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Gender-Based Violence and Post-traumatic Stress Disorder Symptoms Predict HIV PrEP Uptake and Persistence Failure Among Transgender and Non-binary Persons Participating in a PrEP Demonstration Project in Southern California

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Abstract

Gender-based violence (GBV) against transgender and nonbinary (TGNB) persons is a pervasive public health issue. GBV has been linked to mental health problems such as depression and posttraumatic stress disorder (PTSD), as well as risk for HIV seroconversion and HIV treatment nonadherence. However, the impact of GBV on HIV pre-exposure prophylaxis (PrEP) use among TGNB persons has yet to be investigated. In the current study we assessed longitudinal PrEP persistence data from dried blood spots (DBS) collected from 172 racially and ethnically diverse TGNB participants during a 48-week PrEP demonstration project in Southern California from June 2017 to September 2020. Participants were categorized into three levels of PrEP uptake and persistence based on their PrEP levels at the start and end of the study: *low–low*, *high–low*, and *high–high*. Individual-, social-, and structural-level variables were then entered into multinomial logistic regression models to predict levels of PrEP uptake and persistence based on hypotheses informed by syndemic and minority stress theories. The models demonstrated that experience of GBV predicted significantly lower odds of PrEP uptake and persistence and greater PTSD symptoms predicted significantly greater odds of early PrEP discontinuation. Higher levels of coping skills, already being on PrEP at baseline, and being in a steady relationship were associated with greater odds of PrEP uptake and persistence. Implications for future GBV research, advocacy, interventions, and much needed structural changes focused on improving the health and safety of TGNB individuals are discussed.

Keywords Transgender · Health equity · PrEP persistence · Medication adherence · HIV prevention

Introduction

Violence against transgender and non-binary (TGNB) persons (persons whose gender identity differs from the sex they were assigned at birth) has deleterious effects on the

health and wellbeing of TGNB persons including increasing HIV risk [1–3]. While little is currently known about the impact of gender-based violence (GBV) on engagement in HIV prevention behaviors such as pre-exposure prophylaxis (PrEP) among TGNB persons, a recent study found PrEP use

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to be negatively associated with recent experience of violence generally [4]. TGNB persons experience violence on the basis of their gender expression, gender identity, gender nonconformity, and/or their perceived sexual orientation [1]. Prior research suggests that violence against TGNB persons is alarmingly common, with an estimated prevalence as high as 89% in the United States (U.S.) [2]. From 2013 to 2021, there were at least 241 reported murders of TGNB in the U.S., likely an underestimate of murder rates due to frequent misgendering and underreporting of violence against TGNB people by police and the media, as well as a lack of GBV surveillance among TGNB in the U.S. [3]. GBV against TGNB persons is rooted in the broader social and structural context of marginalization that creates environments where anti-transgender violence is tolerated and normalized [2]. Additionally, Black and Latinx TGNB persons are susceptible to violence and further marginalization, based on the intersection of gender with race and ethnicity. Despite the alarming rates of GBV against TGNB persons, there remains a lack of prevention and response programs to address violence against TGNB persons.

Theoretical Framework

The impacts of GBV span far beyond the immediate threats of physical harm to TGNB persons. Syndemic and Minority Stress theories help explain the direct and indirect effects GBV has on the health and wellbeing of TGNB persons. Syndemic Theory suggests that co-occurring psychosocial and structural health conditions such as substance use, mental health problems, incarceration, poverty, and violence are mutually reinforcing and exacerbate risk for deleterious health conditions such as HIV [5–7]. Among TGNB, co-occurring conditions such as structural violence, discrimination, stigma, racism, social exclusion, homelessness, poverty, GBV victimization, and mental health burdens have been found to increase HIV risk [8–12]. Additionally, Minority Stress Theory maintains that individuals who have marginalized identities, such as TGNB individuals and racial/ethnic minorities, may experience burdensome degrees of stigma, discrimination, and violence victimization that result in poor physical and mental health outcomes [10, 13–15]. Both theories are widely used to understand antecedents of HIV disparities among TGNB individuals including experiencing violence [16–26]. These theories provide a framework that helps to explain the impact that GBV has on the health and wellbeing of TGNB persons, and helps to identify potential intervention targets to reduce HIV risk.

Gender-Based Violence, PTSD Symptoms, and HIV Risk

Lifetime experiences of GBV have been associated with mental health burdens [27–29] including PTSD symptoms specifically among TGNB persons [30–32]. Beyond TGNB persons, there is a large body of work linking mental health burdens, including PTSD symptoms, to both substance use and HIV risk behavior [33–35]. While studies have demonstrated the impact of syndemic factors on HIV risk for transgender women, research examining the impact of syndemic factors on HIV risk among transgender men and nonbinary individuals has been more limited. One study found that transgender men who reported sexual partnerships with cisgender men exhibited elevated syndemic factors that were found to be associated with higher HIV risk behaviors [13]. There has been a scarcity of research examining PTSD symptomology among TGNB persons, especially given that TGNB persons experience violence and victimization at such high rates [36].

Although HIV surveillance data are often not collected for TGNB persons in the U.S. [37], meta-analytic and aggregated jurisdictional data suggest that HIV prevalence rates among transgender women are much higher than in other adult populations in the U.S. (18.4–30.6% [38, 39] vs. 0.3–0.4%) [40] with the odds of HIV seroconversion estimated to be 34.2 times higher for trans women than for other U.S. adult populations [38]. HIV rates are especially high among racial/ethnic minority transgender women. GBV has been shown to be a notable correlate of HIV acquisition among transgender women [38, 39]. While transgender men have lower overall HIV incidence than transgender women, recent data suggested HIV rates may also be on the rise [41]. Currently, little is known about HIV incidence among nonbinary individuals.

PrEP Use Among TGNB Persons

PrEP has been shown to significantly reduce risk of HIV infection when taken as prescribed and is part of the current *Ending the HIV Epidemic in the United States* ‘Prevent’ pillar for individuals with elevated risk for HIV exposure, such as TGNB individuals [42]. PrEP is currently approved for TGNB persons as a daily oral pill and as a long-acting injectable formulation. PrEP has shown evidence of preventing HIV transmission among trans women when taken as prescribed [43]. However, uptake of PrEP is low among transgender women [44] due to a multitude of barriers, including intersectional stigma and discrimination at the structural, community, and individual levels [45, 46]. These findings are consistent with previous

research among transgender men indicating that while a substantial proportion of trans masculine-identifying individuals meet PrEP eligibility criteria, few have access to or are receiving PrEP services [47]. Overall, research suggests PrEP uptake is low among TGNB individuals, especially those at highest risk for HIV, transgender women and TGNB individuals of color [48, 49].

Gender-Based Violence, PTSD, and PrEP Use

Currently, little is known about the impact GBV victimization and PTSD symptoms on PrEP uptake and persistence among TGNB persons. While experiences of violence have been linked to HIV risk behaviors, seroconversion, and antiretroviral treatment failure among TGNB [10, 13, 36, 50], no known study has investigated the associations between GBV and PrEP uptake and persistence among TGNB. Further, the existing work examining GBV among TGNB has been limited by small sample sizes, and varying definitions and measurement of GBV [2, 38]. The links between GBV and symptoms of PTSD have also been understudied among TGNB persons [2, 38]. Finally, the majority of PrEP studies that include TGNB persons have historically lumped in relatively small numbers of TGNB individuals with cisgender sexual minority men and the majority of those focused on TGNB populations focused exclusively on transgender women [51–53]. As a first step, the current study sought to examine the association between GBV, PTSD symptoms, and PrEP uptake and persistence among a diverse sample of TGNB individuals participating in a PrEP demonstration project in Southern California. Next, we assessed potential mechanisms by which GBV and PTSD symptoms may directly or indirectly impact PrEP use. We hypothesized that: (1) experience of GBV victimization would be associated with lower rates of PrEP uptake and persistence, (2) PTSD symptoms would also be associated with lower rates of PrEP uptake and persistence, and (3) coping skills would moderate these associations among the TGNB individuals in the prospective study.

Methods

Sample and Recruitment

The current study is a secondary data analysis of quantitative data collected from participants enrolled in a randomized, open, two parallel arms, clinical trial of individualized text messaging for adherence building (iTAB) or iTAB plus brief motivational interviewing to improve daily pill PrEP adherence among TGNB individuals. iTAB is an evidence-based intervention and CDC recommended best practice for HIV prevention [54]. The study was conducted by the California

Collaborative Treatment Group (CCTG) (NCT3086200) as a first-of-its-kind, PrEP demonstration project focused exclusively on TGNB persons. Participants were eligible for the study if they self-identified as TGNB, had a confirmed HIV-negative status at baseline, self-identified as being at risk for HIV infection, and reported willingness to take PrEP as part of an HIV prevention study. Between June 2017 and September 2020, 255 TGNB participants were enrolled from one of five sites (two community-based clinics and three clinics located in academic medical centers) across Los Angeles and San Diego, California. Participants were followed for 48 weeks. Quarterly visits included routine HIV testing and counseling, STI testing, PrEP adherence counseling, and medical monitoring. As part of participation in the demonstration project, all participants were provided tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) as PrEP free-of-charge and \$50 for each visit attended.

All participants were confirmed to be negative for HIV by combined antigen/antibody testing at baseline and had no contraindication to TDF/FTC. Randomization was stratified by CCTG site and by gender assigned at birth. Multiple waves of data were collected including screening, baseline, week 12, 24, 36 and 48 visits and a 60-week post-study telephone visit. Visits for all participants included routine HIV testing and counseling, STI testing, adherence counseling, medical monitoring and a computer-assisted survey for self-reported adherence assessment, demographic, psychological, social, and structural variables, and risk behaviors. Drug level testing was performed for quantitative intracellular TFV-DP levels on banked samples starting at week 12 (except where participant indicated being on PrEP upon enrollment, then baseline sample was used). Uptake was defined by participant reporting being on PrEP at week 12 and confirmed by tenofovir-diphosphate (TFV-DP) levels. Persistence was measured by protected drug level concentrations over time, at week 12 and again at their last study visit, either week 24, 36 and 48. There was an enrollment goal to achieve 20% participants who identified as African American/Black in the study. Latinx enrollment was not benchmarked because it was already estimated to be approximately 38% of the consortium site demographics.

Measures

Sociodemographic

All participants were asked to provide basic demographic information including age, sex assigned at birth, current gender identity, race and ethnicity, education level (i.e. having a college degree or not), income (i.e., monthly income on ordered categories from 0 to 7), relationship status (married, in steady monogamous relationship, steady open relationship, or single), current health insurance provider, and

engagement in medical care (whether the participant indicated having primary care provider they currently see or not).

Gender-Related Minority Stress and GBV

Gender-related minority stress and GBV were assessed with the Gender Minority Stress and Resilience Measure [15]. We included three specific subscales of reported negative experiences because of participant's gender identity or expression: (1) gender-related *discrimination* ($\alpha=0.74$; 5-item; e.g., in getting medical care, finding bathroom, housing and employment); (2) gender-related *rejection* ($\alpha=0.80$; 6-item; e.g., been rejected in relationships, by friends and family) and (3) gender-related *victimization* (GBV; $\alpha=0.86$; 6-item; e.g., being verbally harassed, having personal property damaged, being threatened with physical harm, being physically assaulted, or being forced to have sexual contact against one's will). The original categorical response options were never experienced, experienced before age 18, experienced after age 18, and in the past year. Since respondents could indicate multiple responses to these items, we dichotomized the responses to each of the subscale items as having ever experienced or not. For the purposes of this study, participants were administered an adapted version of the victimization subscale in order to assess the severity of each GBV item by asking participants to rate on a 5-point Likert-type scale the extent to which each of GBV victimization items had occurred.

Coping Skills

Coping skills were measured using the 13-item brief Coping Self-efficacy Scale [55] ($\alpha=0.95$; e.g., finding solutions to the most difficult problems, breaking an upsetting problem down into smaller parts, and making a plan and following it). The responses ranged from 1 to 10 on a Likert-type scale from *cannot do at all* to *certain can do*. This scale is well-validated and unidimensional and thus we used the total scale scores by taking the mean of the 13 items.

Mental Health

We collected data on depression, perceived stress, and symptoms of posttraumatic stress disorder (PTSD). Depression was measured using the validated 9-item Patient Health Questionnaire [56] ($\alpha=0.92$; PHQ-9) with possible PHQ score ranging from 0 to 27 (timeframe: over the last 2 weeks). Perceived Stress was measured using the validated 14-item Perceived Stress Scale [57] ($\alpha=0.86$, e.g., felt that you were unable to control the important things in your life during the last month). Response options were on an ordered categorical scale from 0 (never) to 4 (very

often). The mean of the 14 items was taken as the score for perceived stress. PTSD symptoms were measured using two items from the 20-item PTSD Checklist for DSM-5 Civilian Versions [PTSD scale [58] ($\alpha=0.83$; PC-PTSD)], i.e., in the past month, how much you have been bothered by repeated, disturbing memories, thoughts, or images of a stressful experience; and in the past month, how often you have been bothered by feeling very upset when something reminded you of a stressful experience? Response options were on an ordered categorical scale from 0 (not at all) to 4 (extremely).

Substance Use

Participants were administered the Alcohol Use Disorders Identification Test [59] (AUDIT) to assess for frequency and severity of drinking. The AUDIT has ten questions with a range of possible scores from 0 to 40 where 0 indicates an abstainer who has never had any problems from alcohol. We scored the AUDIT according to World Health Organization guidelines [60] such that scores from 1 to 7 suggest low-risk alcohol consumption, scores from 8 to 14 suggest hazardous or harmful alcohol consumption, and a score of 15 or more indicates likelihood of alcohol dependence (moderate-severe alcohol use disorder). These four categories, based on the AUDIT scores, were used as an ordered categorical variable in the analysis to assess the extent of alcohol use.

Participants completed the Drug Abuse Screening Test [61] (DAST-10) that yields a quantitative index of the degree of consequences related to involvement with drugs, excluding alcohol and tobacco during the past 12 months. Scores range from 0 to 10 where 0 indicates no problems reported and a score of 9 or 10 indicates a severe level of drug use. We computed total scores for the 10-item self-report instrument based on current Centers for Disease Control and Prevention scoring guidelines. [61–63]

PrEP Persistence

PrEP use was measured as part of the PrEP Demonstration Project with collected biospecimen samples via Dried Blood Spot (DBS) assay. Intracellular levels of TFV-DP were assessed at baseline (i.e., week 0) for those participants that reported use at baseline and then for all participants at week 12 and again at their last visit (either week 24, 36 or 48). TFV-DP steady-state concentration levels of ≥ 700 fmol/punch were considered to be protective (≥ 4 doses/week) based on current guidelines for DBS interpretation [64, 65] Participants who had protective TFV-DP levels (≥ 700 fmol/punch) at either baseline (i.e., if reported already on PrEP at baseline) or week 12 if initiating PrEP at baseline, and had protective TFV-DP levels (≥ 700 fmol/punch) at their last visit were considered to have a “high-high” level of persistence (i.e., considered to be adherent to TFV-DP for

study duration), participants who were found to have protective TFV-DP levels (≥ 700 fmol/punch) at either baseline or week 12 but suboptimal TFV-DP levels (< 700 fmol/punch) at their last study visit were considered to have a “high–low” level of persistence, and those who were found to have suboptimal TFV-DP levels (< 700 fmol/punch) at either baseline or week 12 and at their last study visit were considered to have a “low–low” level of persistence. Because the current study aimed to compare participants who had protective levels of TFV-DP (≥ 700 fmol/punch) during the duration of their study participation against those who had protective levels at baseline or 12 week but no longer demonstrated protective levels at their last visit, as well as against those who never achieved protective levels any study time point, we chose not to include the ($n = 7$) “low–high” participants (i.e., suboptimal TFV-DP levels at week 12, but protective TFV-DP at week 48) from the current analysis.

Analytic Approach

As a preliminary step, we sought to refine the measurement of the three specific subscales (i.e., discrimination, rejection, victimization) of the Gender Minority Stress and Resilience measure for our analyses. Because we had asked participants to rate the extent to which they had experienced the GBV items on a continuous scale, we took an exploratory approach to scoring by calculating the factor scores (weighted score obtained through factor analysis) for each of the three gender minority stress categories using a multidimensional factor analytic approach rather than calculating sum scores. We did this with the goal of deriving more precise weighted measurements of each of the minority stress scales for each participant. Specifically, we used exploratory factor analysis (EFA) followed by confirmatory factor analysis (CFA) to determine (1) number of factors to extract; (2) model fit and (3) the scoring mechanism that is comparable to a weighted sum of the extracted latent dimensions. EFA and CFA were conducted using IRTPRO [66], which computed the factor scores for the three subscales simultaneously based on item response theory (IRT). Model fit between alternative CFA models was assessed via the values of $-2 \log$ likelihood, the common fit statistics such as Akaike’s Information Criteria (AIC) [67] and Bayesian Information Criteria (BIC) [68], in addition to the new M_2 statistics that are available in IRTPRO version 4 [69, 70].

To test our first hypothesis that experienced GBV victimization would be associated with lower rates of PrEP uptake and persistence and our second hypothesis that PTSD symptoms would also be associated with lower rates of PrEP uptake and persistence among participants, we utilized a multinomial logistic regression approach. Specifically, we used Monte Carlo integration to model the probability of being categorized into the low–low, high–low, or high–high

PrEP persistence outcome groups, which is estimated in a separate logistic regression for each outcome group. With three levels for the outcome (low–low, high–low, or high–high), two sets of contrasts were created, one for each logistic regression. Because the dependent variable was nominal with three levels, two contrasts were created using the high–high group as the reference group with each of the other two groups (i.e., high–low and low–low), examining (1) the probability of being in the low–low group instead of the high–high group, and (2) the probability of being in the high–low group rather than being in the high–high group.

We used an iterative approach to test the effects of the set of predictors including those that are theoretically related to syndemics and minority stress (gender-related discrimination, gender related rejection, and GBV victimization), mental health problems (depressive symptoms, perceived stress, and PTSD symptoms), substance use levels based on alcohol use categories and DAST scores, and level of coping skills. The variables we controlled for in the current analysis included: age, race and ethnicity, gender identity, monthly income, education level, relationship status, baseline PrEP use, site of enrollment, and the study condition. We also assessed the potential interaction between the predictors to test our third hypothesis that coping skills would moderate the associations between GBV, PTSD and PrEP uptake and persistence. We trimmed the effects that were not statistically significant and did not contribute to the explanation of the outcome according to theory. This process involved evaluating model fit using AIC and BIC and both allowing for comparison of non-nested models. While BIC is the preferred option that is asymptotically consistent in selecting the true model, AIC minimizes the maximum possible risk in model selection (choosing the wrong model) with finite sample (Vrieze, 2012) [71]. We chose AIC in our case due to limited the sample size. The final model was selected based on testing the fit of alternative models and selecting the final model that best fit the chosen set of predictors according to both theory and interpretability of the results.

Multinomial logistic regression was conducted in Mplus using maximum likelihood estimation with robust standard errors (i.e., the MLR option) [72] estimation combined with Monte Carlo integration [73] due to the categorical nature of our outcome. The MLR standard errors were computed using a sandwich estimator that were robust to non-normality. The method (i.e., MLR in Mplus) takes care of missing data using all available information of the existing data, hence preserving the maximum number of participants in each group we were comparing [73]. Overall, these analytic approaches ensured that the effects we found were robust in the different models we tested.

Table 1 Participant characteristics (N = 172)

	n	%
Age (mean = 31; SD = 9.4)		
17–19	12	6.98
20–25	49	28.49
26–29	35	20.35
30–35	32	18.6
36–39	16	9.3
40–45	12	6.98
46–49	9	5.23
50+	7	4.07
Race/Ethnicity		
Multiracial	27	15.70
Hispanic/Latinx only	44	25.58
Non-Hispanic Black	18	10.47
Non-Hispanic White	52	30.23
Other	31	18.02
Gender identity		
Transmasculine spectrum	47	27.33
Transfeminine spectrum	93	54.07
Non-binary spectrum	31	18.02
Other	1	0.58
Relationship status		
Single	107	62.57
Married/Committed relationship	19	11.09
Dating/Casual relationships	28	16.37
Separated/Divorced/Widowed	4	2.33
Educational experience		
Some college or technical training	133	77.78
High school or less	38	22.22
Healthcare access		
Health coverage at baseline	123	75.46
Primary care provider at baseline	123	75.46
Household monthly income		
\$0–\$100	86	50
\$100–\$400	7	4.07
\$500–\$999	22	12.79
\$1000–\$1999	25	14.53
\$2000–\$2999	10	5.81
\$3000–\$3999	9	5.23
\$4000–\$7999	8	4.65
\$8000+	5	2.91
Alcohol misuse past 12 months		
No misuse reported	98	78.4
Harmful or hazardous drinking	15	12
Alcohol dependence	12	9.6
Drug misuse past 12 months		
No misuse reported	95	60.51
Low level	23	14.65
Moderate level	30	19.11
Substantial level	9	5.73
Depressive symptoms		
None	46	27.22

Table 1 (continued)

	n	%
Mild	49	28.99
Moderate	27	15.98
Moderately severe	27	15.98
Severe	20	11.83
PTSD symptoms (experienced quite a lot to extremely)		
Having repeated, disturbing memories, thoughts, or images of a stressful experience	65	39.3
Feeling very upset when something reminded them of a stressful experience	62	38.04
On PrEP at baseline	14	8.14
PrEP persistence pattern		
High/High	52	30.23
High/Low	84	48.84
Low/Low	36	20.93
Discrimination (% ever experienced) due to gender identity or expression		
Had difficulty getting medical or mental health treatment	88	52.38
Had difficulty finding a bathroom to use when I am out in public	111	66.07
Had difficulty getting identity documents that match my gender identity	90	53.89
Had difficulty finding housing or staying in housing	65	39.16
Had difficulty finding/keeping employment, or have been denied promotion	81	48.5
Rejection (% ever experienced) due to gender identity or expression		
Had difficulty finding a partner or have never had a relationship	100	59.88
Have been rejected or made to feel unwelcome by a religious community	106	63.1
Have been rejected by or made to feel unwelcome in my ethnic/racial community	78	46.99
Have been rejected or distanced from friends	93	55.69
Have been rejected at school or work	82	48.81
Have been rejected or distanced from family	114	67.86
Gender-based violence victimization due to gender identity or expression (% agree or strongly agree)		
Have been verbally harassed or teased	115	68.45
Have been threatened with being outed or blackmailed	48	28.57
Have had my personal property damaged	47	27.98
Have been threatened with physical harm	85	50.60
Have been pushed, shoved, hit, or had something thrown at me	68	40.48
Have had sexual contact with someone against my will	51	30.36

Results

Participant Characteristics

Table 1 presents the participant characteristics. While 255 TGNB persons initially enrolled in the study, only 172 participants for whom at least one DBS assessment was collected from baseline to week 48 were included in these analyses, forming three distinct PrEP use groups: 36 (20.9%) were in the low–low PrEP use group; 84 (48.8%) were in the high–low PrEP use group; and 52 (30.2%) were in the high–high PrEP use group. Fourteen (8.1%) participants reported already using PrEP prior to study enrollment as verified by the detection of TFV-DP in their DBS sample at baseline. At week 12, 163 (94.8%) participant DBS samples were collected, and at week 48, 85 (48.8%) DBS samples were collected. The 48-week study had an

attrition rate of 50.6%. Participants were highly diverse in terms of racial and ethnic backgrounds with 44 (25.6%) self-identifying as Hispanic/Latinx; 18 (10.5%) as non-Hispanic Black; 52 (30.2%) as non-Hispanic White; and 27 (15.7%) as multiracial. Most participants 93 (54.1%) identified along the transfeminine spectrum and only 19 (11.1%) reported currently being married or in a stable relationship. The mean age was 31 years old ($SD = 9.4$) with a range of 18–78 years old. Most participants 133 (77.8%) reported at least some college or technical training beyond high school. The mean monthly household income was \$1160 ($SD = \1989) with a range from \$0 to \$12,000. The majority of participants were quite socioeconomically disadvantaged with 115 (66.8%) reporting a monthly income of < \$1000 and 86 (50.0%) reporting a monthly income of < \$100. The majority 123 (75.5%) reported current health coverage and a primary care provider at

baseline. Participants were enrolled in the study at one of two types of sites. Over half of participants 103 (59.9%) were enrolled at one of two community-based clinics and the remaining participants 69 (40.1%) were enrolled at one of three clinics located in academic medical centers.

Minority Stress and Gender-Based Violence

Most of our sample reported previous experiences of discrimination and rejection related to their gender identity or expression (see Table 1 where most of the events > 50% prevalence). For example, 111 (66%) of participants reported having difficulty finding a bathroom to use when out in public due to their gender identity or expression; 114 (68%) reported being rejected or distanced from family. Related to GBV, 115 (68%) reported having been verbally harassed or teased; 85 (51%) reported having been threatened with physical harm; 68 (40%) reported having been pushed, shoved, hit, or had something thrown at them; and 51 (30%) reported having had sexual contact with someone against their will.

To account for our measurement of GBV on a continuous scale and to minimize measurement error, we constructed a measurement model for the minority stress and GBV items. Specifically, we used an advanced software package for item calibration and test scoring to assess individual levels of gender-related discrimination, rejection, and GBV victimization experiences. The calibration part involved both EFA and CFA that supported a 3-factor model from the 17-item questionnaire. Model fit was acceptable (e.g. RMSEA = 0.06 and 0.08 for EFA and CFA respectively). The estimated factor loadings from CFA ranged from 0.61 to 0.95 indicating moderate to strong association between the items and the corresponding subscale. The test yielded a set of three factor scores for each participant that were placed on a standardized scale with mean of 0 and variance of 1 where negative values indicated below-average levels and positive values indicated above-average levels of discrimination, rejection, and victimization experienced, respectively.

Mental Health

Our sample ($n = 172$) had a mean PHQ-9 (depressive symptoms) score of 9.67 ($SD = 7.46$). Using standardized cut points for depression (i.e. scores of 5, 10, 15, and 20 represent cut points for mild, moderate, moderately severe and severe depression, respectively) [74], 46 (27.2%) had no depression, 49 (29.0%) had mild depressive symptoms, 27 (16.0%) had moderate depressive symptoms, 27 (16.0%) had moderately severe, and 20 (11.8%) had severe levels of depression. The mean score on the Perceived Stress Scale was 1.94 ($SD = 0.61$) and the median was 1.97, indicating that our participants reported a moderate level of stress on average. Lastly, related to PTSD symptoms endorsed, 65

(39.3%) reported having repeated, disturbing memories, thoughts, or images of a stressful experience and 62 (38.0%) endorsed feeling very upset when something reminded them of a stressful experience. While the PTSD symptom assessment measures may differ and therefore comparisons must be made with caution, approximately 3.6% of the general adult US population reports PTSD symptoms [75], suggesting the current sample of TGNB participants endorsed elevated levels of psychological distress from prior stressful experiences.

Substance Use

Ninety-eight participants (78.4%) reported no alcohol misuse during the past 12 months. Others reported either harmful or hazardous drinking behavior 15, (12%) or alcohol dependent behavior ($n = 12$, 9.6%). Most participants 95 (60.5%) reported no drug use; ($n = 23$, 14.7%) reported a low level of use; ($n = 30$, 19.1%) reported a moderate level of use, and ($n = 9$, 5.7%) reported a substantial level of use. No participants reported a severe level of drug use.

Coping Skills

Our sample reported moderate to slightly above-moderate coping skills with a mean score of 6.34 ($SD = 2.16$) on the Coping Self-Efficacy Scale (1 *cannot do at all* to 10 *certainly can do*).

Predicting PrEP Persistence

The top panel of Table 2 illustrates the effects of the predictor variables on the probability of being low–low vs. high–high (i.e., the first contrast). The bottom panel illustrates the effects of the predictor variables on the probability of being high–low vs. high–high (i.e., the second contrast). The size and significance of each effect are presented in two ways: (1) the estimated regression coefficient (i.e., betas interpreted as the estimated increase in the log odds of the outcome per unit increase in the value of the predictors) together with its standard error estimates and significance at 0.05 level; (2) odds ratios (OR) that are derived from the beta regression coefficients with 95% confidence interval.

Low–Low vs. High–High

Consistent with our first hypothesis that the experience of GBV victimization would be associated with lower rates of PrEP uptake and persistence, we found a significant association between experiencing GBV and failure to adopt PrEP. Those that reported more experiences of GBV were more likely to be low–low than to be high–high [$\beta = 2.46$, $p < 0.05$; OR 11.69, 95% CI(1.57, 87.08)]. Figure 1 shows a

Table 2 Multinomial logistic regression results modeling the three PrEP persistence patterns

	Adjusted odds ratio and 95% CI		p value
<i>Effects on being low–low vs. high–high</i>			
Discrimination	0.96	(0.27, 3.43)	0.95
Rejection	0.06	(0.00, 1.06)	0.06
Victimization	11.69	(1.57, 87.08)	0.02
Depression via PHQ-9	1.07	(0.92, 1.25)	0.40
Perceived stress	0.61	(0.10, 3.80)	0.60
PTSD	1.26	(0.54, 2.96)	0.59
Alcohol misuse	0.94	(0.21, 4.24)	0.93
Drug misuse	0.74	(0.42, 1.31)	0.30
Coping skills	0.56	(0.32, 1.00)	0.05
Age	0.81	(0.49, 1.32)	0.39
Being trans female	1.27	(0.27, 6.06)	0.77
Being Hispanic only	2.91	(0.32, 26.79)	0.35
Being non-Hispanic Black	9.49	(0.59, 152.77)	0.11
Being non-Hispanic White	1.32	(0.15, 11.67)	0.80
Having at least some technical or college training	0.29	(0.05, 1.75)	0.18
Being enrolled at one of the academic clinics	0.07	(0.01, 0.56)	0.01
Being in stable relationship	0.04	(0.00, 0.51)	0.01
Taking PrEP at enrollment	0.00	(0.00, 0.00)	0.00
Monthly income	0.66	(0.40, 1.10)	0.11
<i>Effects on being high–low vs. high–high</i>			
Discrimination	0.76	(0.36, 1.63)	0.49
Rejection	0.45	(0.14, 1.48)	0.19
Victimization	1.92	(0.75, 4.94)	0.18
Depression via PHQ-9	0.93	(0.82, 1.04)	0.20
Perceived stress	0.82	(0.22, 3.15)	0.78
PTSD	2.13	(1.17, 3.89)	0.01
Alcohol misuse	1.12	(0.37, 3.40)	0.84
Drug misuse	0.74	(0.52, 1.05)	0.09
Coping skills	0.75	(0.52, 1.08)	0.12
Age	0.80	(0.54, 1.20)	0.28
Being trans female	1.34	(0.49, 3.68)	0.57
Being Hispanic only	0.30	(0.06, 1.43)	0.13
Being non-Hispanic black	0.81	(0.08, 8.75)	0.87
Being non-Hispanic white	0.47	(0.15, 1.50)	0.20
Having at least some technical or college training	0.66	(0.11, 3.91)	0.64
Being enrolled at one of the clinical sites	0.34	(0.10, 1.13)	0.08
Being in stable relationship	0.66	(0.14, 3.20)	0.60
Taking PrEP at enrollment	1.78	(0.30, 10.75)	0.53
Monthly income	0.82	(0.62, 1.08)	0.15

comparison of the victimization factor scores by PrEP adherence groups. Higher levels of coping skills were marginally associated with PrEP uptake and persistence among participants (i.e., those that reported having less coping skills were more likely to be in the low–low group than the high–high group [$\beta = -0.57$ $p < 0.05$; OR 0.56, 95% CI (0.32, 1)]).

See Fig. 2 for mean coping score comparison between the groups.

Significant effects were observed among the participant's profiles in predicting the probability of being low–low vs. high–high, including having been enrolled at one of the three academic clinical sites [$\beta = -2.62$, $p < 0.05$; OR 0.07, 95% CI (0.01, 0.56)], being in a stable relationship [$\beta = -3.16$, $p < 0.05$; OR 0.04, 95% CI (0.00, 0.51)] and a strong effect of for those who were taking

Fig. 1 Side-by-side boxplot comparison of estimated violence victimization factor scores between PrEP persistence patterns of low–low ($n = 35$) vs. high–low ($n = 83$) vs. high–high ($n = 50$). *Note* Difference between low–low and high–high is significant, $p < 0.05$. For the box plots, the boxes represent the interquartile range, or the middle half of the values in each group. The middle line is the median. The cross is the mean. The whiskers show the range. The dot is the outlier

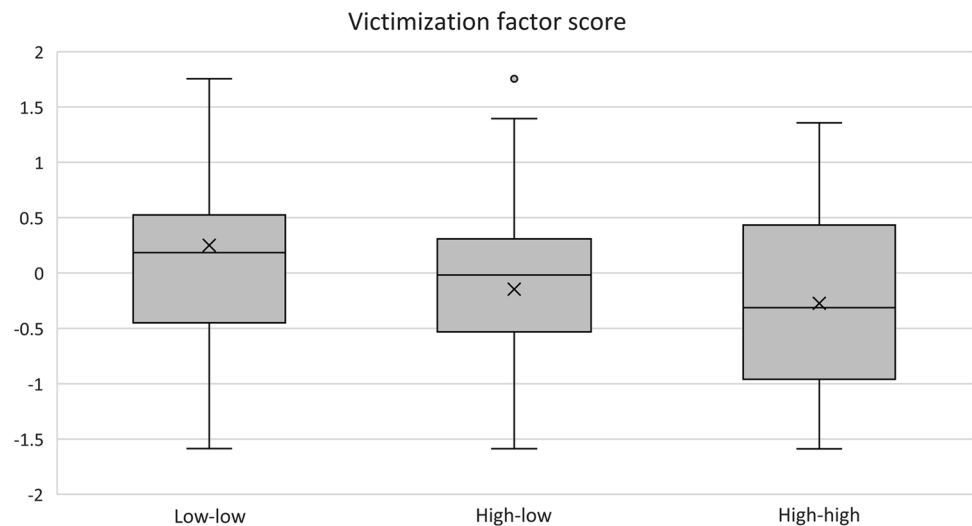
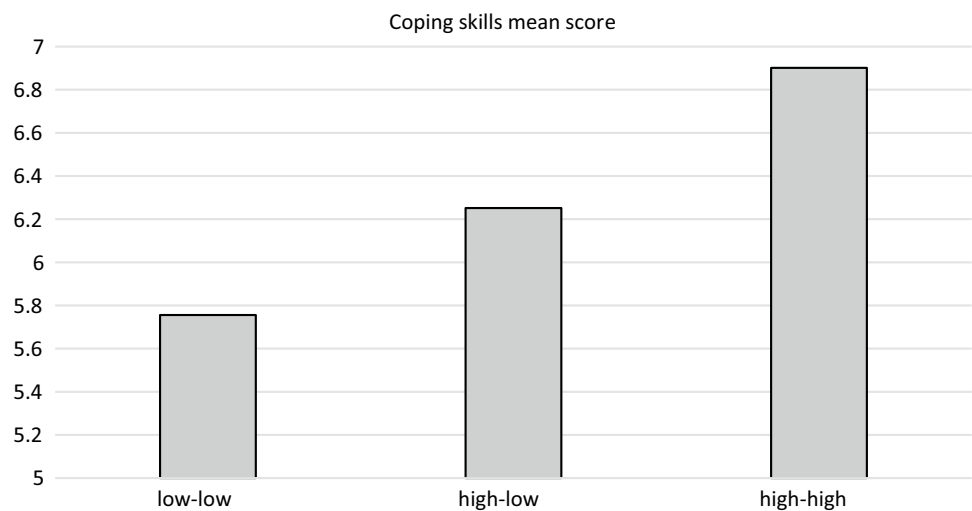


Fig. 2 Comparison of coping skills mean scores between PrEP persistence patterns of low–low ($n = 35$) vs. high–low ($n = 81$) vs. high–high ($n = 50$). *Note* Difference between low–low and high–high is significant, $p < 0.05$



PrEP prior to study enrollment [$\beta = -9.44$, $p < 0.05$; OR 0.00, 95% CI (0.00, 0.00)]. These effects are negative in beta estimates for predicting non-adoption, hence serving as protective factors for PrEP persistence.

High–Low vs. High–High

Consistent with our second hypothesis that PTSD symptoms would also be associated with lower rates of PrEP uptake and persistence, there was a significant association between reported PTSD symptoms and failure to persist on PrEP when comparing high–low with high–high (see bottom panel of Table 2). Those that reported more PTSD symptoms were more likely to be high–low [$\beta = 0.76$, $p < 0.05$; OR 2.13, 95% CI (1.17, 3.89)] than they were to be high–high. Figure 3 shows a mean score comparison of PTSD levels by PrEP adherence groups.

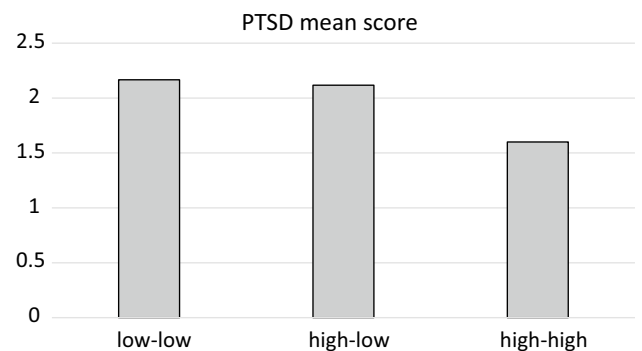


Fig. 3 Comparison of PTSD mean scores between PrEP persistence patterns of low–low ($n = 33$) vs. high–low ($n = 81$) vs. high–high ($n = 50$). *Note* Difference between high–low and high–high is significant, $p < 0.05$

Coping Skills as Moderator

Given significant main effects for both GBV and coping skills in predicting the probability of being low–low vs. high–high, we also tested for the possible interaction effects of each minority stress construct (i.e., discrimination, rejection and victimization) with coping skills as we previously hypothesized that coping skills would moderate the effect on the impact of minority stressors on PrEP uptake and persistence. However, the interactions were not found to be significant, and they were removed from final models as a result.

Discussion

The current study sought to assess the impact of specific gender-related minority stressors including GBV and PTSD symptoms on PrEP uptake and persistence among TGNB persons in a first-of-its-kind PrEP demonstration project. We found that experiences of GBV significantly predicted failure to adopt PrEP. We also found that self-reported PTSD symptoms were significantly associated with PrEP discontinuation. Consistent with the theory of syndemics, the experience of GBV and PTSD symptoms have been previously linked with HIV risk and seroconversion among TGNB [2, 10, 13], and to antiretroviral treatment failure among transgender women living with HIV [50]. However, to our knowledge, this is the first prospective study of the impact of GBV and PTSD on preventive behaviors such as PrEP use among TGNB.

It is widely understood that discrimination and violence enacted against TGNB people based on their gender minority status has detrimental impacts on the health of TGNB people and their communities. What has been less understood historically is how experiences of GBV can impact engagement in preventative healthcare such as the PrEP care continuum [76]. The current findings suggest that TGNB who report GBV at baseline may be less likely to achieve protective levels of PrEP and thus may require tailored approaches to maximize the likelihood of continued PrEP adherence after initial uptake. Given the alarmingly high rates of violence enacted against TGNB persons, this finding may help to explain the disproportionately lower rates of PrEP adoption among certain TGNB persons (e.g., transgender women of color).

The current findings also suggest that PTSD symptoms may serve as a significant barrier to continued engagement in HIV prevention programs and may be predictive of early PrEP discontinuation among some TGNB persons. Given the disproportionately high rates of violence enacted against TGNB persons [2, 3], it is likely rates of PTSD are elevated as well. Failure to enact laws and policies that recognize and protect TGNB people from discrimination in housing,

educational settings, employment, and in health care has enabled the proliferation of ongoing stigma, discrimination, and violence, potentially resulting in higher rates of PTSD [2]. Moreover, PTSD symptoms may also arise when TGNB are targeted and harassed by police under laws related to immigration status, substance use, and sex work [13]. TGNB people can be jailed or imprisoned in housing that is incongruent with their gender identity and where they may be subjected to additional violence, potentially contributing to elevated rates of PTSD [1]. These traumatic interactions with criminal justice systems have harmful effects on TGNB persons' overall health and wellbeing including HIV risk [2].

Consistent with syndemics and minority stress theories [5–7, 10, 13–15], the current study suggests that GBV and PTSD may have downstream effects that extend beyond instances of violence and trauma. The current data suggest that these structural experiences can also impact a person's engagement in individual-level health promotion behaviors, such as adopting and remaining adherent to PrEP to prevent HIV. It is possible that experiences of GBV and the presence of PTSD symptoms may decrease levels of agency, self-efficacy, and may serve to disempower TGNB persons from engaging in preventative healthcare. For example, TGNB persons who have experienced GBV, discrimination, or harassment in their communities, healthcare settings, or on public transportation might be less likely to attend PrEP visits for fear of further victimization, or to avoid re-experiencing disturbing memories that are triggered in these settings [77–80]. GBV enacted by partners may also stand as a direct barrier to accessing care including PrEP use among some TGNB individuals. Finally, consistent with Fundamental Causes Theory [81], TGNB persons who exist at the intersection of multiple minoritized and socioeconomically marginalized identities may experience higher levels of GBV, racism, and stigma, and may also be less likely to access health services including PrEP for largely economic reasons [82–85]. Uncovering the direct and indirect pathways by which GBV and PTSD symptoms impact PrEP use warrants further investigation in future research.

Future work is needed to assess both the additive impact of GBV on PrEP use and differences that may be observed based on the specific type of GBV experienced. For example, it is possible that being verbally harassed may have a different effect than being threatened with physical harm or being physically assaulted. It is also interesting to note that GBV predicted lack of uptake but not failure to persist on PrEP, while PTSD symptoms predicted failure to persist but not lack of uptake of PrEP. This may be due to the measurement of current (i.e., last month) PTSD symptoms versus experiences of GBV that may have occurred further in the past (e.g., prior to age 18). Additional studies are warranted to better understand the temporality of mechanisms by which the experience of violence and resultant psychological

burdens result in the underutilization of PrEP. Further, future research should examine interactions between GBV, mental health burdens, and other syndemic conditions, to provide further evidence for the impact of syndemic production on HIV risk among TGNB individuals [86].

Importantly, both coping skills and stable relationships were found to be related to PrEP uptake and persistence among these TGNB participants. This finding is consistent with the burgeoning literature demonstrating the important role of fostering resilience and strengthening social support to maximize the effectiveness of future HIV prevention interventions [87]. Future PrEP interventions for TGNB should consider adding behavioral content that bolsters coping skills and strengthens social support for PrEP as these appear to be promising targets for increasing uptake and persistence on PrEP among TGNB persons. However, it is important to note that these interventions must be delivered within gender-affirming healthcare and prevention services settings in order to be maximally effective at bolstering PrEP engagement among TGNB persons [4, 88, 89].

Implications for future interventions should address the need for multi-component interventions that address GBV, PTSD and PrEP. For example, training for PrEP providers who work with TGNB persons should extend beyond culturally appropriate, gender-affirming PrEP care, to trauma-informed care that includes appropriate and gender-sensitive assessment of trauma and referral to gender affirming mental health services. Further, key stakeholders and HIV care funders need to prioritize multilevel structural interventions that situate mental health, HIV, and other social/structural services (e.g. safe housing, legal services) together for TGNB persons as these data suggest that violence prevention may be a critical component for effective HIV prevention.

Several limitations should be considered when interpreting these findings. First, this study was conducted as an exploratory secondary analysis of data collected during a prior PrEP demonstrations project, as such we were limited by the available data and variables and therefore a greater understanding of the mechanisms by which GBV and PTSD symptoms impact PrEP use remains warranted. Second, given the significant difference in PrEP uptake and persistence found among participants who were enrolled at the academic medical sites as compared to those enrolled at the community sites, possible differences in the characteristics of TGNB participants attending visits in these settings (e.g., economic hardship, health literacy, etc.), as well as possible site level differences (e.g., clinic location, competing demands on clinic staff, etc.), should be explored in future studies with TGNB persons. Third, the limited sample size, missing data, and study attrition restricted measurement of certain study variables. As a result, we were not able to assess TFV-DP levels across all time points for those who terminated the study early. Finally, since only two items

were used from the PTSD measure to reduce respondent burden from overly long assessments, future studies should use the validated full scales to assess the association of PTSD symptoms with PrEP use among TGNB persons. With a larger sample, collecting repeated DBS measures while accounting for the reasons for study attrition, future studies will be able to capture behavior change better with more advanced modeling techniques (e.g., time-series analysis or latent growth models) to look at trajectories of persistence, and to assess for subgroup differences between those who identify as transfeminine, as transmasculine, and as non-binary individuals.

Despite these limitations, GBV enacted against TGNB persons is a prevalent health and human rights problem. The staggering rates of GBV TGNB people experience stem from the social structures and systems that tolerate and even endorse anti-trans positions and continue to stigmatize and marginalize trans people [2]. Future GBV research, advocacy, and interventions need to include TGNB persons as a central focus to bring about the structural-level changes needed to keep TGNB persons safe and healthy [2]. While some progress has been made towards legal recognition of TGNB identities, specifically in regard to employment, housing, and changing name and gender on legal documents [90], these gains have come slowly and with numerous setbacks which continuously reinforce the structural oppression that fuels the disproportionate violence observed among TGNB persons. While efforts are underway to ban the “trans panic” defense that has been used in cases of violence and murder of TGNB persons [90], further structural change is needed to protect and prevent violence against TGNB persons. Many members of the TGNB community navigate their lives in a constant state of vigilance for their own safety. Living in constant threat of violence has rippling effects for both the mental and the physical health of TGNB people. In order to improve overall trans health and wellness, systems and structures must be confronted and held accountable for both the inequities observed, and for improving the overall health, safety, and protecting the wellbeing of the TGNB community.

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Declarations

Conflict of interest All authors declare that no conflicts of interest to declare that are relevant to the content of this article.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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