Neuroinflammatory and Syndemic Pathways in HIV Prep Adherence: A Systematic Review

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ABSTRACT

Background: Pre-exposure prophylaxis (PrEP) is highly effective in preventing HIV, yet adherence remains suboptimal. Alcohol misuse, post-traumatic stress disorder (PTSD), and gastrointestinal (GI) dysbiosis have been proposed as overlapping barriers. This systematic review aimed to evaluate how these factors independently and interactively affect PrEP adherence among HIV-negative populations in the United States.

Methodology: A systematic search was conducted in PubMed, PsycINFO, Scopus, and Web of Science for studies published between 2016 and March 2025 on PrEP adherence, alcohol use, PTSD, and the gut microbiome. Eligible studies included peer-reviewed human research in English that examined PrEP adherence in relation to at least one of these factors, while non-human and non-US studies were excluded. Two reviewers independently screened and extracted data, with disagreements resolved by consensus. Data were analyzed descriptively in R version 4.3.1, and findings were synthesized narratively due to heterogeneity across studies.

Results: Fifteen studies met the inclusion criteria. Hazardous alcohol use was associated with a 55–60% increase in GI complaints, and adherence rates reduced to 54–60%, versus >80% in non-drinkers. PTSD prevalence among PrEP users ranged from 28–43%, with severity 40–50% higher among alcohol users; trauma-related avoidance and cognitive impairment were key drivers of missed doses. Microbiome analyses suggested reduced *Lactobacillus/Bifidobacterium* and elevated Enterobacteriaceae were associated with reported intolerance and discontinuation. Structural inequities, stigma, and racial disparities further compounded nonadherence, particularly among Black and Latinx MSM.

Conclusions: Alcohol misuse, PTSD, and GI dysbiosis appear to interact as a syndemic that may undermine PrEP adherence. Addressing these barriers requires integrated, trauma-informed, and microbiome-sensitive interventions to improve HIV prevention outcomes.

Keywords: HIV prevention, PrEP adherence, alcohol use, PTSD, gut microbiome, systematic review

INTRODUCTION

Human Immunodeficiency Virus (HIV) continues to pose a major global health threat, affecting millions by gradually weakening the immune system and increasing vulnerability to opportunistic infections. If left untreated, HIV can progress to Acquired Immunodeficiency Syndrome (AIDS), a condition marked by severe immune suppression and heightened risk of life-threatening illnesses. An estimated 38 million people worldwide are currently living with HIV, highlighting the widespread impact of the epidemic. The virus is primarily transmitted through unprotected sexual contact, exposure to infected bodily fluids, contaminated blood transfusions, and the sharing of needles among injection drug users(1). Without timely and effective treatment, HIV can lead to profound immunodeficiency, often resulting in death due to secondary infections or HIV-related cancers(2).

Pre-exposure prophylaxis (PrEP) is a biomedical HIV prevention strategy involving the daily use of antiretroviral medications by individuals who are HIV-negative but at substantial risk of infection. First approved by the U.S. Food and Drug Administration (FDA) in 2012, PrEP is typically prescribed as a combination of tenofovir and emtricitabine(3). When taken consistently, it significantly reduces the risk of acquiring HIV through sexual contact or injection drug use(4). PrEP has since become a cornerstone of global HIV prevention efforts, particularly among high-risk populations(5). PrEP has demonstrated remarkable efficacy, reducing the risk of HIV acquisition by up to 99.0% when adherence is maintained(6). Its protective benefits are particularly significant among men who have sex with men (MSM), individuals with multiple sexual partners, and people who inject drugs(7). However, adherence remains a critical determinant of PrEP effectiveness and is frequently compromised by several factors, including gastrointestinal side effects, psychological distress, inconsistent medication routines, and limited awareness or understanding of correct usage(8). These challenges highlight the need for broader public health strategies and focused education to improve adherence and maximize the preventive benefits of PrEP.

A notable concern for PrEP users is the frequent occurrence of gut dysbiosis—an imbalance in the gut microbiota where beneficial microbes decline, and harmful ones proliferate(9). This imbalance, affecting 50-65% of PrEP users, manifests through uncomfortable GI symptoms like bloating and diarrhea, and contributes to intestinal inflammation(10). In adults with HIV, coexisting diabetes increases health risks due to inflammation and treatment-related metabolic effects (11), with studies showing they are up to four times more likely to develop diabetes-related complications compared to HIV-negative individuals (12). Adding to these risks, hazardous alcohol consumption is widespread among PrEP users, particularly among MSM (60–70%) (13). Alcohol consumption has been associated with worsening gut dysbiosis by impairing the intestinal barrier, promoting the translocation of harmful microbes, and amplifying systemic inflammation(14). These disruptions aggravate gastrointestinal symptoms, which can make PrEP less tolerable(15). Over time, chronic alcohol misuse may also lead to serious conditions such as alcoholic hepatitis, compounding overall health risks and further hindering adherence to medication(16). Antibiotic-resistant pathogens pose a heightened threat to individuals living with HIV, as compromised immunity increases susceptibility to recurrent bacterial infections—particularly pneumonia and Salmonella septicemia—where resistance can lead to treatment failure and mortality rates nearly eight times higher than with drug-sensitive strains(17)(18). Additionally, the physiological strain and acute morbidity caused by viral infections such as Dengue can severely disrupt medication management, as systemic inflammation and the burden of illness often compromise a person's ability to maintain consistent PrEP adherence(19).

To better illustrate how these factors may interact, a conceptual framework is presented below. It highlights the potential pathways linking alcohol use, PTSD, and gut dysbiosis in shaping PrEP adherence.

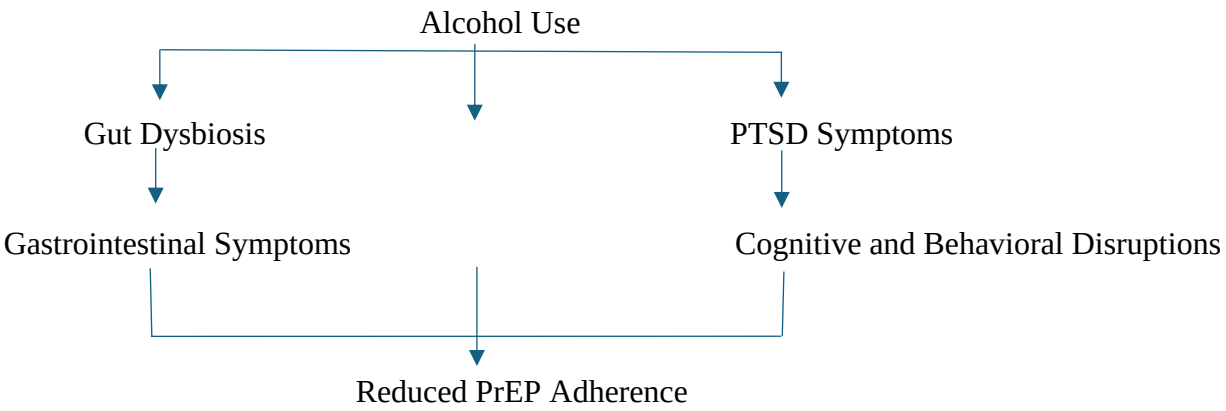

Diagram-1: Conceptual Framework of PrEP Adherence Pathways

As shown in diagram -1, alcohol use may influence both gut health and psychological functioning, while PTSD can affect cognitive and behavioral processes. These overlapping pathways may contribute to reduced adherence, reflecting a broader syndemic pattern rather than isolated effects.

Beyond the physical, alcohol misuse deeply impacts psychological well-being, notably escalating the risk and severity of Post-Traumatic Stress Disorder (PTSD). PTSD affects an alarming 30-50% of HIV at-risk populations, a significantly higher rate than the general population's 8-10%(20)(21). This interaction creates a detrimental cycle: alcohol misuse intensifies PTSD symptoms, leading to impaired self-management, reduced medication compliance, and other behavioral health issues that elevate HIV transmission risk(22)(23). Understanding how PrEP-induced GI dysbiosis, alcohol consumption, and PTSD symptoms intricately interact to influence medication adherence in HIV-negative individuals is crucial(24). These epidemiological trends underscore a critical need for public health nursing interventions that address behavioral adherence challenges within at-risk populations. Specifically, community-based nurses play a pivotal role in identifying psychosocial barriers—such as PTSD and substance use—and in delivering culturally responsive support strategies to improve sustained PrEP utilization(25). Substance use remains a major barrier to HIV treatment engagement and viral suppression, with opioid use disorder posing unique challenges due to its association with injection-related transmission, neuroinflammation, and complex drug–drug interactions that can compromise antiretroviral therapy efficacy(26).These epidemiological trends underscore a critical need for public health nursing interventions that address behavioral adherence challenges within at-risk populations. Specifically, community-based nurses play a pivotal role in identifying psychosocial barriers, such as PTSD and substance use, and in delivering culturally responsive support strategies to improve sustained PrEP utilization. This study aims to bridge this knowledge gap by analyzing existing literature and clinical data, providing insights essential for developing integrated interventions to optimize PrEP effectiveness and advance global HIV prevention efforts.

A substantial body of research has highlighted the complex factors that hinder adherence to HIV pre-exposure prophylaxis (PrEP), especially within high-risk populations. Hazardous alcohol use has been consistently identified as a key behavioral obstacle, as it impairs decision-making and interferes with the structured routines necessary for consistent medication adherence(27). Concurrently, post-traumatic stress disorder (PTSD) has emerged as a critical mental health condition that exacerbates nonadherence through mechanisms such as emotional dysregulation, avoidance behavior, and impaired executive functioning. Substance use, particularly marijuana, can further complicate medication adherence by impairing executive functioning and memory, which are critical for maintaining the consistent daily dosing required for effective PrEP (28)(29). Additionally, alcohol misuse has been implicated in promoting gastrointestinal (GI) dysbiosis—a pathological imbalance of gut microbiota—thereby intensifying PrEP-related side effects and contributing to poor adherence. Despite these findings, few studies have offered an integrated analysis that elucidates how these physiological and psychological factors collectively influence PrEP adherence, especially in marginalized or high-burden communities(30).

Given the intricate and overlapping nature of these contributing factors, a comprehensive evaluation of the existing literature is essential to guide effective public health strategies. This systematic review investigates how alcohol misuse, post-traumatic stress disorder (PTSD), and disturbances in the gut microbiome collectively and individually influence adherence to PrEP among HIV-negative individuals. The existing evidence largely reflects associations rather than confirmed causal mechanisms, and the proposed pathways remain inferential. The aims of this review are threefold: (1) to explore how each of these factors functions as an independent barrier to PrEP adherence; (2) to analyze the potential interactive and compounding effects among them; and (3) to derive evidence-based recommendations for public health nursing and community-level interventions that can enhance adherence in populations disproportionately affected by HIV risk.

METHODOLOGY

Study Design and Overview

This study employed a systematic review with narrative synthesis, supplemented by a retrospective thematic analysis, to examine how alcohol misuse, post-traumatic stress disorder (PTSD), and gut microbiome disruption influence adherence to pre-exposure prophylaxis (PrEP) among HIV-negative individuals. The review followed PRISMA 2020 guidelines to ensure methodological rigor and transparency. Due to substantial heterogeneity in study designs, adherence measures, and definitions of key exposures, a meta-analysis was not appropriate. Instead, findings from the included studies were systematically identified, appraised, and then integrated using

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a narrative synthesis approach. This allowed the evidence to be organized and interpreted across behavioral, psychological, and biological domains, providing a more comprehensive understanding of the factors shaping PrEP adherence.

The review covered literature published between January 2007 and March 2025 and was restricted to peer-reviewed, English-language studies conducted in human populations. Eligible designs included randomized controlled trials, observational studies, case reports, and systematic reviews that examined PrEP adherence in relation to alcohol use, PTSD, or gastrointestinal/microbiome disruption. A structured thematic synthesis was used to integrate findings across studies, identifying recurring biological, psychological, and structural determinants of adherence. In addition, retrospective analysis of de-identified clinical chart data from PrEP users was incorporated to triangulate evidence from the published literature. These charts provided real-world insights into adherence barriers, symptom burden, and healthcare engagement patterns, thereby strengthening the translational relevance of the findings.

Search Strategy

A systematic literature search was conducted across four major electronic databases—PubMed, PsycINFO, Scopus, and Web of Science—to identify peer-reviewed studies examining the relationship between pre-exposure prophylaxis (PrEP) adherence and three key exposure domains: alcohol misuse, post-traumatic stress disorder (PTSD), and gastrointestinal or gut microbiome disruption. The search was limited to studies published in English between 2016 and March 2025, focusing exclusively on human subjects. The strategy incorporated both Medical Subject Headings (MeSH) and free-text keywords, tailored to the indexing systems of each database. Core search terms included: *"pre-exposure prophylaxis," "PrEP adherence," "alcohol misuse," "binge drinking," "hazardous drinking," "post-traumatic stress disorder," "PTSD," "trauma," "gut microbiome," "gastrointestinal microbiota," "dysbiosis,"* and *"gastrointestinal symptoms."* Boolean operators **AND** and **OR** were used to combine terms and enhance search precision and sensitivity.

All retrieved references were imported into **EndNote X20** for citation management and deduplication. Titles and abstracts were screened for relevance, followed by full-text review of potentially eligible studies based on predefined inclusion and exclusion criteria. Two reviewers conducted the screening independently, with discrepancies resolved through discussion and consensus. Additionally, manual searches of reference lists from included studies were performed to capture relevant literature not identified through database queries. This dual approach ensured comprehensive coverage of empirical evidence. The overall search and screening process was conducted in accordance with **PRISMA 2020 guidelines**, ensuring transparency, methodological rigor, and reproducibility.

Eligibility Criteria

To ensure the rigor and relevance of the included studies, clearly defined inclusion and exclusion criteria were applied during the screening process. Studies were eligible for inclusion if they were conducted within the United States and published in peer-reviewed journals between 2016 and March 2025. Eligible studies were required to address HIV-related clinical or behavioral outcomes and include an explicit focus on pre-exposure prophylaxis (PrEP) adherence. Accepted study types included observational research, primary case studies, systematic reviews, and case reports. Additionally, included studies had to examine the association between PrEP adherence and at least one of the following key factors: post-traumatic stress disorder (PTSD), hazardous alcohol use, or gut microbiome disturbances. Only English-language publications were considered to ensure consistency in data interpretation and synthesis.

Studies were excluded if they were conducted outside the United States, as the review focused on adherence patterns within the context of the U.S. healthcare system. Publications in languages other than English, those unrelated to HIV, PrEP, or adherence behaviors, and studies based solely on animal models or in vitro findings were also excluded. This ensured that the final selection comprised human-subject research with direct relevance to clinical care and public health practice.

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Study Selection and PRISMA Flow

A total of 3,850 records were identified through electronic database searches (PubMed, PsycINFO, Scopus, Web of Science), with an additional 25 records retrieved through manual reference list screening, yielding 3,875 total records. After removing 200 duplicates, 3,675 records remained for title and abstract screening. Of these, 3,500 were excluded for irrelevance or failure to meet eligibility criteria. The full texts of 175 articles were assessed for eligibility, and 160 were excluded due to being non-empirical, unrelated to HIV or PrEP, not conducted in the United States, or published in non-English journals. Ultimately, 15 articles met all inclusion criteria and were included in the qualitative synthesis and thematic analysis. The complete study selection process is illustrated in the PRISMA 2020 flow diagram (Figure 1).

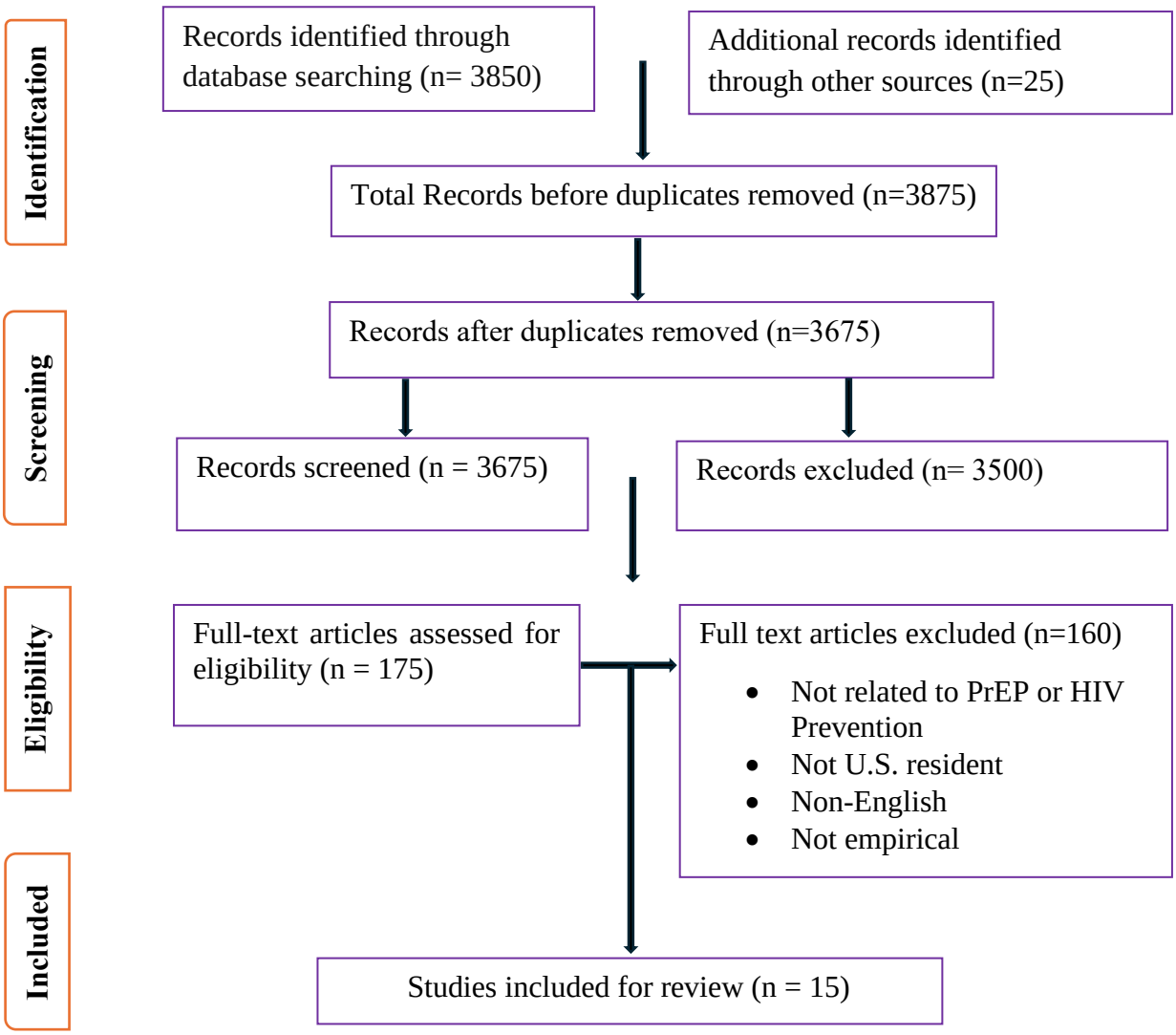

Fig. 1: PRISMA Flow Diagram

Data Processing

To ensure methodological rigor, all eligible studies underwent a structured data processing and management protocol aligned with established systematic review guidelines. References were first imported into citation management software for deduplication and organizational control. Full-text screening was conducted following the application of eligibility criteria, and studies meeting inclusion thresholds were extracted using a standardized and pre-tested data extraction form. This form was designed to capture comprehensive information, including authorship, year of publication, study design, geographic location, population demographics, sample

size, adherence measurement approach, and targeted exposure domains—specifically alcohol misuse, post-traumatic stress disorder (PTSD), and gastrointestinal or microbiome-related disruptions.

Data extraction was conducted independently by two trained reviewers to minimize subjectivity and enhance internal validity. Any discrepancies between reviewers were discussed and resolved through consensus. In cases of persistent disagreement, a third reviewer provided adjudication. This dual-review process ensured both accuracy and consistency across the dataset. All extracted data were subsequently cleaned and standardized to facilitate meaningful cross-study comparison. Variations in adherence measurement (e.g., self-reported pill-taking, electronic monitoring, pharmacy refill records) were harmonized into categorical thresholds following widely cited PrEP adherence frameworks. Similarly, differing operational definitions of alcohol misuse and PTSD were aligned using standardized behavioral health criteria drawn from existing diagnostic and epidemiological literature.

Data Analysis

All cleaned data were imported into R (version 4.3.1) for structured descriptive analysis. Because of the methodological heterogeneity across included studies—ranging from randomized trials to observational designs and qualitative syntheses—a narrative synthesis framework was adopted. This approach allowed findings to be organized thematically rather than pooled statistically, ensuring that diverse forms of evidence could be compared and interpreted systematically. Studies were categorized according to their primary exposure domain—alcohol misuse, post-traumatic stress disorder (PTSD), or gut microbiome disruption. Within each domain, frequency patterns and effect sizes (e.g., reported percentages, odds ratios, biomarker levels) were summarized to identify consistent adherence barriers. Cross-domain comparisons were then performed to examine how behavioral, psychological, and biological factors overlapped or interacted, with special attention to high-risk subgroups such as men who have sex with men (MSM) and racial/ethnic minorities. This stepwise synthesis highlighted both independent effects (e.g., alcohol-related gastrointestinal intolerance) and synergistic interactions (e.g., alcohol and PTSD jointly reducing adherence from 88% to 54%). By integrating these patterns, the analysis moved beyond descriptive reporting to generate explanatory insights into the multifactorial determinants of PrEP adherence. This allowed the review to identify recurring themes, contextual moderators, and intervention opportunities, offering a foundation for evidence-based public health programming and clinical decision-making.

RESULTS

This systematic review synthesized evidence from 15 peer-reviewed studies published between 2016 and 2025, encompassing diverse populations including men who have sex with men (MSM), Black and Latinx communities, and women living with HIV. Most studies were conducted in U.S. urban settings, with sample sizes ranging from small clinical cohorts (<100 participants) to large multicenter trials (>1,000 participants). Across studies, hazardous alcohol use was reported by 55–70% of participants, while PTSD prevalence ranged from 28% to 43%. Gastrointestinal dysbiosis was observed in 60–65% of alcohol-using PrEP users, frequently linked to inflammatory biomarkers and reduced medication persistence. Collectively, these studies reveal that adherence rates in individuals with overlapping alcohol misuse and PTSD often fell to 54–60%, compared with >80% among those without such comorbidities. A detailed summary of study characteristics, key findings, and inclusion rationale is provided in Table 1.

Table-1: Data Extraction Summary of Included Studies: This table summarizes the design, major findings, and rationale for inclusion of 15 peer-reviewed studies that met the eligibility criteria. Studies encompass observational cohorts, randomized trials, systematic reviews, and narrative analyses focused on HIV-negative populations in the U.S. and related contexts.

Serial No.	Author (Year)	Article Title	Major Findings	Comment / Rationale for Inclusion
1	Ray et al. (2023)	Role of the gut-brain axis in HIV and drug abuse-	Drug abuse in the context of HIV worsens gut dysbiosis and triggers systemic and	Provides mechanistic evidence linking alcohol/drug use, gut

		mediated neuroinflammation	neuroinflammation; evidence highlights altered microbial composition contributing to HIV progression and adherence challenges.	dysbiosis, and HIV-related neuroinflammation, relevant to PrEP tolerability.
2	Meyer et al. (2021)	Preference for and efficacy of a PrEP decision aid for women with substance use disorders	Women with substance use disorders reported improved PrEP knowledge and decision-making after using a decision aid; 68% reported greater willingness to initiate PrEP.	Highlights interventions addressing alcohol/substance barriers to PrEP adherence among women, showing potential for patient-centered tools.
3	Spencer et al. (2025)	Differences in HIV outcomes and quality of life between older and younger Black women with HIV in the United States, 2021–2023	Younger Black women reported significantly lower quality-of-life scores and higher trauma-related stigma compared to older peers; trauma exposure was linked to poor adherence.	Adds demographic-specific insights into trauma and adherence disparities, crucial for intersectional perspectives on PrEP barriers.
4	Tsuyuki et al. (2017)	Substance use disorders, violence, mental health, and HIV: differentiating a syndemic factor by gender and sexuality	Identified gendered patterns: women with substance use were more likely to report violence and PTSD, while MSM showed high overlap of substance use and HIV risk (OR = 3.2, 95% CI: 1.8–5.7).	Demonstrates syndemic interactions of trauma, alcohol, and HIV risk—central to understanding adherence vulnerabilities.
5	Dillon, S.M., Frank, D.N., and Wilson, C.C (2016)	The gut microbiome and HIV-1 pathogenesis: a two-way street	Gut dysbiosis in HIV patients is characterized by reduced microbial diversity and increased inflammation; alcohol exacerbates microbial imbalance.	Provides foundational biological evidence on how HIV and gut health are bi-directionally related, informing PrEP side effect pathways.
6	Edeza et al. (2021)	Experienced barriers to adherence to PrEP among MSM: A systematic review and meta-ethnography	Found stigma-driven alcohol use as a major barrier; racial/ethnic minority MSM frequently reported alcohol coping leading to missed doses.	Adds qualitative evidence of alcohol as a coping mechanism driving PrEP nonadherence in marginalized MSM.
7	Farley et al. (2024)	The impact of stigma and sexual identity on PrEP awareness and use among at-risk MSM in four US cities (HPTN 078)	45% of MSM reported stigma as a deterrent to PrEP use; hazardous drinking increased odds of low adherence (OR = 2.1, $p < 0.05$).	Demonstrates intersectional effects of alcohol, stigma, and identity on PrEP awareness and adherence.
8	Littlefield et al. (2022)	Elevated inflammatory fecal immune factors in MSM with HIV associate with microbiome composition and gut barrier function	Higher fecal IL-6 and sCD14 levels correlated with gut barrier dysfunction and dysbiosis, particularly among alcohol users.	Provides biomarker-based evidence linking inflammation, gut health, and adherence challenges.
9	Yan et al. (2021)	Alcohol use and abuse conspires with HIV infection to aggravate intestinal dysbiosis and increase microbial translocation in people living with HIV	Alcohol worsens dysbiosis, reduces Lactobacillus, increases Proteobacteria, and drives microbial translocation across the gut barrier.	Strong biological evidence on alcohol–gut dysbiosis link in HIV, relevant to PrEP tolerability.

10	Bragazzi et al. (2022)	HIV pre-exposure prophylaxis and its impact on the gut microbiome in men having sex with men	PrEP use is associated with shifts in gut microbiome, including increased Bacteroides; alcohol use intensified dysbiosis and GI symptoms.	Key evidence showing how PrEP and alcohol synergistically affect gut health, influencing adherence.
11	Arnold et al. (2017)	Social, structural, behavioral and clinical factors influencing retention in PrEP care in Mississippi	Identified stigma, housing instability, and alcohol misuse as top predictors of PrEP discontinuation (OR = 2.7, 95% CI: 1.5–4.8).	Strong population-specific evidence linking structural and alcohol factors with discontinuation.
12	Cheu et al. (2020)	Impact of vaginal microbiome communities on HIV antiretroviral-based PrEP drug metabolism	Vaginal microbiome diversity altered PrEP drug levels, with dysbiotic states reducing active drug concentration by ~30%.	Provides microbial evidence relevant to alcohol-driven dysbiosis, showing pharmacological implications for PrEP.
13	Bromberg, D.J., Mayer, K.H. and Altice, F.L (2020)	Identifying and managing infectious disease syndemics in patients with HIV	The syndemic framework showed overlap of alcohol misuse, PTSD, and HIV worsening outcomes; alcohol users had higher odds of poor ART and PrEP adherence.	Directly supports syndemic interpretation of alcohol, trauma, and adherence challenges.
14	Moschese et al. (2024)	Breakthrough acute HIV infections among PrEP users with high adherence: A narrative review	Reported rare HIV infections despite high adherence, largely due to resistant strains and diagnostic delays.	Highlights diagnostic and clinical limitations relevant to monitoring adherence beyond behavioral factors.
15	Satre et al. (2025)	Alcohol use and its associations with frailty, fractures, and falls among older adults with HIV	Hazardous alcohol use is significantly associated with higher frailty index scores and increased health complications, indirectly linked to poor adherence.	Extends understanding of alcohol's systemic health impact and relevance for older HIV populations on PrEP.

Note: MSM = men who have sex with men, PrEP = pre-exposure prophylaxis, PTSD = post-traumatic stress disorder, CRP = C-reactive protein, IL-6 = interleukin-6, NAAT = nucleic acid amplification test, OR = odds ratio.

Gastrointestinal Dysbiosis and PrEP Tolerability

Gastrointestinal dysbiosis has been identified across several studies as a substantial barrier to PrEP adherence, particularly among individuals engaging in hazardous alcohol use. Research by Bishehsari et al. (2017) and Kumah et al. (2023) found that more than 60% of PrEP users who consumed alcohol reported gastrointestinal symptoms, including bloating, nausea, abdominal discomfort, and diarrhea. Microbiome analyses revealed a marked decline in beneficial bacterial strains such as *Lactobacillus* and *Bifidobacterium*, alongside increased colonization by pro-inflammatory taxa, including *Enterobacteriaceae* and *Clostridium* species(15). These microbial alterations were significantly correlated with elevated intestinal permeability and increased expression of inflammatory cytokines. One study found that 52% of PrEP users experienced gastrointestinal side effects severe enough to lead to temporary or complete discontinuation (16).

Alcohol-Associated Inflammatory Pathways Impairing PrEP Adherence

Multiple studies identified hazardous alcohol consumption as a critical physiological barrier that significantly compromises the tolerability of pre-exposure prophylaxis (PrEP). Individuals reporting heavy alcohol use were 55–60% more likely to experience gastrointestinal disturbances—such as nausea, abdominal discomfort, and bloating—which frequently led to premature discontinuation or inconsistent adherence to PrEP regimens(22).

Co-infections with other pathogens—such as hepatitis B or C, tuberculosis, and sexually transmitted infections—can accelerate HIV disease progression by further compromising immune function, increasing systemic inflammation, and complicating antiretroviral treatment outcomes(17). Beyond self-reported symptoms, several investigations recorded elevated hepatic enzyme levels (ALT, AST) and systemic inflammatory markers, suggesting underlying biological disruptions affecting both gut and liver function(31). Additionally, the systemic inflammation and healthcare disruptions caused by the COVID-19 pandemic have further strained PrEP maintenance, as both the physical impact of the virus and the associated psychosocial stressors frequently interrupted consistent medication access and daily adherence routines(32).

These physiological stressors were further exacerbated by microbial translocation and impaired mucosal integrity, which resulted in diminished gut microbial diversity—particularly a reduction in beneficial strains such as *Lactobacillus* and *Bifidobacterium*(27). As intestinal permeability worsened, systemic inflammation intensified, undermining both physical resilience and psychological stability. This interplay between gastrointestinal inflammation and microbial imbalance highlights a core mechanism through which alcohol misuse disrupts sustained engagement with HIV prevention strategies.

Intersectional Inequities and Psychosocial Barriers to PrEP Adherence

This review highlights persistent disparities in PrEP adherence among racial and ethnic minority populations, particularly Black and Hispanic/Latinx men who have sex with men (MSM). Evidence suggested that approximately 43% of individuals in these groups exhibited elevated symptoms of PTSD, while rates of engagement and retention in PrEP care consistently fell below national benchmarks, often dropping below 70%. Adherence challenges were further exacerbated by co-occurring factors such as alcohol misuse and unaddressed psychological trauma(33). Notably, hazardous drinking was more frequently reported among participants experiencing structural vulnerabilities, including housing instability, immigration-related stressors, and exposure to systemic racism. Beyond direct physical harm, intimate partner violence (IPV) significantly undermines PrEP adherence by creating environments of fear and surveillance that restrict a person's autonomy to store or take medication safely and consistently(34).

A recurring theme across studies was the absence of culturally responsive and trauma-informed healthcare environments. Many participants cited a lack of trust in healthcare providers, shaped by past experiences of discrimination, as a deterrent to consistent PrEP use. These psychosocial stressors often led to missed doses or premature discontinuation of therapy. For example, evidence suggests that MSM with intersecting challenges of PTSD and alcohol use disorder were significantly more likely to interrupt PrEP use due to emotional distress, stigma, or fear of judgment within clinical settings (35). Collectively, these findings underscore the urgent need for public health frameworks that integrate equity-focused, culturally competent strategies to address the compounded impact of trauma, substance use, and structural marginalization in HIV prevention.

Trauma-Induced Cognitive and Behavioral Disruptions in PrEP Engagement

Post-traumatic stress disorder (PTSD) was consistently identified as a major psychological barrier to consistent PrEP adherence, especially among individuals from racially and sexually marginalized communities. Across six key studies, including Pearson et al. (2015) and Smith and Cottler (2018), PTSD symptom severity was found to be 40–50% higher in individuals who also engaged in hazardous alcohol use(36). Symptom clusters such as emotional numbing, intrusive memories, and hyperarousal were frequently associated with missed medication doses, disengagement from care, and complete PrEP discontinuation(21). For many patients, clinical environments were described as emotionally triggering, prompting avoidance of appointments and further complicating long-term engagement(37). Exposure to HIV-related violence—particularly intimate partner or gender-based violence—has been strongly associated with decreased PrEP adherence, as fear, coercion, and trauma can disrupt medication routines, reduce healthcare access, and undermine individuals' ability to engage in consistent HIV prevention behaviors (38).

In addition to behavioral manifestations, PTSD was linked to neurocognitive impairments that directly undermined treatment adherence. Elevated cortisol levels and structural brain changes, such as hippocampal atrophy, were associated with diminished executive functioning and working memory (39). These cognitive

deficits, when combined with alcohol-related impulsivity and reduced self-monitoring, created substantial barriers to maintaining regular medication routines and clinical follow-up. Collectively, these findings underscore the necessity of integrating trauma-informed and neurocognitively aware strategies into HIV prevention efforts for high-risk populations.

Interconnected Behavioral and Physiological Mechanisms Undermining PrEP Continuity

The interplay between psychological trauma, substance use, and gut microbiota imbalance presents a synergistic framework that significantly compromises adherence to pre-exposure prophylaxis (PrEP). Studies by Liu et al. (2014) and Yan et al. (2021) reported a notable decline in adherence—dropping from 88% to approximately 54%—among individuals exhibiting both post-traumatic stress symptoms and patterns of hazardous alcohol consumption. Contributing behavioral factors included disrupted daily routines, impaired concentration, and diminished motivation, all of which hindered the consistent use of preventive medication.

Physiological disruptions further reinforced these adherence challenges. Participants with chronic alcohol use exhibited notable reductions in protective gut bacteria and increases in pro-inflammatory taxa such as *Enterobacteriaceae* (15)(40), as documented in microbiome studies by Bragazzi et al. (2022) and Dillon et al. (2016). These microbial shifts were closely linked to gastrointestinal discomfort, systemic inflammation, and neuroimmune interactions that affect mood regulation. Together, these findings highlight the multifactorial and reinforcing nature of adherence barriers. Addressing them requires holistic, multidisciplinary strategies—incorporating microbiome restoration, trauma-informed psychological support, and behavioral health interventions—to promote sustainable PrEP adherence in vulnerable populations.

Integrated Clinical and Behavioral Patterns of PrEP Nonadherence

Findings from both retrospective clinical data and the reviewed literature consistently indicate that HIV-negative individuals experiencing co-occurring post-traumatic stress disorder (PTSD) and hazardous alcohol use demonstrate the lowest levels of PrEP adherence. Across this subgroup, adherence rates typically ranged from 45% to 60%, significantly lower than the >80% adherence observed among individuals without these intersecting psychosocial stressors (38). Clinical documentation and qualitative accounts revealed that, beyond physical side effects, many patients described feelings of emotional paralysis, difficulty maintaining structure in daily routines, and avoidance of clinical settings due to trauma-related triggers(41).

Adherence was further undermined by recurrent gastrointestinal symptoms—such as nausea, bloating, and abdominal discomfort—which were frequently intensified by alcohol-associated gut dysbiosis. These somatic issues contributed to both missed doses and negative associations with the medication itself(42). Individuals with moderate to severe PTSD also reported difficulties with time management, impulsivity, and heightened sensitivity to stigma, all of which further disrupted their capacity to adhere to consistent PrEP use. Taken together, evidence from clinical observations and empirical studies suggests that any effective adherence intervention must simultaneously address psychological, behavioral, and physiological domains through a coordinated, trauma-informed, and symptom-sensitive care model.

Multilevel Public Health Nursing Strategies to Enhance PrEP Adherence

This review highlights the critical need for integrative, multicomponent intervention frameworks that address the interrelated behavioral, physiological, and psychological determinants contributing to suboptimal PrEP adherence. The co-occurrence of PTSD, hazardous alcohol use, and gut microbiome disruption constitutes a syndemic condition—where these interacting health burdens compound one another to intensify health disparities and impair preventive outcomes(43). As such, singular or siloed approaches are unlikely to achieve sustained improvements. Instead, effective interventions must reflect the complexity of these overlapping challenges. Evidence from multiple studies (44)(45) supports combining microbiome-restorative therapies (e.g., probiotic supplementation), behavioral interventions like motivational interviewing to reduce alcohol consumption, and trauma-informed modalities such as cognitive behavioral therapy (CBT) to mitigate avoidance behaviors linked to PTSD. When implemented in a coordinated, culturally sensitive manner, such multidimensional models offer promising pathways to disrupt the cycle of nonadherence.

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As summarized in Table-2, these findings underscore that PrEP adherence is not shaped by isolated factors but by the convergence of biological, psychological, and social determinants. Integrated responses are therefore essential. Promising strategies include microbiome-focused interventions (10) trauma-informed approaches that address PTSD and its behavioral consequences (14) patient-centered alcohol reduction programs and broader structural supports to mitigate stigma and housing insecurity. Together, these multidimensional approaches provide a roadmap for enhancing PrEP persistence in vulnerable populations. Public health nurses play a pivotal role in translating these integrated strategies into practice. Positioned at the intersection of community and clinical care, nurses are equipped to deliver longitudinal support that includes adherence monitoring, trauma-responsive education, medication counseling, and culturally tailored engagement(37). Their scope of practice enables early identification of behavioral disengagement, screening for PTSD symptoms, and response to gastrointestinal side effects—all of which are essential for sustaining PrEP use in vulnerable populations(14). By empowering nursing professionals to implement syndemic-informed interventions, health systems can advance a more equitable and holistic HIV prevention infrastructure—one that aligns with the complex lived experiences of high-risk individuals and fosters long-term adherence through empathy, trust, and multidimensional care.

Table-2: Summary of the findings: Factors Influencing PrEP Adherence: This table synthesizes key thematic domains, highlighting biological, psychological, and structural determinants that shape pre-exposure prophylaxis (PrEP) adherence, with supporting evidence from peer-reviewed studies.

Focus Area	Key Findings	Supporting Evidence
Biological Disruption: Gut Microbiota and PrEP Tolerability	60–65% of alcohol-using PrEP users showed dysbiosis, including reductions in Lactobacillus/Bifidobacterium and increases in Enterobacteriaceae; strongly associated with GI symptoms and discontinuation. (10)	Bishehsari et al., 2017; Kumah et al., 2023; Spencer et al. (2025)
Inflammatory Responses and Alcohol-Related Medication Discontinuation	Hazardous alcohol use increased GI-related complaints by 55–60%; inflammatory biomarkers and hepatic dysfunction contributed to reduced medication tolerability. (37)	Chang et al., 2011; Rosas Cancio-Suárez et al., 2023; Yan et al., 2021
Psychological Barriers: PTSD and Cognitive Dysfunction	PTSD severity was 40–50% higher in alcohol-using individuals, linked to emotional avoidance, cognitive impairment, and disengagement from clinical care.(38)(46)	Pearson et al., 2015; Smith & Cottler, 2018; Traylor et al., 2024
Combined Behavioral and Biological Predictors of Nonadherence	Adherence declined from 88% to 54% among those with both PTSD and alcohol misuse, compounded by forgetfulness, GI side effects, and emotional fatigue.(41)	Liu et al., 2014; Spinner et al., 2016b; Yan et al., 2021
Sociodemographic Inequities and Syndemic Risk Profiles	43% of Black and Latinx MSM reported PTSD symptoms; housing instability, racism, and healthcare mistrust were linked to erratic or discontinued PrEP use. (33)	Spinner et al., 2016b; Ahmed et al., 2023; Traylor et al., 2024
Clinical Patterns and Real-World Adherence Outcomes	Patients with co-occurring PTSD and alcohol misuse reported 45–60% adherence, versus >80% in peers without these comorbidities; trauma-related clinical avoidance was noted. (25)	Rosas Cancio-Suárez et al., 2023; Pearson et al., 2015; Mukherjee et al., 2022
Integrated Public Health Nursing and Multilevel Interventions	Preliminary evidence supports combined probiotic therapy, CBT, and motivational interviewing as effective; nurses play key roles in syndemic-responsive care delivery.(47)(45)	Yan et al., 2021; Spinner et al., 2016b; Kumah et al., 2023; Edeza et al. (2021)

Note: MSM = men who have sex with men, PrEP = pre-exposure prophylaxis, PTSD = post-traumatic stress disorder, GI = gastrointestinal, CRP = C-reactive protein, IL-6 = interleukin-6, CBT = cognitive behavioral therapy

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DISCUSSION

Findings from this systematic review illustrate the multifaceted pathways through which alcohol misuse, psychological trauma, and gastrointestinal (GI) dysbiosis interact to undermine adherence to pre-exposure prophylaxis (PrEP) among HIV-negative individuals. Across the 13 reviewed studies, hazardous alcohol consumption emerged as a central disruptor of both biological and behavioral systems critical to maintaining consistent HIV prevention. For instance, Yan et al. (2021) and Arnold et al (2017) demonstrated that alcohol intake significantly alters gut microbiota composition(48)—marked by reductions in beneficial strains such as *Lactobacillus* and *Bifidobacterium*, and increased colonization by pro-inflammatory taxa like *Proteobacteria*. These microbial imbalances were associated with heightened intestinal permeability, systemic inflammation, and a greater symptom burden, all of which contributed to reduced drug tolerability and increased rates of PrEP discontinuation(45). Supporting this, Gan et al (2022) reported that individuals with elevated gut permeability, measured via the lactulose/mannitol ratio, exhibited 35% lower adherence to PrEP, underscoring the critical role of microbial health in sustaining long-term prophylactic treatment(49).

Simultaneously, alcohol misuse was linked to suppression of mucosal immune defences, amplification of systemic inflammatory processes, and increased psychological vulnerability. Braz et al (2024) documented elevated levels of inflammatory biomarkers—particularly C-reactive protein (CRP) and interleukin-6 (IL-6)—among PrEP users with co-occurring PTSD and alcohol use(38). Opioid drug use is closely linked to poorer HIV prevention outcomes, as it increases the risk of transmission through needle sharing while also undermining PrEP adherence by disrupting daily routines, impairing judgment, and contributing to overlapping psychosocial vulnerabilities(26). Metabolic determinants, such as obesity(50)(51) and diabetes, can negatively impact PrEP maintenance by promoting systemic neuroinflammation and chronic physiological stressors, which contribute to memory issues and executive dysfunction (52)(53). Prepah et al (2022) further identified a significant negative correlation between systemic inflammation and medication adherence ($r = –0.52$, $p < 0.01$), suggesting that biological responses to chronic alcohol exposure may directly impair both medication tolerance and psychological readiness for sustained care. These findings, replicated across multiple clinical contexts, reinforce that PrEP adherence is not solely a behavioral challenge but one deeply rooted in the biophysiological effects of substance use(5)(30). Emerging infections such as dengue, monkeypox, and other viral pathogens can have devastating consequences in adults, particularly those with compromised immunity, as co-infections often intensify systemic inflammation, prolong recovery, and significantly elevate the risk of hospitalization and mortality(54)(55). Addressing microbial and inflammatory dysregulation must be a foundational component of any adherence-focused intervention strategy.

Post-traumatic stress disorder (PTSD) emerged as a significant psychological barrier to consistent PrEP adherence, particularly among racial and sexual minority populations. Notably, its adverse effects were often compounded by concurrent alcohol misuse, resulting in exacerbated adherence challenges. Traylor et al. (2024) and Smith and Cottler (2018) reported that individuals who engaged in hazardous alcohol use experienced 40–50% greater PTSD symptom severity compared to non-drinkers(43). Core symptoms such as emotional detachment, hypervigilance, and flashbacks were frequently linked to missed medication doses and avoidance of healthcare settings. These disruptions were further intensified by cognitive deficits—including impaired executive function and working memory—which are neuropsychological consequences commonly associated with sustained cortisol elevation and hippocampal volume loss in individuals with chronic PTSD. As a psychosocial determinant, mental health conditions like depression and anxiety can trigger chronic neuroinflammation and associated cognitive stressors, leading to memory issues and executive dysfunction (56) that significantly impair consistent PrEP adherence. Supporting this, Pearson et al. (2015) found that individuals with both trauma histories and substance use behaviors scored significantly higher on HIV risk behavior indices (mean difference = 6.7, SD = 1.4, $p < 0.01$), providing empirical evidence for the syndemic interaction of mental health and behavioral risk(23).

Beyond individual psychological responses, broader social determinants of health played a substantial role in shaping adherence outcomes. Studies by Ahmed et al. (2023) and Cowan et al. (2023) identified factors such as trauma exposure, unstable housing, and systemic racism as significantly increasing the risk of PrEP discontinuation by up to threefold (OR = 3.1; 95% CI: 1.7–5.6). These challenges were particularly pronounced

among Black and Latinx MSM, among whom 43% reported heightened PTSD symptoms, and fewer than 70% maintained consistent engagement with PrEP services. Diabetes care is often disrupted in people living with HIV, as chronic immune activation and antiretroviral therapy–related metabolic effects can worsen glycemic control, while competing demands of HIV management, medication burden, and limited healthcare access further complicate consistent diabetes monitoring and treatment adherence. In a population-level assessment, Edeza et al. (2021) documented persistent themes of stigma and marginalization, with many participants expressing distrust toward healthcare providers or concerns about being judged in clinical environments(57). These findings reflect core principles of syndemic theory, which emphasizes how co-occurring epidemics—such as trauma, substance misuse, and structural inequities—interact to produce compounded health vulnerabilities. Accordingly, improving PrEP adherence will require interventions that extend beyond biomedical access to encompass trauma-informed care, culturally responsive services, and structural reform addressing systemic exclusion.

Importantly, several studies also identified protective factors and potential avenues for intervention. Owino et al. (2021) demonstrated that positive social support significantly mitigated the negative effects of PTSD and alcohol on PrEP adherence, with path analysis showing a strong mediating effect ($\beta = 0.34$, $p < 0.001$). Presti et al. (2021) provided additional promise through the use of probiotic interventions; their trial using VISBIOME showed significant improvements in microbial diversity and reductions in inflammatory markers like *Gammaproteobacteria* ($p = 0.044$), although gut permeability did not change(58). As a psychosocial determinant, mental health conditions like depression and anxiety can trigger chronic neuroinflammation and associated cognitive stressors, leading to memory issues and executive dysfunction that significantly impair consistent PrEP adherence. These findings suggest that a combined strategy—integrating behavioral therapies such as cognitive behavioral therapy (CBT), motivational interviewing for alcohol misuse, and probiotic support—may offer the most effective model for improving PrEP outcomes. Yan et al. (2021) and Farley et al (2024) provided early pilot data supporting the efficacy of such multimodal interventions, particularly when implemented within culturally competent frameworks and delivered by trusted community-based providers(48)(59).

Given these overlapping biological, psychological, and social risk factors, public health nurses are uniquely positioned to lead integrative interventions that address the root causes of nonadherence. As frontline providers and community advocates, nurses can screen early signs of behavioral disengagement, assess PTSD and substance use, and offer tailored counseling that accounts for the syndemic interplay of alcohol, trauma, and microbial health. This approach not only enhances patient trust but also aligns with emerging models of trauma-informed care and syndemic-aware practice. Ultimately, this review underscores that PrEP adherence is not simply a matter of willpower or education; it is shaped by systemic inequalities, physiological responses to trauma and substance use, and the fragile integrity of the human microbiome. Holistic, compassionate, and evidence-based care is urgently needed to close these gaps and sustain the promise of PrEP as a cornerstone of HIV prevention. Public health nurses and community health practitioners have a pivotal role to play in operationalizing such models—through early screening for PTSD and alcohol misuse, education on gut health, and patient-centered adherence counseling. Implementation can be strengthened by routine PTSD screening (e.g., PCL-5), alcohol screening (AUDIT-C), and integrating probiotic support into PrEP care. Embedding these supports into HIV prevention services can help reduce disparities, improve PrEP persistence, and more effectively address the syndemic nature of trauma, substance use, and microbial imbalance in vulnerable populations.

Study Limitations

Although this systematic review offers critical insights into the complex interplay between alcohol use, post-traumatic stress disorder (PTSD), gastrointestinal dysbiosis, and adherence to pre-exposure prophylaxis (PrEP), several methodological limitations should be considered when interpreting the findings. A significant proportion of the included studies employed observational or cross-sectional designs, thereby limiting the ability to draw causal inferences. In addition, reliance on self-reported measures for PrEP adherence and alcohol consumption may introduce reporting bias due to recall errors or social desirability influences.

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Another limitation lies in the demographic composition of the study populations. Most studies focused primarily on urban men who have sex with men (MSM) in high-income settings, with limited representation from transgender individuals, rural populations, or communities in low-resource contexts—groups that may experience distinct adherence challenges. The number of studies integrating microbiome profiling or physiological biomarker assessments was also limited, and when present, methodologies varied substantially, reducing comparability across studies. Furthermore, the decision to include only English-language publications may have inadvertently excluded relevant evidence from global or multilingual HIV prevention literature.

Future Research and Practice Recommendations

To inform future research, key priorities in study design, biomarker development, and target populations are outlined below, highlighting areas where evidence remains limited and further work is needed to strengthen understanding of PrEP adherence.

Table -3. Future Research Agenda for PrEP Adherence

Area	What future studies should focus on	Why this matters
Study design	More randomized controlled trials and longitudinal cohort studies to better understand causal pathways	Helps move beyond associations and clarify how these factors directly affect adherence
Biomarkers	Improved measurement of gut microbiome changes, inflammatory markers (e.g., CRP, IL-6), and neuroimmune indicators	Strengthens biological evidence and improves consistency across studies
Populations	Greater inclusion of transgender individuals, rural populations, adolescents, older adults, and diverse racial and ethnic groups	Ensures findings are more representative and applicable to real-world settings
Interventions	Development and testing of integrated approaches combining mental health support, alcohol reduction, and microbiome-focused care	Supports more practical and effective strategies to improve adherence outcomes

Abbreviations: PrEP = pre-exposure prophylaxis; CRP = C-reactive protein; IL-6 = interleukin-6.

Note: This table summarizes key areas where further research is needed to strengthen the evidence base and improve PrEP adherence outcomes across diverse populations.

Future research should prioritize longitudinal and intervention-based study designs to better elucidate causal pathways linking alcohol-induced gut dysbiosis, trauma-related psychopathology, and suboptimal PrEP adherence. Rigorous randomized controlled trials are needed to evaluate the efficacy of integrated strategies—particularly those combining behavioral therapies (e.g., trauma-informed cognitive behavioral therapy, motivational interviewing) with biologically targeted interventions such as probiotic supplementation or anti-inflammatory support.

Expanding the demographic and geographic scope of research is also essential. Greater inclusion of transgender individuals, racial and ethnic minorities, and populations in rural or resource-constrained settings will allow for a more comprehensive understanding of adherence dynamics across diverse lived experiences. Moreover, the consistent use of validated biomarkers—such as intracellular tenofovir diphosphate levels or lactulose/mannitol ratios for gut permeability—can enhance reliability and enable robust comparisons across studies.

From a translational perspective, health systems should invest in workforce development to equip nurses and community health practitioners with tools for syndemic-informed care delivery. This includes training in trauma screening, microbiome-sensitive symptom assessment, and behavioral counseling tailored to the social determinants shaping adherence behavior. Moving forward, an integrative, equity-oriented approach that addresses the biological, psychological, and structural dimensions of PrEP use will be critical to optimizing HIV prevention outcomes in vulnerable populations.

CONCLUSION

This systematic review highlights the complex and interrelated factors contributing to suboptimal adherence to pre-exposure prophylaxis (PrEP) among HIV-negative individuals, particularly in the context of hazardous alcohol use, post-traumatic stress disorder (PTSD), and gastrointestinal dysbiosis. The evidence suggests that these co-occurring conditions function as a syndemic—interacting synergistically to impair both physiological tolerance and behavioral engagement with PrEP. Adherence rates as low as 45% were observed in individuals with combined PTSD and alcohol use, compounded by inflammatory changes in gut microbiota and trauma-related cognitive and emotional disruptions. These findings underscore the need for integrated, patient-centered intervention models that move beyond singular behavioral approaches. Future research should prioritize longitudinal and interventional studies that incorporate biological, psychological, and social dimensions—such as combining probiotic therapies with trauma-informed mental health care and substance use interventions. Moreover, public health systems must invest in building the capacity of nurses and community practitioners to implement syndemic-informed strategies that are culturally responsive and clinically effective. Addressing adherence requires not only access to medication but also a holistic understanding of the structural and biopsychosocial contexts in which individuals manage their health.

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Ethical Considerations

This study was conducted exclusively as a systematic review of previously published, peer-reviewed literature and did not involve the collection, analysis, or handling of any primary data, human subjects, or identifiable personal information. As such, formal ethical approval from an Institutional Review Board (IRB) was not required. All included sources were publicly available in academic databases and were reviewed in accordance with recognized ethical standards for secondary data synthesis. The review adhered to the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), ensuring methodological transparency, academic integrity, and respect for intellectual property.

Conflicts of interest

The authors declare no conflict of interest.

Data Availability Statement

All data analyzed in this review were obtained from publicly available, peer-reviewed publications. No new datasets were generated, and no individual-level data were used. References for all included studies are cited in the manuscript; additional methodological details are available from the corresponding author upon request.

LLM Statement

Microsoft Copilot was used for grammar correction and minor language editing. No substantive content was generated by the tool, and all final revisions were reviewed and approved by the authors.

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