average by 3 months than participants belonging to other racial/ethnic groups. Participants who received the P3+ intervention (P3 with the addition of human adherence counselors accessible through the app) earned $12.48 (CI = 1.47, 23.50) more on average those who received the standard P3 app through the 3-month trial period. Finally, for each additional year of age, participants earned on average an additional $2.55 (CI = -0.19, 5.29). The CI for relationship between age and engagement narrowly overlaps the null value of 0 with a corresponding p-value of 0.07, meaning this relationship is technically statistically insignificant.

Total effects for the relationship between baseline intrapersonal measures and PrEP non-adherence at 3 months are reported in Table 2 as non-adherence ratios. For every dollar earned above the mean throughout the 3-month trial period, participants had 2% (NAR = 0.98, CI = 0.97, 0.99) lower odds PrEP of non-adherence at 3 months. Participants who reported using phone apps twice or more per day had 34% lower odds of PrEP non-adherence at 3 months (NAR = 0.66, CI = 0.17, 2.88). Participants who spent more than 7 hours on the internet beyond work or school had 2.31 (CI = 0.80, 6.46) times higher odds of PrEP non-adherence at 3 months compared to participants who reported less than 7 hours on the internet beyond work or school. Both of these measures which aimed to describe broad patterns of phone and internet usage had a relatively large effect on the odds of PrEP non-adherence. However, neither were statistically significant as the 95% CI covers the null value of 1. Participants who reported at least one disconnect from their internet service or phone in the past year had 3.84 (CI = 1.14, 12.81) times higher odds of PrEP non-adherence at 3 months than participants who reported no disconnects. Participants who reported that they frequently used phone apps to track their personal health information had 71% (NAR = 0.29, CI = 0.06, 0.96) lower odds of PrEP non-adherence at 3 months. Participants who reported depressive symptoms (PHQ8 score >= 10) had 3.42 (CI = 0.95, 12.00) times higher odds of PrEP non-adherence at 3 months. Participants who reported anxious symptoms also had 3.51 (CI = 1.06, 11.55) times higher odds of PrEP non-adherence at 3 months. Participants who reported their race and ethnicity as non-Hispanic White had 83% (NAR = 0.17, CI = 0.05, 0.48) lower odds of PrEP non-adherence at 3 months. For each additional year of age, participants had 18% (NAR = 0.82, CI= 0.65, 1.02) less odds of PrEP non-adherence at 3 months. The CI for relationship between age and PrEP non-adherence narrowly overlaps the null value of 1 with a corresponding p-value of 0.08, meaning this relationship is technically statistically insignificant.

Mediation Analysis

Table 4. direct and indirect effects of intrapersonal measures on effective engagement with P3, a PrEP adherence DHI, among 140 US YSGMMSM youth aged 16-24

	Direct Effect (95% CI)[c]	Indirect Effect (95% CI)[c]	% Mediated[a]

High Internet User	1.92 (0.80,5.42)	1.11 (0.84,1.55)	18%
Disconnect from phone in past 12 months	3.28 (0.91,11.42)	1.04 (0.74,1.84)	5%
Frequent Phone App User	1.19 (0.37,6.03)	0.76 (0.49,1.00)	n/a
Frequiently use phone apps for:			
Chat with family	1.23 (0.48,3.19)	0.83 (0.59,1.03)	n/a
Find romantic dates	0.63 (0.19,2.25)	1.01 (0.80,1.16)	n/a
Look for casual sex	0.74 (0.15,2.02)	1.05 (0.81,1.37)	n/a
Track health	0.31 (0.00,0.92)	0.98 (0.71,1.33)	1%
Depressive Symptoms	2.52 (0.79,6.81)	1.25 (0.78,2.14)	30%
Anxious Symptoms	2.12 (0.58,5.49)	1.55 (1.00,3.34)	51%
Non-Hispanic White[b]	0.20 (0.04,0.59)	0.84 (0.46,2.54)	4%
Intervention Arm: P3+[b]	1.34 (0.54,3.62)	0.84 (0.58,1.04)	n/a
Age[b]	0.95 (0.68,1.02)	0.92 (0.59,1.07)	60%

Models are adjusted for age, race/ethnicity, intervention arm, dollars accrued at 3 months, and dollars accrued at 3 months * intrapersonal measure.

[a] % mediated cannot be calculated when direct and indirect effects are in opposite directions.

[b] Intrapersonal measure is also a control measure. age, race/ethnicity, intervention arm, dollars accrued at 3 months, and dollars accrued at 3 months * intrapersonal measure.

[c] Null value is 1.

Experiencing disconnects in the past year was primarily directly related to a higher odds of PrEP non-adherence at 3 months (PM = 5%), with a direct effect of 3.28 (CI = 0.91, 11.42). Despite the statistically insignificant total effect, using phone apps twice or more per day was significantly indirectly associated with lower odds of PrEP non-adherence at 3 months (0.76, CI = 0.49, 1.00). Conversely, spending more than 7 hours on the internet beyond work or school was primarily a direct relationship (1.92, CI = 0.80, 5.42, PM = 18%). However, similar to the total effect on PrEP non-adherence, this relationship did not rise to the level of statistical significance for either the direct or indirect relationship. Frequently using phone apps to track health information was directly associated (0.3, CI = 0.00, 0.92, PM = 1%) with a lower odds of PrEP non-adherence. Symptoms of depression had a statistically significant total effect on PrEP non-adherence (Table 2) and was partially mediated by engagement with P3 with a direct effect of 2.52 (CI = 0.79, 6.81), an indirect effect of 1.25 (0.78,

2.14), and a percent mediated of 30%. However, neither the direct nor indirect effect raised to the level of statistical significance on their own. Experiencing anxious symptoms was primarily indirectly related to a higher odds of PrEP non-adherence through engagement with P3 (1.55, CI = 1.00, 3.34, PM = 51%). Being non-Hispanic White was directly related to a lower odds of PrEP non-adherence (0.20, CI = 0.04, 0.59, PM = 4%). For each additional year of age, odds of PrEP non-adherence was decreased, operating through both direct (0.95, CI = 0.68, 1.02) and indirect (0.92 CI = 0.59, 1.07, PM = 60%) relationships.

Discussion

This study leveraged data from the P3 RCT in a secondary data analysis to characterize whether and how engagement with P3 mediated the relationship between baseline intrapersonal measures and PrEP non-adherence at 3 months. The present study found that several measures (e.g., twice or more daily phone app usage) were positively related to engagement, measured as dollars accrued by 3 months. In contrast, measures such as anxious symptoms were negatively related to engagement. Further, this study found that P3 engagement, behavioral patterns of phone and app usage, mental health symptoms, and sociodemographic measures were significantly related to PrEP non-adherence. Utilizing causal mediation analysis, this study decomposed these total effects into direct effects to isolate the effect of each intrapersonal measure on PrEP adherence irrespective of P3 engagement and indirect effects to evaluate if and how each measure may be contributing to effective engagement with P3. This process helps to illuminate possible mechanisms which precipitate or protect against susceptibility to PrEP non-adherence.

Principal Findings

Phone and Phone App Usage

Digital literacy, defined as an understanding of how technology and digital media are used to communicate with others, has been linked to engagement in DHIs in both HIV and non-HIV related domains.[46,51–61,71–73,90] Participant's propensity to use phone apps twice or more daily may or may not be a direct reflection of their digital literacy. However, this broader representation of their affinity to use phone apps empirically impacted their engagement with P3 (via dollars accrued at 3 months). Further, despite a statistically insignificant total effect on PrEP non-adherence, the moderate to large reduction in odds of PrEP non-adherence combined with the statistically significant indirect effect from the causal mediation analysis, suggests that participants affinity to use phone apps could be a facilitator of effective engagement in the context of PrEP adherence DHIs. Conversely, participants who were categorized as high internet users had higher odds of PrEP non-adherence at 3 months, but this effect was not statistically significant. Further these participants did not significantly engage with P3 more or less than the average participant. The combination of these contrasting findings suggests that a minimum affinity for phone apps may be related to effective engagement, but time spent online is likely not related effective engagement. This aligns with theories of digital literacy which describe literacy as more of a minimum capacity to use and understand technology as opposed to merely time spent using it.[90,91] Furthermore these results substantiate the recent trend of constructing validated and reliable scales of digital literacy.[92–96] Studies of effective engagement (such as this) would benefit greatly from a scale which can measure and test relevant core constructs of digital literacy against effective engagement.

While the present study did not have the opportunity to implement a reliable and validated scale of digital literacy, several measures captured more specific patterns of behavior with respect to phone apps, including using phone apps for dates, tracking health information, or to chat with one's family. Of these, only frequently using phone apps to track health information significantly reduced the odds of PrEP non-adherence at 3 months. However, this effect was overwhelmingly a direct effect and

participants who frequently use phone apps to track health information did not engage with P3 significantly more than average. This suggests that individuals who are prone to using apps for health tracking may be more health conscious independent of app usage and therefore more likely to adhere to PrEP. This aligns with the idea of health specific digital literacy, sometimes referred to as "eHealth Literacy", defined as "the ability to seek, find, understand, and appraise health information from electronic sources and apply the knowledge gained to addressing or solving a health problem."[90] Previous work found that high digital health literacy YSGMMSM perceived the information of a digital health intervention aimed to promote HIV and sexually transmitted infection testing as more useful when the intervention tailored information to the participants.[46] The present study supports the hypothesis that health related digital literacy is an important measure in DHI efficacy, especially when the content is tailored for the population the DHI is serving. Further, the present study suggests that while digital health literacy likely improves health outcomes through DHIs, it also likely does not operate through increases in engagement with the intervention itself. Instead, the baseline capacity for digital health literacy seems to act as a catalyst for the participant to incorporate the information presented in the DHI into their life.

Participants who experienced disconnects from their phone in the past year had higher odds to be non-adherent to PrEP at 3 months, overwhelmingly operating as a direct effect. Participants who experienced disconnects did not earn significantly more or less money than average throughout the trial period. This suggests that disconnecting from one's internet service is not a key engagement barrier. Instead, this measure is likely reflecting the broader social and structural environment in which a given participant exists. This aligns with previous work which has highlighted the difficulties in adapting DHIs to varying infrastructure levels (e.g., low internet connectivity). [50,52–54,57,60,62–64,70,97–100] Similarly, non-Hispanic White participants had significantly lower odds of being PrEP non-adherent at 3 months and earned significantly more money than average throughout the trial period. However, the effect this had on PrEP non-adherence was also largely a direct effect, suggesting that despite the increases in superficial engagement (via dollars accrued), those increases in engagement were not driving the lower odds of PrEP non-adherence at 3 months. Therefore, it seems more likely that non-Hispanic White individuals are experiencing less social and structural barriers in life external to the intervention which afford an easier adoption of adherence behaviors. Previous work reinforces this hypothesis, as significant adherence disparities have been found among black patients relative to white patients in non-DHI settings.[101–103] Further, previous research has also established that HIV disproportionately effects economically disadvantaged individuals.[104] Collectively, the results of the present study combined with this body of literature suggest structural measures likely impact PrEP adherence DHI efficacy directly (i.e., not through engagement). The implications of this finding align with a systematic review of qualitative studies on engagement conducted by O'Connor et al., which describe several recommendations for future DHI development and implementation. Firstly, this systematic review highlights the need for DHI developers to lessen the burden of self-care through DHIs.[50] This aligns with the present study, where the preponderance of direct effects suggests several mechanisms for tailoring which do not operate through increases in DHI usage. For example, DHIs may be able to adapt interventions elements to low internet connectivity environments (e.g., allow for participants to download any video content so that it is viewable offline). While this may not increase engagement levels of those living in low internet connectivity environments to a level significantly above the average, this may allow for those participants to interact with the DHI more meaningfully by consuming DHI content uninterrupted during an optimal time for the participant. Further, this systematic review recommends incorporating interpersonal relationships (e.g., family, friends, and care providers) and public health institutions in designing, utilizing, and implementing DHIs to mitigate the effects of structural disparities. [50]

Mental Health

While past literature has highlighted the impact of DHIs on improving mental health outcomes, to our knowledge this is the first study which directly measures the impact of baseline mental health symptoms on effective engagement in a study focused on a non-mental health related outcome.[105] Depressive symptoms (PHQ8) and anxious symptoms (GAD7) both increased the odds of PrEP non-adherence at 3 months in multivariate models. Despite both measures having significant total effects, only anxious symptoms were significantly indirectly related to PrEP non-adherence. This divergence in effects is congruent with how symptoms of depression and anxiety might influence PrEP adherence in the primary RCT. Depressive symptoms can include, depressed mood, diminished interested or pleasure in activities, changes in sleep patterns, and diminished ability to think or concentrate.[77,78] Each of these symptoms suggests a mechanism for decreased PrEP adherence which operates irrespective of P3 engagement. For example, if a depressed person is having a hard time concentrating, they may be less likely to remember to take PrEP every day. Conversely, symptoms of anxiety include restlessness, feeling on edge, or irritability and often these symptoms stem from or impact social situations.[106,107] Further, while the GAD7 does not explicitly screen for social anxiety disorder, there is symptom overlap between the two conditions and a high degree of comorbidity, with previous clinical trials finding 57% to 77% of individuals aged 7-17 with generalized anxiety disorder also have social anxiety disorder.[106,108–110] If the observed anxiety symptoms in the present study are driven by social interactions, then the social elements of P3 or other DHIs may serve as engagement barriers for these participants. A 2020 global study of social anxiety rates found that 58% of US individuals aged 18-24 had scores on the Social Anxiety Scale consistent with social anxiety (>=29).[111] This suggests that DHIs aimed at youth should implement measures to tailor intervention experiences to those with and without social anxiety. Further, this also suggests that potentially combining a DHI aimed at a health outcome of interest (e.g., PrEP adherence) with a social-anxiety DHI, which have established efficacy,[112,113] may improve anxious symptoms and thereby improve PrEP adherence as well.

Strengths and Limitations

This study has several methodological and analytical strengths. Firstly, the research design of the primary RCT is complementary to the theoretical constructs of effective engagement and causal mediation analysis. RCTs provide clear temporality which is simultaneously necessary to establish effective engagement (i.e. engagement leading to a downstream health outcome) and causal mediation analysis.[25,38–41] This study demonstrates the clarity causal mediation analysis provides to engagement research by disentangling total effects into direct and indirect effects, allowing for a causal and mechanistic characterization of how baseline intrapersonal measures relate to effective engagement. This approach helps to avoid mischaracterizations which can occur with traditional regression techniques, as these techniques often model engagement as the outcome and rely on the assumption that increases in engagement would precipitate increases in the behavior change of interest. For example, quantitative research into medication adherence disparities has found disparities exist among racial or ethnic groups after adjusting for other socioeconomic confounders[102] and qualitative research into engagement with DHIs has largely lacked a focus on race/ethnicity[50] which suggest that race and/or ethnicity might play a role in effective engagement for adherence DHIs. In the present study, non-Hispanic white participants earned significantly more money than other trial participants ($17) by 3 months into the trial period. However, effect decomposition demonstrated that the effect of race/ethnicity on PrEP non-adherence was largely direct, suggesting that race/ethnicity is related to PrEP adherence irrespective of the observed increases in dollars accrued (i.e., engagement) among non-Hispanic White participants. This example illustrates how traditional regression and causal mediation approaches would arrive at divergent conclusions based on the same data. Traditional approaches assume engagement leads to behavior,

whereas causal mediation analysis estimates behavior change based on changes in engagement. In this example, given the results from the causal mediation analysis, it seems substantially more likely that reported non-Hispanic White race/ethnicity is a proxy for the systematic inequalities non-white people face in the US, and that these inequalities propagate difficulties with PrEP adherence in ways P3 cannot or did not address.

One limitation of this study is the small and select sample. The small sample size limits power to detect effects. This means that some of the null results in this study may in fact be more significant in a study with a larger sample. However, this also means that this study is likely a conservative measure of effective engagement. The significant results from this study which have relatively small effect sizes may in truth be much larger. Similarly, the sample of individuals in the primary RCT is relatively homogenous (small age range, relatively high digital literacy, generally non-rural, same sexual orientation). Therefore, the results of this study may or may not generalize to other populations. However, while this feature of the primary RCT limits generalizability, it also strengthens confounding assumptions necessary to carry out causal mediation analysis. By having a more homogenous sample, many of the measures which may have been conceived as confounders have been controlled for through the primary RCTs study design such as sexual orientation and English literacy. Furthermore, while several aspects of the population are homogenous, there is a high degree geographic diversity as the primary RCT was carried out at 9 study sites. Another limitation is the degree of missingness in the biological measures of adherence. Prior to the COVID-19 pandemic, participants completed study activities in-person at study sites, which included the collection of biologic specimens by study site staff. Once COVID-19 restrictions were in place and study activities resumed, most activities were completed remotely to enable the continuation of data collection. Participants were asked to complete at-home dried blood spot (DBS) collection. The change from site directed biologic specimen collection to DBS self-collection likely impacted the amount of missing biologic specimen data. However, self-report measures are sufficient for estimating protective serum levels of PrEP[68,69] and the area under the receiver operating characteristics curve between self-report measures and biological measures among participants without missing biological measures was high (>= 0.7). Finally, inclusion of a validated digital literacy scale and social anxiety specific scale (as opposed to only a scale of generalized anxiety disorder) would have been ideal to measure digital literacy and social anxiety, respectively.

Conclusions

This study employed a causal mediation approach utilizing secondary data from the P3 RCT, including clinical trial data, biological PrEP adherence measures, and paradata, to characterize how baseline intrapersonal measures relate to effective engagement in P3 participants. Broadly, P3 (dollars accrued) was strongly related to lower odds of PrEP non-adherence. Specifically, this study identified digital literacy as a potential engagement facilitators and measures of structural disparity (e.g., disconnection from phone or internet in the past year) and mental health (e.g., anxious symptoms) as engagement barriers. Study results suggest tailoring as a critical DHI mechanism to address barriers to engagement and emphasize engagement facilitators in indicated individuals. Further, these findings highlight the suitability of causal mediation analysis for effective engagement research by delineating the total effect of each intrapersonal measure into direct and indirect effects (effective engagement). Future research into effective engagement would benefit from adopting a causal mediation approach. Further, as hypotheses regarding exact mechanisms for fostering engagement arise, future research should measure engagement with measure-specific areas of the DHI as a mediator.

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Authors' Contributions

Michael Williams and Danielle F. Haley conceived and designed the study. Lisa Hightow-Weidman conceived and designed the primary study (P3). Michael Williams and the P3 study team, namely Crissi Rainer, constructed the analytic dataset. Louisa Smith, Justin Manjourides, and Michael Williams built the statistical models. All authors revised the manuscript and interpreted data.

Conflicts of Interest

None declared.

Abbreviations

CI: confidence interval
DBS: dried blood spot
DHI: digital health intervention
FTC-TP: emtricitabine-triphosphate
GAD7: generalized anxiety disorder-7
HIV: human immunodeficiency virus
IQR: interquartile range
LTFU: loss to follow up
NAR: non-adherence ratio
P3: Prepared, Protected, emPowered: PrEP adherence DHI for YSGMMSM
PHQ8: personal health questionnaire-8
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
SD: standard deviation
SOC: standard of care
TFV-DP: tenofovir-diphosphate
YSGMMSM: young sexual and gender minority men who have sex with men

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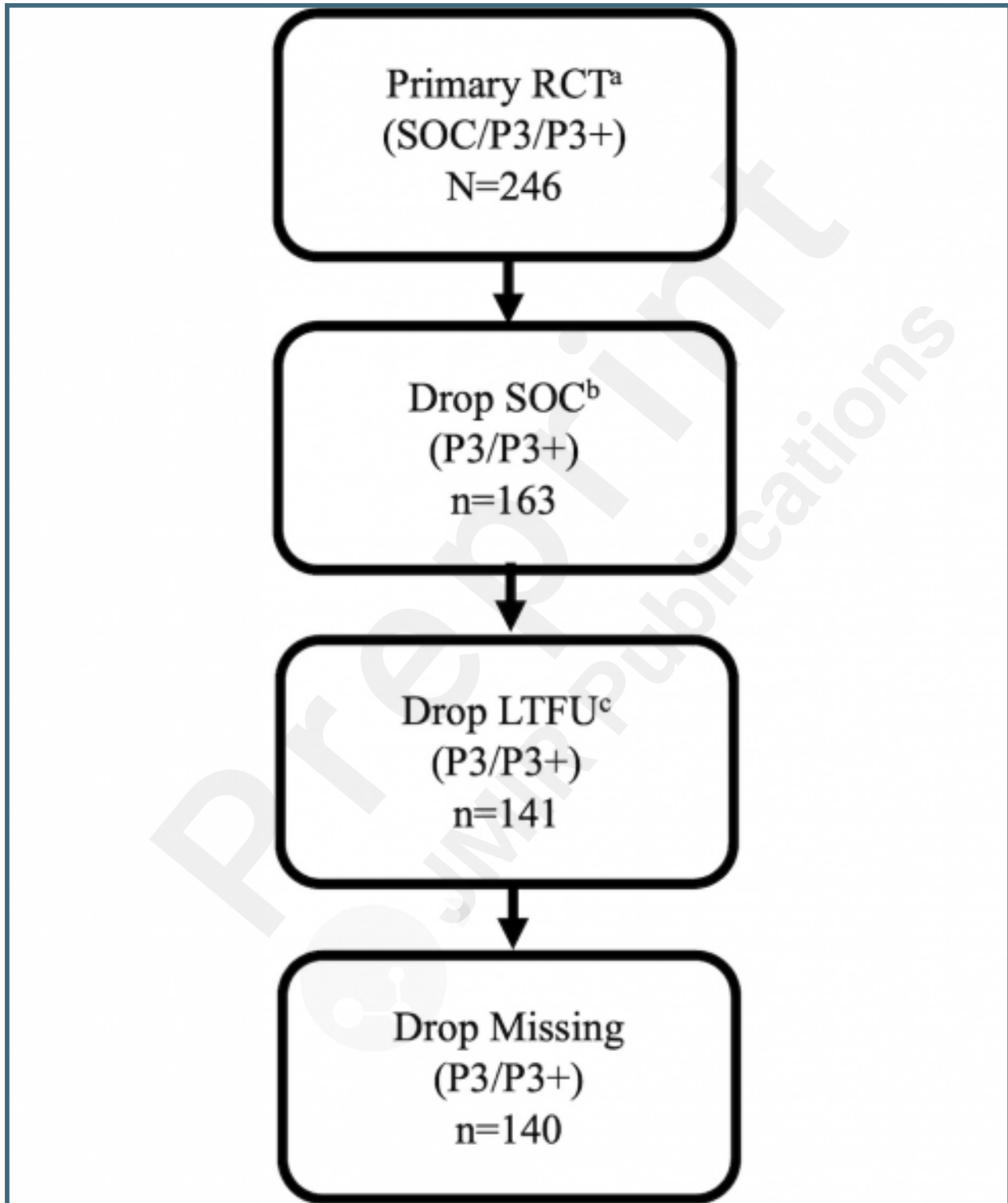
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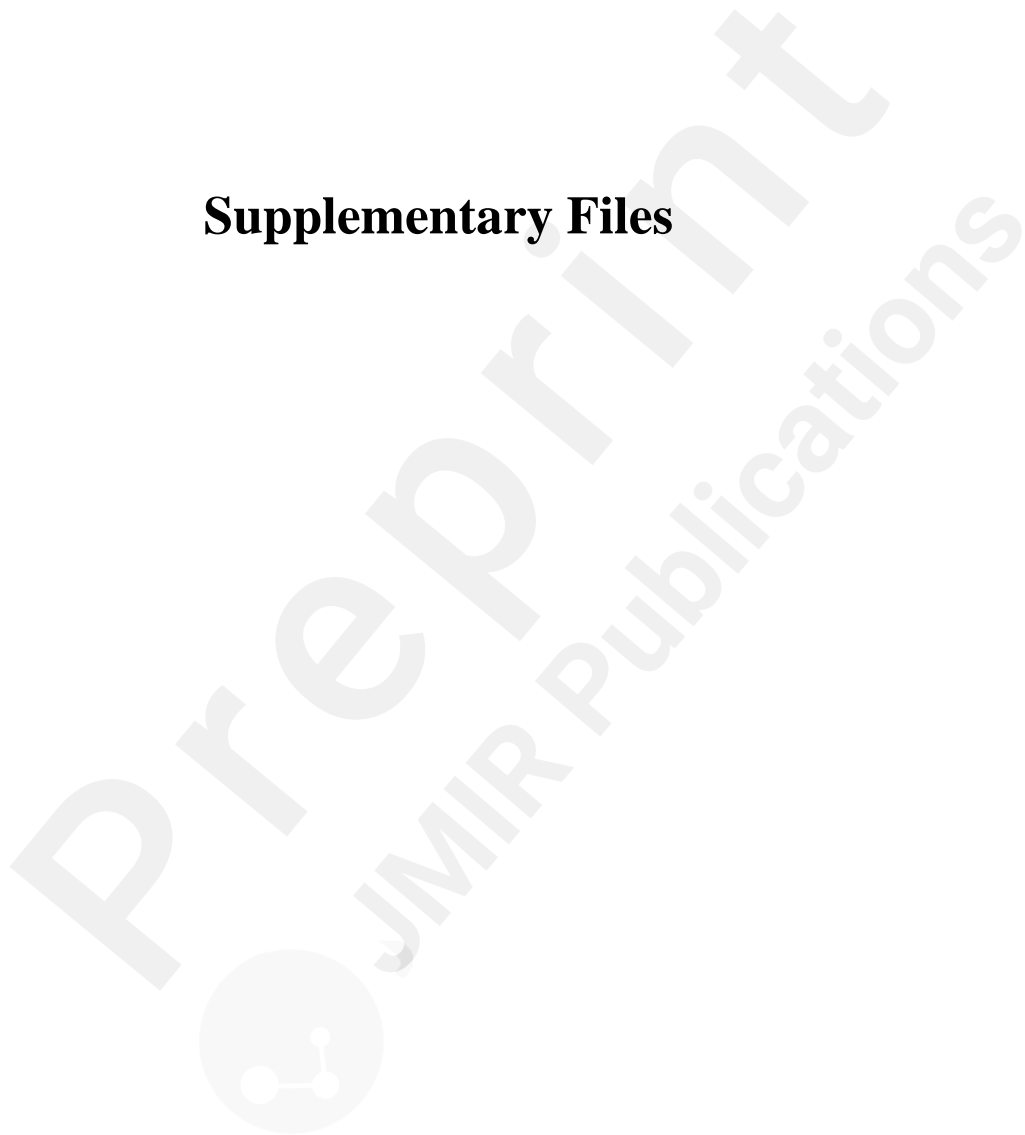
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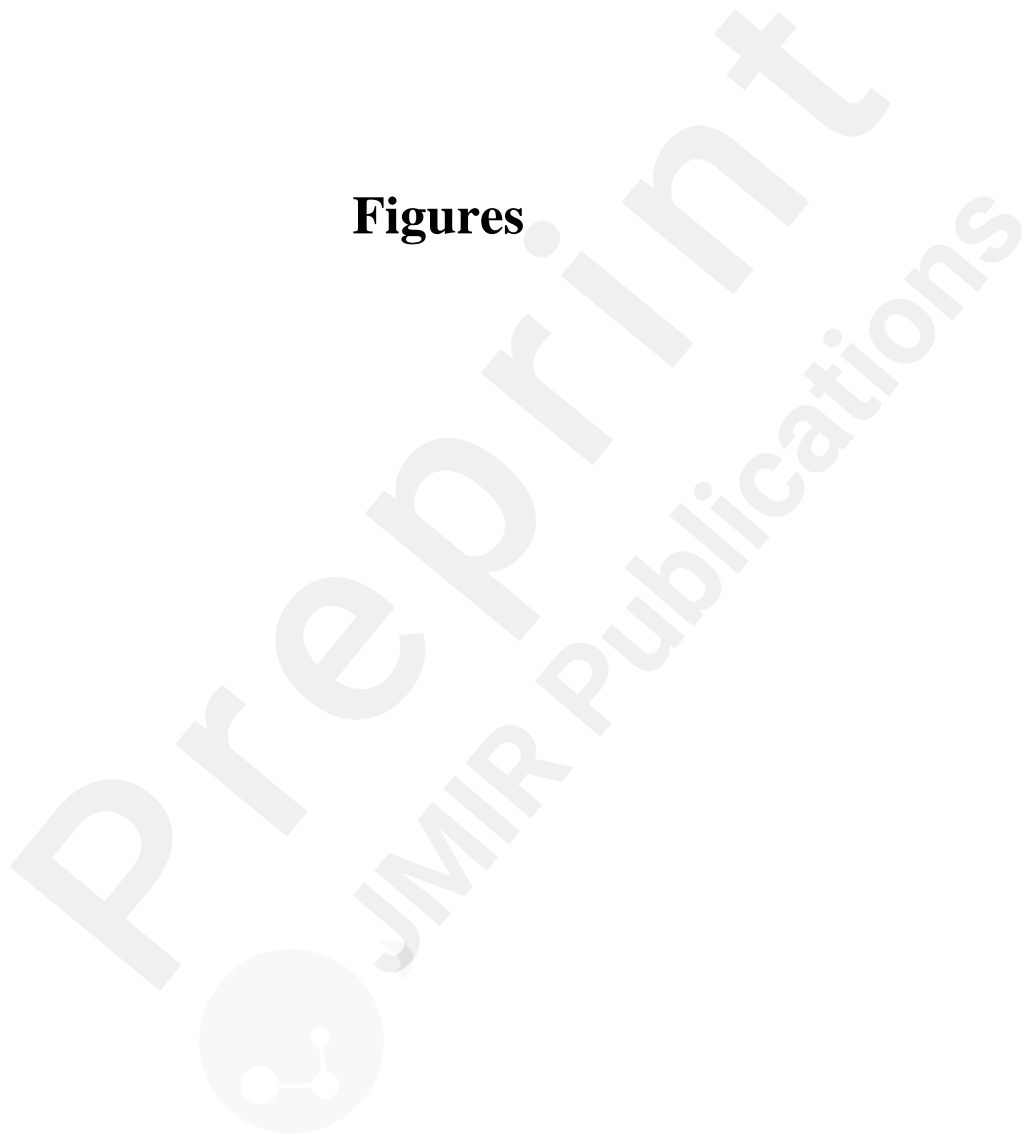
Primary P3 RCT participants eligibility for inclusion into present study, a secondary analysis of effective engagement with respect to PrEP adherence in young sexual and gender minority men who have sex with men. a RCT: randomized; controlled trial; b SOC: standard of care; c LTFU: loss to follow up.

Integration of effective engagement and causal mediation frameworks in a causal diagram. Direct effects represent relationships between intrapersonal measures and PrEP adherence controlling for engagement with P3. Indirect effects represent relationships between intrapersonal measures and PrEP adherence operating through P3 engagement (i.e., mediated effects).