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Self-initiated continuation of and adherence to HIV pre-exposure prophylaxis (PrEP) after PrEP demonstration project roll-off in men who have sex with men: associations with risky decision making, impulsivity/disinhibition, and sensation seeking

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Abstract

The objective of this study was to examine differences in the levels of risky decision making and other frontal system behavior constructs in relation to self-initiated continuance of HIV pre-exposure prophylaxis (PrEP) and PrEP adherence outcomes among men who have sex with men (MSM) following completion of a clinical PrEP trial. At the last PrEP trial visit, study provided PrEP was discontinued and participants were navigated to the community for PrEP continuation. In this cross-sectional analysis, 84/187 (45%) MSM who completed a prospective observational post-PrEP trial follow-up visit at the University of California San Diego were included. PrEP adherence was measured using dried blood spot tenofovir diphosphate (TFV-DP) levels. Risky decision making was assessed using the Iowa Gambling Task (IGT) and the Balloon Analogue Risk Task (BART), while impulsivity/disinhibition, sensation seeking, and substance use were assessed via standardized self-report questionnaires. A total of 58/84 (69%) of MSM who completed the 12-month post-study visit continued PrEP. Of those, $n = 46$ (79%) reached TFV-DP levels associated with adequate adherence. Individuals who elected to continue PrEP 12 months post-trial had riskier decision making on BART, but less impulsivity/disinhibition compared to individuals who did not continue PrEP. Neither risky decision making nor impulsivity/disinhibition/sensation seeking nor substance use correlated with PrEP adherence. Our findings suggest that those with risky decision making may have greater insight into their HIV risks, and therefore be more likely to continue to use PrEP. However, elevated impulsivity/disinhibition, indicative of greater neurobehavioral alterations, was negatively associated with PrEP continuance and is a potential target for future interventions to help people link to PrEP.

Keywords Sensation seeking · Stimulant substance use · Seroconversion · Dried blood spot · Adherence

Introduction

While the overall number of new HIV infections has declined, HIV continues to have a disproportionate impact on certain populations, particularly men who have sex with men (MSM). While MSM are the predominant risk group for HIV infection in the USA and most of Europe, the risk of HIV infection within MSM is not uniform, and is driven by risk behaviors as well as underlying HIV prevalence in MSM populations (Stecher et al. 2018, Hoenigl et al. 2016a, 2016b, c, 2015). The efficacy of tenofovir disoproxil fumarate (TDF) combined with emtricitabine (FTC) for HIV pre-exposure prophylaxis (PrEP) has been well documented in several randomized controlled

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trials (Grant et al. 2010; Molina et al. 2015; Baeten et al. 2012). For MSM, the iPrEx study was pivotal in showing that FTC/TDF reduced the risk of HIV infection in MSM by 44% compared to placebo (Grant et al. 2010) and by > 90% in those with adherence defined by tenofovir diphosphate (TFV-DP) drug levels commensurate with four or more tablets per week (Anderson et al. 2012). However, these studies do not inform us about the neurobehavioral disturbances related to risk behavior in MSM and how they may be associated with PrEP use and adherence, particularly after roll-off from PrEP studies.

Risky decision making, a symptom of "frontal system" behavior disturbances, is characterized as difficulty selecting a safer choice with a long-term reward, such as prevention of HIV acquisition through condom use or sustained PrEP adherence, over an immediate reward that would be more satisfying. Risky decision making plays an important role in the expression of risk behaviors associated with HIV transmission (Fujiwara et al. 2015; Coulehan et al. 2014; Martin et al. 2004; Wardle et al. 2010). HIV-uninfected individuals with higher levels of risky decision making may therefore represent ideal candidates for PrEP, due to a predilection towards engaging in risky behaviors. Risky decision making, however, may also affect both decisions regarding PrEP continuance and adherence. Thus, it needs to be determined whether PrEP can sustainably prevent HIV among individuals prone to risky decision making. Related constructs of frontal-mediated neurobehavioral disturbances—including elevated impulsivity, disinhibition and sensation seeking, illicit substance use—may also be relevant obstacles to PrEP continuance and adherence outside of study settings (Heaton et al. 2010; Kohno et al. 2014; Moore et al. 2012; Plankey et al. 2007; Semple et al. 2006; Hoenigl et al. 2016a). The objective of this study was to examine differences in levels of risky decision making and other frontal system behavior constructs in addition to substance use by HIV PrEP continuation and adherence outcomes among MSM following the completion of a clinical PrEP trial.

Methods

Setting and participants

To achieve this goal, we leveraged the ending of an existing PrEP demonstration project for MSM and transgender women, the TAPIR study (CCTG595). The TAPIR study was a randomized controlled trial of individualized text messaging versus standard care for adherence to daily TDF/FTC PrEP, conducted between 2014 and 2016 (http://www.clinicaltrials.gov/ct2/show/NCT01761643) (Moore et al. 2018; Hoenigl et al. 2018). In TAPIR, PrEP was given in combination with safety monitoring, HIV testing, and risk reduction counseling to 395 MSM (plus three transgender women) (Moore et al. 2018; Milam et al. 2018). Patients were enrolled at four Southern California medical centers, including University of California, San Diego (UCSD) (Moore et al. 2018). At the last TAPIR study visit (week 48 or later for most participants), study-provided PrEP was discontinued. At the final study visit and the visit prior to the last study visit, participants were provided with information regarding local PrEP providers, but were on their own to self-initiate PrEP continuation. As part of the current study, we planned a prospective observational follow-up visit at 12 months following TAPIR roll-off of study participants at UCSD ($n = 187$) to determine whether risky decision making (measured by the Iowa Gambling Task and the Balloon Analog Risk Task) and impulsivity/disinhibition and sensation seeking (assessed via standardized self-report questionnaires) were predictors of self-reported PrEP continuation and adherence measured by intracellular drug levels. At UCSD, 84 (45%) in 12-month clinic visits after TAPIR roll-off, maximum incentive was $30 per visit.

The study was approved by the University of California, San Diego institutional review board (IRB), and written informed consent was obtained from all participants.

Measures

PrEP continuation and adherence

PrEP continuation was defined as participant self-report of linking to a provider and continuing to receive PrEP from a provider during 12-month post-TAPIR study visits, respectively. Adherence was measured by dried blood spot (DBS) intracellular TFV-DP levels. A concentration of > 719 fmol/punch was used to estimate four or more tablets per week on average (i.e., "adequate" adherence). This value is the unrounded lower quartile corresponding to 700 fmol/punch level used in the iPrEx OLE study, which showed 0 out of 28 seroconversions when TFV-DP was at or above 700 fmol/punch (Grant et al. 2014). A concentration of > 1246 fmol/punch was defined as "near-perfect" adherence, associated with taking seven doses of TDF in past week (Grant et al. 2014; Castillo-Mancilla et al. 2013). Intracellular TFV-DP concentrations were performed at the last on-drug visit that occurred on or before the TAPIR 48-week visit, and at the 12-month post-study visits only in participants who reported PrEP continuance at the respective time points via a validated methodology (Castillo-Mancilla et al. 2013). In brief, 25 μL of whole blood was pipetted five times into a Whatman 903 Protein Saver card. These cards were allowed to dry at room temperature for at least 2 h, after which they were stored in plastic bags with humidity indicators at − 80 °C until analysis. TFV-DP was quantified from a 3-mm punch using liquid chromatography/tandem mass spectrometry.

Risky decision making, impulsivity/disinhibition and sensation seeking, and substance use

Risky decision making was assessed at the 12-month post-study visit with two computerized measures: (i) the Iowa Gambling Test (IGT) and (ii) the Balloon Analog Risk Task (BART). The IGT is a computerized measure designed to assess cognitive decision making, defined as the ability to select the most advantageous response from an array of possible behavioral choices (Bechara et al. 1997). The IGT was created to assess real-world decision making in a lab-based setting and has been adapted as a clinical instrument and shown to be sensitive to frontal system dysfunction (Bechara et al. 2000). The IGT is designed to mimic "real-world" contingencies of reward and punishment (i.e., winning and losing money); the goal of the task is to maximize profit on a loan of play money. Individuals are presented with an array of four decks of cards (A, B, C, and D) and are told that their goal is to maximize profit over 100 trials. Choices from two "advantageous" decks (decks C and D) result in small gains with some small loses but ultimately yield modest long-term gains. Choices from the other two decks (decks A and B) result in immediate high gains but ultimately lead to substantial losses. Thus, choices from these two decks are considered "disadvantageous." Participants' total net score (i.e., total number of advantageous choices minus total number of disadvantageous choices across all five blocks), converted to demographically adjusted scores using the published test manual (range 0–100), were used as the primary outcome measure for the IGT.

The BART is also a computer-based measure of risky decision making, which has shown good psychometric properties and has been validated in other high-risk taking groups (Hunt et al. 2005). On the BART, propensity towards risk is measured by rewarding behavior (decisions) up to a point, after which continued engagement in that behavior leads to poorer outcomes (Lejuez et al. 2002). Participants earn simulated money by inflating a simulated balloon. The participant can choose to continue to inflate the balloon or "collect" the money earned. If the balloon explodes, the accrued gains are lost. Participants are told that balloons will explode, but they do not know the tolerance of each balloon. One of the first balloons explodes within the first few trials to show participants that the balloons can explode at any point. Subsequently, the amount of money to be lost increases on each trial whereas the relative gains from each pump decrease. The primary outcome measure is total money earned, and this outcome measure is translated to the incentive each participant received for completing the two risky decision-making evaluations (i.e., 15 USD baseline incentive plus BART earning [1 cent per balloon pump up to a maximum of 10 USD], with a maximum of 25 USD total).

Self-reports of sensation seeking ($n = 84$ at 12 months) and impulsivity/disinhibition ($n = 84$ at 12 months) were obtained at the 12-month post-TAPIR study visits. Sensation-seeking questionnaires included the Kalichman sexual and non-sexual sensation-seeking scales and the UPPS Impulsive Behavior Scale (sensation-seeking subscale) (Marquine et al. 2014). Impulsivity/inhibition questionnaires included the disinhibition of the Frontal Systems Behaviors (FrSBe) instrument, the UPPS Impulsive Behavior Scale (Urgency and Lack of Premeditation subscales), and Barratt Impulsiveness Scale (Marquine et al. 2014). Raw scores from subscales assessing sensation seeking and impulsivity/inhibition were converted to *T* scores, with standardization based on the performance of a healthy comparison group utilized in previous studies (Marquine et al. 2014). *T* scores were then averaged within each construct to yield separate composites of sensation seeking and impulsivity/disinibition (Marquine et al. 2014).

Recent use of substances commonly associated with abuse was assessed using questions adapted from the Structured Clinical Interview for DSM-IV (SCID) at 12-month visits. The SCID elicits whether or not participants used specific stimulant and non-stimulant substances of abuse ≥ 1 or ≥ 5 times over the past month.

Statistical analysis

Statistical analyses were performed using SPSS 23 (IBM Corp., Armonk, NY, USA). *t* tests and Mann-Whitney *U* tests where indicated were used to examine cross-sectional differences between risky decision-making outcomes and *T* scores of the domains of impulsivity/disinhibition and sensation seeking with substance abuse as well as PrEP continuance and adherence by DBS. In addition, we calculated cross-sectional correlations between risky decision-making outcomes and *T* scores of impulsivity/disinhibition and sensation seeking and PrEP levels using Pearson and Spearman correlation coefficients, depending on normality of distributions. Fisher's exact test was used to study associations between current substance use, PrEP continuance, and adherence at 12 months post-TAPIR, as well as associations between PrEP adherence at the last TAPIR study visit with subsequent post-TAPIR study PrEP continuance and adherence.

Results

Demographics and characteristics of study population

The 12-month post-study visit was completed by 84 MSM (45% of TAPIR participants) with median age 39 (range 23–68 years): 21% advanced degree, 2% some post-graduate studies, 30% bachelor's degree, and 44% some college or high school diploma. Of those, 12 (14%) were Hispanic, 55 (65%) were non-Hispanic white, 12 (14%) were non-Hispanic black, and 5 (6%) were non-Hispanic but reported other/mixed races.

Demographics did not differ between participants of TAPIR who completed the 12-month post-study visit versus those who did not, except for Hispanic ethnicity which was less frequently reported among those who completed the post-study visit ($p = 0.001$). Participants who completed the post-study visit had significantly higher DBS TFV-DP levels at the week 48 TAPIR visit (median [IQR] = 1282 [1007, 1604] fmol/punch vs. 1074 [829, 1396] fmol/punch, $p = 0.027$).

Continuation of PrEP and stimulant substance use

T scores of frontal system behaviors in the different subgroups who completed the 12-month post-study visits are displayed in Table 1.

Overall risky decision making on BART was significantly correlated with total time spent on the task ($r = 0.478$; $p < 0.001$). Individuals who remained on PrEP at 12 months after TAPIR (58/84; 69%) had riskier decision making on BART (median [IQR] = 751 [663, 850] vs. 871 [777, 935], $p < 0.001$; Table 2), but less impulsivity/disinhibition ($p = 0.020$; Table 1) compared to individuals who did not continue PrEP at the 12-month post-TAPIR visit. There were no differences in sensation seeking and IGT scores between those on or off PrEP at the 12-month post-study visit. Additionally, neither substance use nor adherence at the last completed TAPIR study visit was associated with established PrEP care at the 12-month post-study visit. Increased sensation seeking at the 12-month visit was also weakly, although significantly, correlated with less risky decision making on BART (Spearman $r = 0.240$; $p = 0.031$), while impulsivity/disinhibition was not. Frontal system behavior constructs were not correlated with IGT scores. A significant moderate positive correlation was observed between earnings on BART and *T* scores on IGT (Spearman $r = 0.300$, $p = 0.007$).

Stimulant substance users at the 12-month post-TAPIR visit (52/84, 62%) had more sensation seeking ($p = 0.017$; Table 1) and a trend towards higher earnings on BART (median [IQR] = 791 [723–890] vs. 743 [650–856], $p = 0.059$; Table 2), but no difference in IGT performance or impulsivity/disinhibition *T* scores compared to individuals not reporting stimulant substance use. Non-stimulant substance users (27/84, 32%) had significantly higher demographically corrected IGT *T* scores (mean 52.3, SD 7.9 vs. mean 47.7, SD 9.6; $p = 0.040$), but there were no differences in BART ($p = 0.109$), sensation seeking, or impulsivity/disinhibition compared to other participants.

PrEP adherence

At the 12-month post-study visit, 58 participants reported remaining on PrEP, with 46/58 (79%) having adequate

Table 1 *T* scores of frontal system behaviors in the different subgroups at 12-month post-PrEP demonstration project visits, $N = 84$

PrEP continuation/substance use	Impulsivity/disinhibition *T* score (mean, SD; *n*)	*p* value (*T* test)	Sensation seeking *T* score (mean, SD; *n*)	*p* value (*T* test)
12 months post-study				
Current PrEP continuation ($n = 84$)		0.020		0.313
No	61.47 (12.54; 26)		60.85 (9.30; 26)	
Yes	54.81 (11.35; 58)		58.85 (7.27; 58)	
PrEP adequate adherence (i.e., TFV-DP > 719 fmol/punch; $n = 58$)		0.791		0.790
No	53.69 (14.98; 12)		59.45 (8.61; 12)	
Yes	55.03 (10.63; 46)		58.72 (7.62; 46)	
PrEP near perfect adherence (i.e., TFV-DP > 1246 fmol/punch; $n = 58$)		0.735		0.229
No	55.23 (11.97; 35)		59.88 (7.24; 35)	
Yes	54.20 (10.64; 23)		57.39 (8.30; 23)	
Stimulant substance use (i.e., poppers, methamphetamine, cocaine, ecstasy, amphetamine, other stimulants; $n = 84$)		0.227		0.017
No	54.96 (12.64; 32)		56.87 (8.89; 32)	
Yes	58.26 (11.70; 52)		61.32 (7.56; 52)	
Any substance use (alcohol and marijuana excluded; $n = 84$)		0.258		0.108
No	54.93 (12.88; 29)		57.61 (9.00; 29)	
Yes	58.09 (11.64; 55)		60.69 (7.83; 55)	

Table 2 Risky decision-making assessments with the Iowa Gambling Test (IGT) and the Balloon Analog Risk Task (BART) in the different subgroups at 12-month post-PrEP demonstration project visits, $N = 84$

PrEP continuation/substance use	IGT: demographically adjusted total net score (mean, SD; *n*)	*p* value (*t* test)	BART: total earnings (median, IQR; *n*)	*p* value (Mann-Whitney *U* test)
12 months post-study				
Current PrEP continuation ($n = 80$)		0.110		*< 0.001*
No	51.86 (8.57; 22)		871 (777–935; 22)	
Yes	48.12 (9.46; 58)		751 (663–850; 58)	
PrEP adequate adherence (i.e., TFV-DP > 719 fmol/punch; $n = 58$)		0.988		0.346
No	48.08 (8.53; 12)		683 (653–830; 12)	
Yes	48.13 (9.78; 46)		754 (667–856; 46)	
PrEP near perfect adherence (i.e., TFV-DP > 1246 fmol/punch; $n = 58$)		0.677		0.440
No	48.57 (8.37; 35)		719 (663–832; 35)	
Yes	47.43 (11.09; 23)		772 (598–864; 23)	
Stimulant substance use (i.e., poppers, methamphetamine, cocaine, ecstasy, amphetamine, other stimulants; $n = 80$)		0.318		0.059
No	47.84 (9.15; 31)		743 (650–856; 31)	
Yes	49.98 (9.44; 49)		791 (723–890; 49)	
Any substance use (alcohol and marijuana excluded)		0.280		*0.046*
No	47.61 (9.37; 28)		730 (594–853; 28)	
Yes	49.98 (9.28; 52)		800 (722–888; 52)	

adherence and 23/58 (40%) near perfect adherence. Of these 58 participants, 57 had a TFV-DP level obtained at the week 48 TAPIR visit, with 52 (91%) having adequate adherence and 31 (53%) near perfect adherence. Individuals with adequate adherence at their week 48 TAPIR visit were significantly more likely to have adequate adherence at the 12-month post-study visit than those without adequate adherence at their last TAPIR visit (44/52 vs. 2/5; $p = 0.045$, Fisher's exact test). The same was true for near perfect adherence at their last TAPIR visit and the 12-month post-study visit (18/31 vs. 5/26; $p = 0.004$). Risky decision making, frontal system behaviors, and substance use variables were not associated with PrEP adherence 12 months post-TAPIR.

Among those who reported using PrEP at the 12-month post-study visit, there was no correlation between continuous TFV-DP levels and sensation seeking (Pearson $r = -0.127$; $p > 0.2$), impulsivity/disinhibition (Pearson $r = -0.029$; $p > 0.2$), risky decision making on BART (Spearman $r = 0.234$; $p = 0.082$), or IGT demographically corrected *T* scores (Pearson $r = -0.008$; $p > 0.2$).

In a subanalysis of the 58 individuals who continued to use PrEP at the 12-month post-study visit, stimulant substance users (36/58, 62%) demonstrated greater sensation seeking (mean *T* scores 61.18, SD 6.78 vs. mean 55.03, SD 7.79; $p = 0.002$) and less risky decision making on the BART (median [IQR] = 767 [683–870] vs. 686 [528–825], $p = 0.024$), but no significant difference in PrEP adherence by TFV-DP levels ($p > 0.2$), impulsivity/disinhibition, or IGT scores. Individuals with non-stimulant substance use (18/58, 31%) had higher demographically corrected IGT scores (mean, SD 52.8, 8.5 vs. 47.7, 9.3; $p = 0.027$) but no significant differences for other variables.

Discussion

We evaluated differences and correlations of risky decision making, impulsivity/disinhibition, sensation seeking, and illicit substance use with PrEP continuation and adherence in a well-characterized cohort of MSM at risk for HIV acquisition after completing a clinical PrEP trial. Overall, less than half (45%) of the eligible study population from the UCSD TAPIR site completed the 12-month post-study visit. However, among those who completed the 12-month post-study visit, 69% remained on PrEP, 79% of whom had protective PrEP drug levels. Furthermore, adequate adherence at the end of TAPIR was predictive of adequate adherence during the post-study period. Individuals who continued to use PrEP had riskier decision making on BART but significantly less impulsivity/disinhibition compared to individuals who did not continue to use PrEP. Risky decision making, frontal system behaviors, and substance use did not correlate with PrEP adherence.

Our primary result was that risky decision making did not negatively affect desire/ability to seek continued PrEP. In fact, those with riskier decision making were more likely to elect longer term PrEP use. If we assume that risky decision making translates to higher HIV risk behaviors, this finding suggests that these individuals may have had insight into their HIV risk and were appropriately motivated to continue PrEP outside of the clinical trial.

Two previous studies have indicated that levels of neurobehavioral disturbance in domains of executive dysfunction, apathy, and disinhibition may be elevated before HIV seroconversion and therefore precede HIV infection (Vo et al. 2013; Kamat et al. 2012, 2016). These findings suggest that certain neurobehavioral disturbances may play a role in the expression of risk behaviors associated with HIV transmission (Vo et al. 2013; Kamat et al. 2012) and that those with neurobehavioral disturbances may be good PrEP candidates. Our findings imply that elevated impulsivity/disinhibition, indicative of greater neurobehavioral alterations, was negatively associated with PrEP use after study roll-off but was not associated with PrEP adherence in those who sought and obtained PrEP outside of the clinical trial. Elevated impulsivity/disinhibition may therefore be a potential target for future interventions to facilitate PrEP uptake and continuation, such as making PrEP access easier through immediate access programs.

A secondary result of interest was that substance use was associated with increased sensation seeking but did not seem to affect PrEP continuation or adherence among those who performed the post-study follow-up visits. This is in line with findings during TAPIR where substance use was not associated with lower PrEP adherence (Hoenigl et al. 2018).

There are important limitations to note, including the small number of participants who completed the 12-month post-study visit, who not surprisingly had higher PrEP adherence during the TAPIR trial. We might hypothesize that many individuals who did not attend post-study visits did not link to PrEP after the study ended, but our conclusions are limited to data on the individuals who did follow up after the end of the clinical trial. Also, both BART and IGT may be insufficient indicators of real-world risk-tasking behaviors.

Our findings suggest that those with measurably higher risky decision making may have insight into their HIV risk and are appropriately continuing PrEP although this neurobehavioral disturbance does not necessarily translate to sustained adherence. On the other hand, those with elevated impulsivity/disinhibition may be less likely to continue PrEP. Risky decision making and impulsivity/disinhibition may be important to consider when working with PrEP candidates who have diverse needs and barriers to sustained PrEP use and adequate adherence as some patients may require additional assistance in navigating the health care environment to obtain PrEP and others may require greater adherence support. Researchers and policy makers may need to consider these inherent neurobehavioral factors when designing future interventions to increase long-term PrEP persistence and adherence.

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Compliance with ethical standards

Conflict of interest MH received research funding from Gilead, paid to his institution. PLA receives research grants and contracts from Gilead Sciences, paid to his institution. JB received educational research funding from Gilead. She also has served as a Gilead PrEP advisor. DJM has been supported as a co-investigator on an educational grant from Gilead. All other authors: no COIs.

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