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

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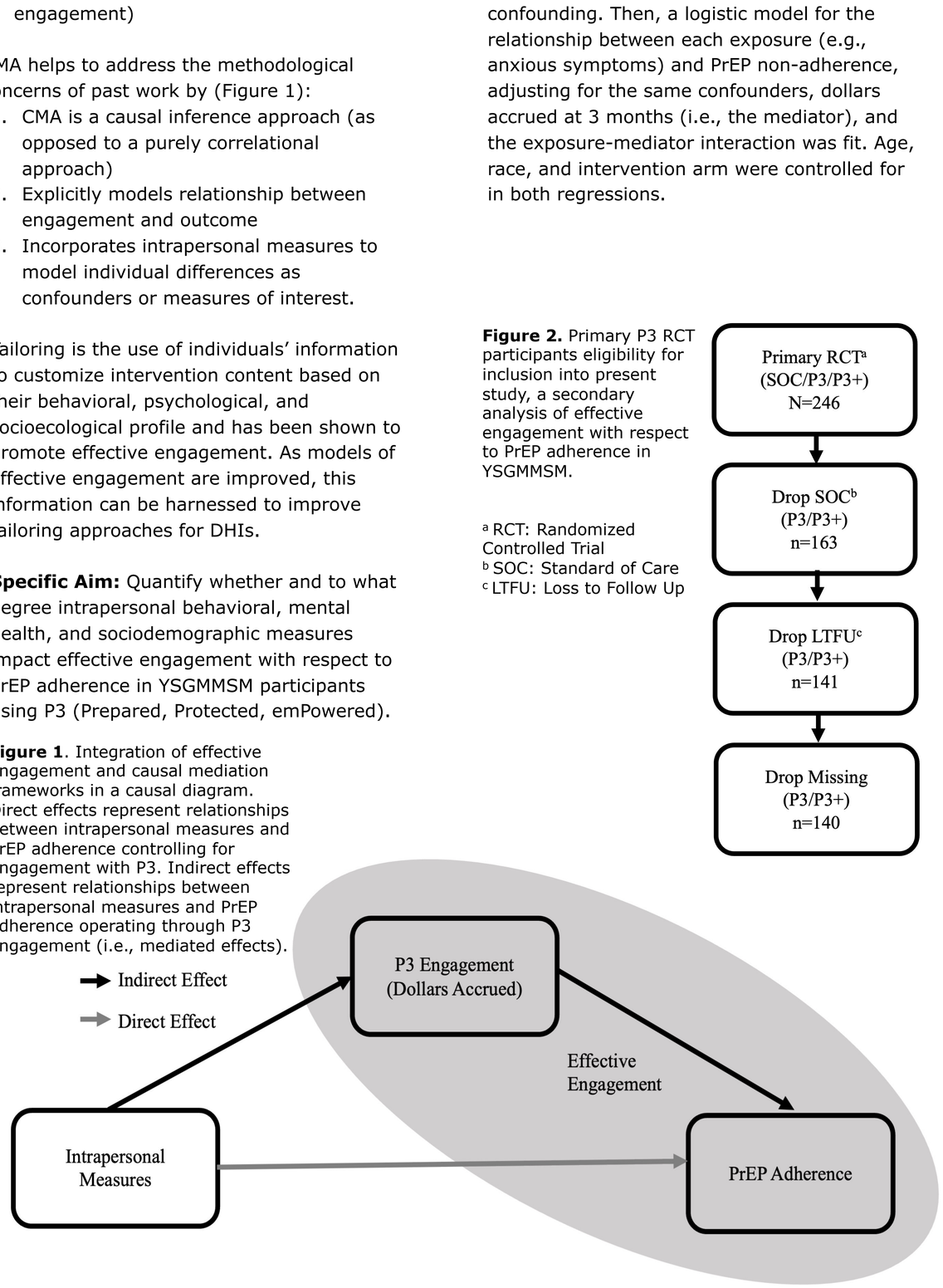
Background

- Young sexual and gender minority men who have sex with men (YSGMMSM) are burdened with a disproportionate vulnerability to HIV. Pre-Exposure Prophylaxis (PrEP) has been shown in clinical trials to be safe and efficacious. However, real-world adherence has been suboptimal for reducing transmission. PrEP adherence digital health interventions (DHIs) for YSGMMSM show promise for improving real world PrEP adherence and therefore reducing HIV burden.
- Paucity of trials examining PrEP adherence DHIs. DHI-adjacent intervention studies (e.g., digital pill monitoring systems) have shown mixed results, with low evidence that they independently increase PrEP adherence.
- **Effective engagement:** Engagement sufficient to solicit behavior change (e.g., PrEP adherence).[1]
- Due to documented barriers to medication adherence among adolescents, effective engagement with DHIs aimed at medication adherence is likely a critical factor for efficacy.
- Several methodological concerns in current effective engagement research:
  1. Past work is largely correlational
  2. Relies on an assumption that engagement is necessarily a precursor to the intended outcome (e.g., more time using DHI → PrEP adherence)
  3. Does not account for individual differences among DHI participants. These differences can confound estimates of effective engagement and serve as characteristics of interest. For example, how does a participant's pre-existing mental health condition affect effective engagement and DHI efficacy?
- **Causal medication analysis[2] (CMA)** is an apt statistical framework for effective engagement research due to effect decomposition, where total effects are decomposed into direct and indirect effects:
  - **Direct Effect:** The effect of a given measure on PrEP adherence controlling for engagement with the intervention.
  - **Indirect Effect:** The effect of a given measure on PrEP adherence operating through engagement (effective engagement)
- CMA helps to address the methodological concerns of past work by (Figure 1):
  1. CMA is a causal inference approach (as opposed to a purely correlational approach)
  2. Explicitly models relationship between engagement and outcome
  3. Incorporates intrapersonal measures to model individual differences as confounders or measures of interest.
- Tailoring is the use of individuals' information to customize intervention content based on their behavioral, psychological, and socioecological profile and has been shown to promote effective engagement. As models of effective engagement are improved, this information can be harnessed to improve tailoring approaches for DHIs.
- **Specific Aim:** Quantify whether and to what degree intrapersonal behavioral, mental health, and sociodemographic measures impact effective engagement with respect to PrEP adherence in YSGMMSM participants using P3 (Prepared, Protected, emPowered).

Figure 1. 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).



Methods

- Secondary analysis of the 3-month P3 randomized controlled trial (RCT).[3]
- Utilized causal mediation to quantify whether and to what extent baseline survey measures of phone and phone app usage, mental health, and sociodemographics were related to effective engagement for PrEP adherence in YSGMMSM.
- 140 of 246 YSGMMSM participants aged 16-24 in the primary RCT were eligible for the secondary analysis (Figure 2):
  - retained at follow-up
  - received DHI condition
  - complete trial data
- **Measures:**
  - **Outcome (binary):** PrEP non-adherence – Determined using blood serum levels of tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP). TFV-DP and FTC-TP consistent with less than or equal to 4 doses per week was considered PrEP non-adherent. Where missing, self-report number of doses in last 7 days was used.
  - **Mediator (continuous):** Engagement - Participants earned and lost US currency for daily usage/non-usage of P3 (+$0.5/-$1.0, respectively) from a starting bank of $90. Dollars accrued at 3-month follow-up was used to measure engagement.
  - **Exposures (binary):**
    - Frequently Track Health Information with Phone (self-reported)
    - Anxious Symptoms (Generalized Anxiety Disorder – 7 score >= 10)
    - Depressive Symptoms (Patient Health questionnaire-8 score >= 10)
    - Non-Hispanic White Racial Identity
    - Disconnect from Internet Service in past 12 months
- Logistic regression was used in a causal mediation approach to estimate the total effects of exposures, represented as non-adherence odds ratios (NAR). This effect was then decomposed into direct effects and indirect effects mediated by engagement. This was accomplished by first fitting a linear regression for the effect of each exposure (e.g., anxious symptoms) on the mediator (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. Age, race, and intervention arm were controlled for in both regressions.

Figure 2. Primary P3 RCT participants eligibility for inclusion into present study, a secondary analysis of effective engagement with respect to PrEP adherence in YSGMMSM.

[a] RCT: Randomized Controlled Trial
[b] SOC: Standard of Care
[c] LTFU: Loss to Follow Up

Results

- Engagement was strongly related to the outcome: 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 (Table 1).
- 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 (Table 1). This was overwhelmingly a direct effect, not mediated by engagement, with a percent mediated (PM) of 1% (Table 2).
- Participants with depressive symptoms had 3.4 (NAR=3.42, CI=0.95,12.00) higher odds of non-adherence to PrEP at 3 months (Table 1). This was largely a direct effect (PM = 30%) (Table 2).
- Participants with anxious symptoms earned $15.95 (CI=-31.57,-0.32) less over the 3-month trial period compared to those without anxious symptoms. Similarly, participants with anxious symptoms had 3.5 (NAR=3.51, CI=1.06,11.55) higher odds of non-adherence to PrEP at 3 months (Table 1). Anxious symptoms largely operated through P3 engagement (Indirect NAR= 1.55, CI= 1.00,3.34, PM=51%) (Table 2).
- Non-Hispanic White participants engaged significantly more than participants of other racial and/or ethnic identities, earning $17.02 (CI=5.95,28.10) dollars more on average over the course of the 3-month trial period. They also had significantly lower odds of PrEP non-adherence (NAR=0.17,CI=0.05,0.48) (Table 1). However, despite the significantly higher average engagement among non-Hispanic White participants, the significantly lower odds of PrEP non-adherence was overwhelming a direct effect (PM = 4%) (Table 2).
- Participants who experienced disconnects from their internet service in the past year did not engage significantly more or less than those who did not experience disconnects. However, these experiences were associated with higher odds of PrEP non-adherence (NAR=3.84, CI= 1.14,12.81) (Table 1). This was largely a direct effect (PM=5%) (Table 2).

Discussion

- This study leveraged data from the P3 RCT in a secondary analysis which characterized how baseline measures of mental health, sociodemographics, and technological behaviors impact effective engagement with the P3 PrEP adherence DHI.
- P3 engagement was strongly related to lower odds of PrEP non-adherence.
- Participants who frequently track health information with their phone were less likely to be PrEP non-adherent, but this effect was direct and these participants did not engage more than others on average. This suggests that these participants may be more fluent in "eHealth Literacy" and therefore do not need high levels of engagement to see positive effects related to PrEP adherence.
- Anxiety symptoms significantly negatively impacted engagement and increased odds of PrEP non-adherence at 3 months. This suggests that participants experiencing anxious symptoms may interact less or differently than those who without anxious symptoms, and this change in engagement pattern may negatively impact their ability to adherence to PrEP.
- Non-Hispanic White participants engaged more than participants of other racial/ethnic identities, but this engagement did not drive the observed differences in PrEP non-adherence, as this was overwhelmingly a direct effect. Similarly, participants who experienced disconnects with their internet service in the past year had significantly higher odds of PrEP non-adherence, also overwhelmingly a direct effect. This suggests that these are not engagement barriers, but instead point to a larger social and structural environment which may impact DHI efficacy.
- Broadly, PrEP adherence DHIs for YSGMMSM should tailor intervention content to emphasize engagement facilitators and abate engagement barriers.
- Evaluating effective engagement in DHIs with causal mediation approaches provides a clarifying and mechanistic view of how DHIs impact health behavior.

Table 1. Multivariate relationships between intrapersonal measures and Engagement with P3, PrEP non-adherence among 140 US YSGMMSM youth aged 16-24

Intrapersonal Measure	Engagement[a]		PrEP Non-Adherence[b]	
	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
Frequently Track Health Information	2.00 (-10.42,14.41)	0.75	0.29 (0.06,0.96)	0.06
Anxious Symptoms	-15.95 (-31.57,-0.32)	0.05	3.51 (1.06,11.55)	0.04
Depressive Symptoms	-8.16 (-24.82,8.51)	0.34	3.42 (0.95,12.00)	0.05
Non-Hispanic White[f]	17.02 (5.95, 28.10)	<0.01	0.17 (0.05,0.48)	<0.01
Disconnect from Internet Service	-6.42 (-24.00,11.16)	0.48	3.84 (1.14,12.81)	0.03

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

Intrapersonal Measure	Direct Effect (95% CI)[c]	Indirect Effect (95% CI)[c]	Percent Mediated[a]
Frequently Track Health Information	0.31 (0.00,0.92)	0.98 (0.71,1.33)	1%
Anxious Symptoms	2.12 (0.58,5.49)	1.55 (1.00,3.34)	51%
Depressive Symptoms	2.52 (0.79,6.81)	1.25 (0.78,2.14)	30%
Non-Hispanic White[b]	0.20 (0.04,0.59)	0.84 (0.46,2.54)	4%
Disconnect from Internet Service	3.28 (0.91,11.42)	1.04 (0.74,1.84)	5%

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

[a]Percent mediated: proportion of total effect which is accounted for by the indirect effect (mediated effect).

[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.

[1]Yardley L, et al. Understanding and Promoting Effective Engagement With Digital Behavior Change Interventions.https://doi.org/10.1016/j.amepre.2016.06.015.
[2]VanderWeele TJ. Mediation Analysis: A Practitioner's Guide. https://doi.org/10.1146/annurev-publhealth-032315-021402.1
[3]LeGrand S, et al. Testing the Efficacy of a Social Networking Gamification App to Improve Pre-Exposure Prophylaxis Adherence (P3: Prepared, Protected, emPowered): Protocol for a Randomized Controlled Trial. https://doi.org/10.2196/10448.

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