



Predictors of Re-Initiation of Daily Oral Preexposure Prophylaxis Regimen After Discontinuation

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Abstract

Daily oral preexposure prophylaxis (PrEP) for reducing HIV transmission is recommended for those at elevated risk, including sexual gender and minorities assigned male at birth (SGM-AMAB). Few studies have examined re-initiation among PrEP discontinuers, which is critical to ensuring optimization of PrEP's protection. The current study examined predictors of re-initiation in a longitudinal sample of SGM-AMAB PrEP discontinuers ($n=253$) from 10 waves of an ongoing cohort study (analytic $n=1,129$). Multilevel structural equation models were used to examine the effects of psycho-social variables on re-initiation. In adjusted models, health insurance, and partner HIV positive status were significantly positively associated with PrEP re-initiation. Being bisexual was significantly negatively associated with re-initiation relative to gay participants. Single status and open relationship agreements were associated with higher odds of re-initiation relative to monogamous relationships. Findings suggest that demographic, partnership characteristics and structural factors influence decisions to re-initiate PrEP after discontinuation.

Keywords PrEP · Pre-exposure prophylaxis · HIV · Re-initiation

Resumen

Se recomienda la profilaxis previa a la exposición al VIH (PrEP) en una formulación diaria para reducir la transmisión del VIH para las personas con un riesgo elevado, incluido las minorías de género y sexualidad que se les asignó el sexo masculino al nacer (SGM-AMAB). Pocos estudios han examinado el reinicio entre los que suspenden la PrEP, lo cual es fundamental para garantizar la optimización de la protección de la PrEP. El estudio actual examinó los predictores de reinicio en una muestra longitudinal de personas que interrumpieron el uso de SGM-AMAB ($n=253$) de 10 oleadas de un estudio de cohorte en curso (muestra analítico $n=1129$). Se utilizaron modelos de ecuaciones estructurales multinivel para examinar los efectos de las variables psicosociales en el reinicio. En los modelos ajustados, el seguro de salud y el estado VIH positivo de la pareja principal se asociaron significativamente de manera positiva con el reinicio de la PrEP. Ser bisexual se asoció significativamente de manera negativa con la reiniciación en relación con los participantes homosexuales. El estatus de soltero y los acuerdos de relación abierta se asociaron con mayores probabilidades de reinicio en relación con las relaciones monógamas. Los hallazgos sugieren que las características demográficas, de asociación y los factores estructurales influyen en las decisiones de reiniciar la PrEP después de haber suspendido el uso.

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Introduction

Sexual and gender minorities assigned male at birth (SGM-AMAB), such as young cisgender men who have sex with men, transgender women, and gender diverse people assigned male at birth, are at heightened risk for HIV acquisition (1, 2). The advent of daily oral preexposure prophylaxis (PrEP) has provided a highly effective strategy for HIV prevention (3). However, since its release in 2012, researchers have found substantial increases in PrEP initiation among young SGM-AMAB, but not at levels optimal to substantially decrease incidence in this population (3–6). Discontinuation is also prevalent among those who have initiated PrEP previously. Studies estimate as many as 62% of daily oral PrEP users discontinue the regimen within the first year following initiation, and youth are particularly likely to discontinue (7–10). While research has begun to examine the reasons for discontinuation, very little research has examined re-initiation after a previous discontinuation, which would elucidate factors that might facilitate re-engagement of these individuals in PrEP care. Given that it is unrealistic to expect SGM-AMAB to stay on PrEP for the rest of their lives, we cannot simply study factors that influence adherence and persistence. Understanding how and why SGM-AMAB re-initiate PrEP after a prior discontinuation is critical to ensuring the optimal preventive benefit of PrEP during periods of elevated risk for HIV acquisition.

What little is currently known about re-initiation is primarily derived from literature addressing discontinuation. Some authors have described “seasons of risk” or “seasons of PrEP,” which is a concept that suggests some individuals initiate PrEP for time-limited periods that coincide with perceived heightened risk for HIV acquisition (11–13). Qualitative evidence supports the idea of fluctuating PrEP use that coincides with changes in perceived risk in that PrEP discontinuers described potential interest in re-initiating PrEP in the future if and when their perceived risk were to increase (7). High rates of discontinuation among teens and young adult MSM have been documented (10). Moreover, evidence from a longitudinal analysis of 131 young Black MSM who initiated PrEP further supports the idea of seasons of risk (14); in this sample, 69% stopped taking PrEP at least once, 64% of whom restarted PrEP at a later date (14). Some PrEP discontinuers frame periods of non-use as coinciding with periods of reduced risk; however, the story may be more complicated. First, this shift in risk needs to be considered within a broader context. For example, the median time to first discontinuation is within 6 months of initiating PrEP, which suggests fairly rapid shifts in PrEP use among some (14, 15). This shift in PrEP use may coincide with a reduction in risk, but discontinuation in PrEP use due to a potentially temporary reduction in risk may necessitate rapid

re-initiation if risk for HIV transmission increases at a later date. If a change from a low-risk period to a high-risk period is equivalently rapid these periods of reduced risk may be too brief and transient to truly optimize protection from PrEP regimens, which require re-initiation prior to periods of risk to be effective. Second, perceptions of risk may not be accurate. In fact, there is growing documentation from cohort studies of incidence of HIV infection among discontinuers (14, 16). This calls into question whether decisions to discontinue and to reinitiate are being made based off of true risk for HIV transmission. Lastly, it is unlikely that risk perceptions are the exclusive factor influencing PrEP discontinuation or re-initiation. For example, in a mixed-methods examination of discontinuation the top three reasons for discontinuation were a mix of access issues and low perceived risk such that 21.5% reported having trouble getting to doctor appointments, 20% had an issue with insurance, and 18.5% didn’t perceive themselves to be at risk for HIV (17). To date, no known study has examined predictors of re-initiation among a sample of PrEP discontinuers longitudinally; however, one can derive a tentative idea of potential predictors of PrEP re-initiation from existing literature on initiation and discontinuation (e.g. risk behaviors, psychosocial predictors, or access-related predictors).

As described above, variation in risk or in perceived risk have been identified as a significant factors in predicting PrEP initiation (4, 7, 18–20), so it would follow that re-initiation would be associated with a number variables indicating risk for HIV acquisition, such as an increased number of sexual partners (14), entry into a non-monogamous relationship agreement (21, 22), and having a partner who is living with HIV (23). These factors are also related to initial eligibility for PrEP, which is based primarily on indicators of sexual risk (24). Having a partner who is living with HIV is an important indicator, because it may increase risk of HIV acquisition if that partner’s viral load is not consistently suppressed, and in line with this, research has found that having an HIV-positive partner is associated with PrEP use (23). Having condomless anal sex is also an indicator for PrEP eligibility (24). With regard to partnered MSM, condomless anal sex may not always be an indicator of HIV risk, particularly for seroconcordant HIV negative couples who have, and adhere to, a monogamous relationship agreement. Logically, literature suggests that partnered MSM who agreed to have condomless sex with outside partners are more likely to be on PrEP than those who do not have such agreements (21, 22). Monogamous relationship agreements may be associated with a lower perceived risk for HIV acquisition; however, it should be noted that these agreements are not always adhered to by both partners, which can also lead to HIV acquisition in the context of a monogamous agreement (25, 26). While actual and perceived HIV risk are clearly

important determinants of PrEP use, the fact that a large proportion of those MSM who are eligible for PrEP based on behavioral risk criteria do not uptake PrEP (27) means that other structural factors are likely important influences on use.

Table 1 Demographics (n = 253)

Variable	Mean (SD)
Age	22.9 (3.0)
Sexual Identity	Frequency (%)
Gay	189 (74.7)
Bisexual	26 (10.28)
Other sexual identity	38 (15.02)
Race	
Black	77 (30.4)
Latinx/Hispanic	68 (27.0)
White	65 (25.4)
Other racial identity	43 (17.1)
Gender	
Cisgender Man	215 (85.0)
TGD-AMAB	38 (15.0)
Education	
Some High School	17 (6.8)
High school diploma or GED	53 (21.0)
Some College or Trade School	124 (49.2)
College degree or higher	58 (23.0)
Re-initiated at least once	
Yes	85 (33.7)
No	167 (66.3)
Re-initiated and later discontinued	
Yes	35 (13.9)
No	217 (86.1)
Re-initiated twice	
Yes	10 (4.0)
No	242 (96.0)
Tested positive for HIV at follow-up	
Yes	14 (5.6)
No	238 (94.4)
Housing insecurity at baseline	
Housing insecure	6 (2.37)
Housing secure	240 (94.86)
Insurance at baseline*	
Yes	122 (75.31)
No	40 (24.29)
Relationship Agreement/Status at Baseline*	
Monogamous agreement with main partner	16 (6.32)
Open relationship with a main partner	66 (25.09)
No relationship with main partner	20 (7.91)
Single	144 (56.92)
Condomless Anal Sex at Baseline	1.53 (1.93)
Main Partner living with HIV at Baseline	
Yes	13 (5.1)
No	240 (94.9)

*N varies due to missing values at baseline

The literature on initiation and discontinuation has also identified correlates and predictors of PrEP use that do not necessarily align with risk or perception of risk. This includes issues of cost, and in particular, access to insurance that can defray the cost of the PrEP regimen (4, 7, 19, 20, 28–31). Access to medical professionals and insurance are among the most frequently cited reasons for PrEP discontinuation among young SGM-AMAB (17). Moreover, individuals with insurance are nearly 3 times more likely to initiate PrEP use than those without insurance (32). Other socio-economic indicators, such as housing instability, are also likely negatively associated with PrEP re-initiation, because they are negatively associated with PrEP uptake (33). Thus, it may be inferred that a change in insurance status or other indicators of socioeconomic status may influence the likelihood of reinitiating. While researchers can make inferences based on studies addressing initiation and discontinuation, ultimately studies are needed to examine re-initiation among PrEP discontinuers to understand what may motivate someone to re-initiate PrEP.

Current Study

The current study utilized an analytic sample of young SGM-AMAB who had discontinued PrEP use, which was drawn from 5 years of longitudinal cohort data. Multilevel Structural Equation Modeling (MSEM) was utilized to examine potential predictors of PrEP re-initiation. The current analyses included variables that may be related to risk perception, such as having a partner living with HIV, number of condomless anal sex partners, relationship status, and (among those in relationships) relationship agreement type. Socio-economic factors examined included insurance status and housing instability.

Method

Participants and Procedures

This analysis uses data from 10 waves of an ongoing longitudinal study of SGM-AMAB youth assigned male at birth living in the Chicago metropolitan area spanning 5 years of data collection, called RADAR (n = 1,129) (34). Data were collected between February 2015 and March 2020 using computer assisted self-interview (CASI) software as well as the collection of biological samples. Visits were collected at 6 month intervals. The primary goal of RADAR is to examine multi-level influences on HIV and substance use. All participants spoke English, had a sexual encounter with a man in the year prior or identified with a sexual minority identity. Recruitment for this study used an

incentivized snowball sampling approach, meaning that an initial set of participants are recruited directly who could then refer up to 5 peers. The recruitment for the initial set of participants included venue-based (e.g., community organizations) and social media advertisements (e.g., Facebook). To be included in this analysis, the participants additionally had to: (1) be HIV negative at all included waves, and (2) have indicated discontinuation of PrEP after being on a daily oral PrEP regimen. The first visit at which a participant indicated discontinuation of PrEP was then designated as the first wave in this analysis, and all available waves after discontinuation were included.

Sample Characteristics

Sample characteristics were measured at the first wave included in the analysis and reported in Table 1. The analytic sample of young SGM-AMAB included 253 individuals. The majority of participants identified as gay, then bisexual and other sexual identities, which were combined due to small numbers. Other sexual identities included queer ($n=19$), unsure/questioning ($n=1$), straight/heterosexual ($n=11$), and other participant-specified identities ($n=7$). The largest racial/ethnic group was Black followed by Latinx/Hispanic, White and other racial identities, which was combined due to small numbers. Other race identities included Asian ($n=10$), multiracial ($n=30$), and “other” ($n=3$). All participants were assigned male at birth. Most participants were cisgender men. Gender minorities were combined into a single group due to small numbers and included transgender ($n=20$) and other gender minority ($n=18$). The majority of participants had some college or trade school.

Measures

PrEP Re-Initiation

Participants were asked if they were currently taking PrEP at each time point. PrEP re-initiation was identified as a visit where a participant reported currently taking PrEP after having previously indicated discontinuation. This variable was constructed as a dichotomous variable indicating a re-initiation event (1) or no re-initiation event (0). PrEP re-initiation was then examined relative to the current PrEP use variable to assess for persistent PrEP use across consecutive time points as well as multiple re-initiation events. We censored events where participants reported consistent PrEP use after re-initiating (more detail on this can be found under the [Results](#) section). This means that PrEP re-initiation as measured in this study represented unique re-initiation events after periods of non-use and do not represent subsequent

visits where participants reported persistent PrEP use across consecutive time points. While they are not modelled as an outcome, patterns of persistence or discontinuation after re-initiation are described in the results (Table 1).

Time Since Discontinuation

Since visits did not occur exactly 6 months apart, time was derived by calculation. This was calculated by subtracting age at first wave (the visit at which participants indicated discontinuation) from age at each subsequent wave included in this analysis. Time was measured in years from exact date to 2 decimal places. For example, if a participant was 18 at first visit and 18.8 at first follow-up then time would be calculated as follows: $18.8-18=0.8$ years.

Insurance Status

Participants were asked about their current insurance status at each wave. Insurance status was coded as 1 = currently has health insurance, or 0 = does not currently have health insurance.

Housing Insecurity

Housing insecurity was asked at each time point using the question “Which of the following best describes your current living situation?” Participants could choose from a list of 7 possible responses. Two types of responses were coded to indicate housing insecurity. These included: “Living in a shelter, group home or residential treatment facility” and “No permanent address (for example: you are homeless, squatting, etc.)” The variable was coded as housing secure = 0 and housing insecure = 1.

Relationship Agreement and Status

Relationship agreement was measured at each wave for participant’s who indicated that they were currently in a serious romantic relationship. The question was asked: “Which of the following scenarios best describes the sexual agreement that you and [partner name] have?” There were four response options. The two responses that indicated open relationships were combined into an “open relationship” category. These included: “We can have sex with outside partners but with some restrictions” and “We can have sex with outside partners without any restrictions.” Participants who indicated that they do not have a main partner were coded as “single.” The final responses included “exclusive,” “open relationship,” “no agreement,” and “single” which

Table 2 Multilevel Associations between participant, relationship status and PrEP Re-initiation Events (n=252[^])

Level	Predictor	Unadjusted OR (95% CI)	Adjusted OR (95% CI) (n=229) [^]	
Within-Person Association	Time since discontinuation	1.02 (1.01, 1.03)**	1.17 (0.97, 1.41)	
	Relationship Agreement (ref=has monogamous main partner)			
	Open relationship with main partner	2.72 (1.20, 6.18)*	3.65 (1.42, 9.39)**	
	No relationship agreement with main partner	0.62 (0.14, 2.79)	1.03 (0.18, 5.86)	
	Single	2.37 (1.26, 4.43)**	4.18 (1.92, 9.10)***	
	Housing insecurity (Housing insecure vs. housing secure)	1.30 (0.40, 4.87)	1.10 (0.28, 4.35)	
	Health insurance status (yes vs. no)	2.38 (1.17, 4.83)*	2.48 (1.15, 5.35)*	
	Condomless anal sex partners	1.00 (0.99, 1.00)	0.99 (0.99, 0.99)*	
	Main partner living with HIV	2.91 (2.89, 2.91)*	3.48 (1.36, 8.91)**	
	Between Person Associations	Race (ref=white)		
		Black	1.07 (0.65, 1.76)	0.71 (0.36, 1.38)
		Latinx	1.21 (0.73, 2.00)	0.83 (0.45, 1.57)
		Multiracial or other race	1.18 (0.69, 2.03)	1.07 (0.55, 2.09)
		Sexual Identity (ref= gay)		
Bisexual		0.50 (0.22, 1.13)	0.19 (0.05, 0.75)*	
Other sexual identity		1.12 (0.68, 1.80)	0.55 (0.23, 1.31)	
Gender (ref= cisgender male)				
TGD-AMAB		1.78 (1.22, 2.61)**	2.15 (0.96, 4.82)	
Age		1.05 (0.99, 1.11)	1.06 (0.98, 1.14)	
Education (ref= less than high school)				
High school diploma or GED	1.04 (0.48, 2.27)	0.64 (0.26, 1.90)		
Some college or trade school	1.34 (0.66, 2.75)	0.68 (0.31, 1.49)		
College degree or above	1.85 (0.88, 1.85)	0.88 (0.33, 2.32)		
Average number of CAS Partners	1.02 (0.99, 1.04)	1.01 (0.96, 1.07)		

* p < 0.05, ** p < 0.01, *** p < 0.001, [^]Full model sample was reduced through list-wise deletion due to missing values for health insurance status

were dummy-coded for inclusion in statistical models. The referent category was monogamous relationship agreement.

Partner Living with HIV

Participants with primary partners were asked for the HIV status of their primary partner. Participants who indicated a partner living with a known HIV positive status were coded as 1 and participants who did not have a primary partner with a known HIV positive status (including single participants or participants whose partner had an unknown HIV status) were coded as 0.

Condomless Anal Sex Partners

Sexual risk was assessed using the HIV-Risk Assessment for Sexual Partnerships (H-RASP) which is a computerized self-administered interview to assess sexual behavior (35). Participants reported sexual behaviors and relationship characteristics for up to 4 partnerships during the preceding 6 months. Those who had more than 4 partnerships reported sexual behaviors for additional partnerships in aggregate. Using these variables, we derived a total number of condomless anal sex partners for the preceding 6 months. Number of condomless anal sex partners was mean centered for the purpose of this analysis. The mean number of sex partners across visits for each participant was included at the between-persons level in regression analyses.

Demographics

Demographics were measured at first visit. These included self-report of age, race, gender, education, and sexual identity.

Analysis

All univariate and bivariate statistical analyses were run in SAS version 9.4. Between-person measures were taken from the first wave. Univariates and bivariate analyses were used to examine distributions and bivariate associations. Given that waves were spaced out by 6-month increments, exposures were measured and modelled at the same time point as the outcome (e.g. insurance status at wave 2 and re-initiation event at wave 2). This approach was determined as more appropriate rather than a lagged approach (e.g. examining associations between insurance status at wave 1 and re-initiation at wave 2) which examines if an exposure at a previous time point impacts the outcome at the following time point. A lagged approach would measure exposures as much as 12 months prior to the outcome which may be too wide of a lag to detect an effect. The non-lagged design

allows us to assess what is associated with time-points where a PrEP re-initiation occurred relative to periods of PrEP non-use. Categorical variables were dummy-coded for inclusion in statistical models. References for dummy-coded variables are indicated in Table 2. Unadjusted models were used to present unadjusted associations between dependent variables and PrEP re-initiation.

MSEMs were conducted in Mplus version 7. There were a total of 664 observations from 253 participants with varying numbers of waves (min = 1, max = 10). Varying numbers of waves were due to two factors: (1) only waves following indication of PrEP discontinuation were included, (2) recruitment for the cohort study is conducted on a rolling basis, so participants reach different visit numbers at different dates, meaning that not all included participants had reached their tenth visit prior to this analysis; and (3) some participants missed visits between waves which was accounted for with the time variable. In the model within- and between-person components were modelled relative to the outcome (re-initiation events). Given the large number of within-person variables, each within-person association was assessed to examine if they should be allowed to vary across individuals. This assessment included modelling random slopes for the associations between within-person time since discontinuation and re-initiation. Other within-person effects were modelled as fixed due to non-significance of random slope variance when examining each association. Though the variance of having a partner living with HIV was significant it was modelled as fixed due to non-convergence in the final model likely due to infrequent observations of HIV positive partners. Final MSEM Models were estimated using maximum likelihood estimation with robust standard errors (MLR).

Results

In this analytic sample of PrEP discontinuers ($n=253$) from the RADAR cohort study most participants had no re-initiation event (66.4%, $n=168$) or a single re-initiation event (29.6%, $n=75$). Only 4.0% ($n=10$) had two re-initiation events over the course of the study period. As they were defined, the total number of re-initiation events was $n=95$. Out of those who reported at least one initiation event 41.2% ($n=35$) had discontinued again during the course of the study, while 86.1% ($n=50$) did not. Out of all the participants who were included in the study after discontinuing PrEP, 5.5% ($n=14$) tested positive for HIV during a follow-up visit. For more detail see Table 1. Final model results are presented in Table 2.

Within-Person Associations

Within-person odds ratios compare a time-varying characteristic relative to other time points within an individual. For example, in the case of having a main partner living with HIV the odds ratio compares time points when a participant had a main partner living with HIV relative to time points where the same participant did not have a partner living with HIV.

In unadjusted associations, time since discontinuation was significantly associated with PrEP re-initiation (OR = 1.02, 95% CI: 1.01, 1.03, $p < 0.01$) such that odds of re-initiation were higher at each subsequent time point. Partner characteristics were related to PrEP re-initiation such that time points where participants indicated having a main partner living with HIV had nearly threefold higher odds of coinciding with PrEP re-initiation relative to timepoints when they did not report having a main partner living with HIV (OR = 2.91, 95% CI: 2.89, 2.92, $p < 0.05$). Time points where a participant indicated being in an open relationship had higher odds of coinciding with PrEP re-initiation compared to time points where they were in a monogamous agreement (OR = 2.72, 95% CI: 1.20, 6.18, $p < 0.05$), and time points where participants were single were significantly associated with PrEP re-initiation relative to times when they were in monogamous relationships (OR = 2.37, 95% CI: 1.26, 4.43, $p < 0.01$). We did not observe a statistically significant difference in odds of PrEP re-initiation between time points where participants indicated not having an explicit relationship agreement and time points where participants indicated being in a monogamous relationship. A follow-up model was estimated using being single as the reference category. In this follow-up analysis time points where a participant indicated having a relationship without an explicit relationship agreement were less likely to coincide with re-initiation than being single (OR = 0.24, 95% CI: 0.06, 0.97, $p < 0.05$). No difference was observed between time points where participants reported being single and time points where participants indicated being in an open relationship. Insurance was also significantly associated, meaning that time points where participants indicated having health insurance had higher odds of coinciding with PrEP re-initiation relative to times when they did not have insurance (OR = 2.38, 95% CI: 1.17, 4.83, $p < 0.05$). Housing insecurity and number of condomless anal sex partners were non-significant.

In the adjusted models, having a main partner living with HIV, having insurance, being in an open relationship, and being single remained significantly positively associated with PrEP-re-initiation (See Table 2). Number of condomless anal sex partners became significant with a small negative association (aOR = 0.99, 95% CI 0.99, 0.99, $P < 0.05$).

Time since discontinuation became non-significant and housing insecurity remained non-significant.

Between-Person Associations

In unadjusted estimates only one between-person association was significant. Gender minority participants were more likely to re-initiate than cisgender men (OR = 1.78, 95% CI: 1.22, 2.61, $p < 0.01$). Race, sexual identity, age, and education were all non-significant.

In the adjusted model the significant association for gender identity became non-significant; however, one other between-person associations became significant. Sexual identity was associated with PrEP re-initiation in that bisexual participants were less likely to re-initiate compared to gay participants (OR = 0.19, 95% CI: 0.05, 0.75, $p < 0.05$). No significant differences in odds were detected between participants with other sexual identities and gay participants. In a follow-up model with bisexual as the reference category, no additional significant associations were observed. Race/ethnicity and average rate of condomless anal sex across waves were not associated with re-initiation.

Discussion

This exploratory analysis contributes to our limited understanding of PrEP re-initiation and is one of the first analyses to use longitudinal data to examine possible factors for PrEP re-initiation among PrEP discontinuers. Three broader types of variables were examined in relation to PrEP re-initiation in addition to demographics: (1) variables that may be associated with perceived risk for HIV transmission, and (2) socio-economic variables and (3) demographics. Results suggested that variables from all three broader variable categories were associated with PrEP re-initiation.

First, relationship agreements were associated with PrEP re-initiation, indicating that being in an open relationship or being single was associated with a higher likelihood of PrEP re-initiation, relative to being in a monogamous relationship. No difference was detected between open relationships and being single. This aligns with previous research which suggests that relationship agreements are associated with HIV risk in that individuals in open relationships are more likely to have secondary sexual partners than those who are in monogamous relationships (36) and relationship agreements are linked to risk perceptions in that couples in a perceived mutually monogamous relationship tend to perceive themselves to be at lower risk for HIV transmission (37). Moreover, being single is associated with HIV risk factors such as condomless anal sex with casual partners (38). However, that is not to say that monogamous relationship

agreements eliminate HIV risk. In fact, literature suggests that some young MSM may be at risk for HIV transmission in perceived monogamous relationships, as a result of broken relationship agreements and decreased condom use with primary partners (25, 26). The results of the current analysis do suggest that changes in relationship agreements and relationship status are associated with PrEP re-initiation within-persons and may serve as an indicator of perceived risk for PrEP discontinuers.

Second, insurance status was associated with PrEP re-initiation within-persons suggesting that gaining access to reduced cost or fully-covered medication, along with accompanying clinical care requirements, through insurance may promote PrEP re-initiation. This is unsurprising when taking into account the considerable research suggesting that factors related to access are predictive of PrEP initiation and discontinuation (4, 7, 19, 20, 28–31); however, the current finding further emphasizes the importance of addressing issues of access such as insurance. This finding suggests that fluctuating insurance status may force PrEP users to discontinue their regimen, but then re-gaining insurance facilitates re-initiation. This may be particularly relevant in the age of the COVID-19 pandemic, where there is a great deal of unemployment and underemployment (39), given that most insurance in the U.S. is employment-based and many unemployed individuals do not have health insurance (40). Of note, all data included in these analyses were collected prior to the onset of the COVID-19 pandemic in the U.S., so the analyses cannot speak to factors related to PrEP re-initiation unique to the pandemic era.

Third, having a main partner who is living with HIV was associated with PrEP re-initiation. This is consistent with literature suggesting that having a partner who is living with HIV is associated with uptake of PrEP (23). This finding is unsurprising, because sero-discordance in couples aligns with recommendations for PrEP eligibility from the Centers for Disease Control and Prevention (24); however, it does highlight alignment between a factor related to risk for HIV-transmission and PrEP re-initiation. Also, evidence suggests that MSM decide condom-use in part by matching on biomedical prevention status (41). For example, deciding not to use condoms when a partner living with HIV reaches undetectable status and the HIV-negative partner is consistently on PrEP. Thus, HIV negative partners of people living with HIV may be motivated to take PrEP in part to reduce or cease condom use while maximizing biomedical protection.

Fourth, bisexual identity was negatively associated with PrEP re-initiation, which is in alignment with literature that suggests that bisexual individuals and men who have sex with men and women are less likely to engage at multiple points in the PrEP-care continuum (42, 43). However, it should be noted that the bisexual individuals in this sample

had previously been able to get on PrEP, so they reflect a group of bisexual people who had access to HIV care at one point in time. It is not known if discontinuation and re-initiation for these bisexual individuals were due to issues related to risk-perception or PrEP access. For example, bisexual MSM or TGD-AMAB may not perceive themselves to be at risk for HIV transmission during periods when they have primarily cisgender women partners. Bisexual individuals also may experience barriers to PrEP access in healthcare engagement if they are not perceived to be at elevated risk for HIV by their healthcare providers, such as if they are perceived to be heterosexual by their medical doctor. It is also possible that bisexual individuals experience stigma or did not feel welcome at SGM community-based organizations given that many have historically catered to gay-identified people. More research is needed to understand the factors that may contribute to bisexual individuals' reduced likelihood of re-initiation of PrEP.

Having a better understanding of PrEP re-initiation may help facilitate the development of strategies for increasing PrEP re-initiation among SGM-AMAB who are at risk for HIV transmission. Consistent with the current analyses, PrEP re-initiation is likely determined by perception of risk for HIV transmission, and consistent with the concept of "seasons of risk," people view their risk for HIV as ebbing and flowing over time (11–13); however, these perceptions may not coincide perfectly with real risk. In this analysis 5.6% tested positive for HIV during a follow-up appointment after having discontinued PrEP use, which suggests that periods of non-use did not necessarily align with a sustained reduction in true risk for HIV transmission. Re-initiation events also do not necessarily mean sustained PrEP use. In this sample 41.2% of participants who reinitiated discontinued again with 28.6% of those who indicated re-initiating a second time. This represents considerable shifts in PrEP use in relatively short periods of time. For example, a young person may immediately stop PrEP use when entering a new relationship. If that relationship dissolves after a few months and the participant has casual condomless anal sex prior to re-initiating PrEP, then there may be heightened risk for HIV transmission. Other examples may include discontinuation upon entry into a relationship before establishing an agreement or confirming HIV status between partners. Interventions could be developed to help PrEP eligible individuals better assess their current true risk for HIV transmission, and perhaps more important to this context, assess whether shifts in their risk for HIV transmission will have a long enough duration to warrant a break from PrEP. Interventions may help PrEP eligible individuals better identify when they may experience a durable low-risk period that may warrant discontinuation, encourage assessment of risk in the long-term, and dispel myths about HIV risk,

such as monogamous relationships being free of HIV risk. Additionally, further consideration of strategies to increase access to PrEP for individuals who may have fluctuations in insurance may be warranted. People who initiate PrEP while on insurance may not be made aware of programs to defray the cost of the PrEP regimen or the opportunities for switching to generic prescriptions. It may be helpful to educate all PrEP users about options for cost reduction or assistance in coverage even if they are presumed to have stable insurance status when initiating PrEP as they may have a lapse of insurance status later on.

Limitations

While this sample did include TGD-AMAB there were not enough transgender women and non-binary individuals to generate stable estimates for individual TGD-AMAB identities. Future studies should include larger samples of TGD-AMAB populations. The time intervals between visits in these data are 6 months, which means that the data do not capture fluctuations at a smaller time scale. For example, insurance status may lapse for a brief period, which may mean that we did not observe some re-initiation events. Also, it is feasible that there were brief reinitiation events followed by discontinuation events within the 6 month timeframe that happened between visits; however, this study was not set up to detect re-initiation and discontinuation patterns at shorter intervals. Future studies should examine factors contributing to re-initiation on a smaller time scale. A couple notes regarding measurement should be considered. First, we did not have a suitable measure of healthcare access available for this analysis. Future analyses may examine healthcare access in relation to PrEP re-initiation. Second, while many included variables were related to risk, we did not have a measure of risk perception. Future studies should examine fluctuations in risk perception, and actual risk in relation to PrEP re-initiation to identify how these phenomena coincide.

Conclusions

This analysis examined potential factors associated with PrEP re-initiation among young SGM-AMAB finding that both risk-related and socio-economic related factors were associated with PrEP re-initiation. In specific, being single or being in an open relationship (compared to in a monogamous relationship), having insurance, and being gay (compared to bisexual) were positively associated with PrEP re-initiation among young SGM-AMAB who had discontinued PrEP use. Interventions are needed to assist with PrEP access among SGM-AMAB who have fluctuating insurance

statuses as well as to assist with more accurate risk assessment, particularly in regard to the potential long-term fluctuations in risk.

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Availability of Data Data is available upon request and approval by corresponding author.

Conflict of Interest Authors don't have conflicts of interest to report.

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