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| RESEARCH ARTICLE

A Multilevel Perspective on PrEP Adherence in HIV Prevention: An Integrative Review Guided by the Socioecological Model

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| ABSTRACT

Pre-exposure prophylaxis (PrEP) remains one of the most effective strategies for preventing HIV infection, yet its success depends on sustained adherence. Evidence increasingly shows that adherence lapses are not purely behavioral but stem from interacting biological, psychological, and social factors. This review aimed to synthesize existing evidence on how hazardous alcohol use, post-traumatic stress disorder (PTSD), and gut microbiome dysbiosis interact as syndemic determinants of PrEP adherence, using the Socioecological Model (SEM) to interpret multilevel influences.An integrative review was conducted following Whittemore and Knafl's (2005) five-stage framework—problem identification, literature search, data evaluation, data analysis, and presentation. Systematic searches were performed in PubMed, PsycINFO, Scopus, and Web of Science for studies published between 2016 and March 2025. Inclusion criteria covered peer-reviewed, English-language human studies linking PrEP adherence with alcohol use, PTSD, or microbiome disruption. Two reviewers independently screened, extracted, and appraised data for methodological rigor and conceptual relevance. Findings were integrated thematically and interpreted across SEM levels.Fifteen studies met inclusion criteria. Hazardous drinking (55–70%) and PTSD (28–43%) were independently associated with reduced adherence, with combined exposure decreasing adherence from >80% to approximately 54–60%. Odds ratios for nonadherence ranged 1.8–3.2. Microbiome dysbiosis, particularly reduced *Lactobacillus* and elevated inflammatory markers, was linked to gastrointestinal intolerance and discontinuation. Six recurring themes reflected syndemic reinforcement across biological, psychological, and structural domains.Adherence to PrEP is shaped by interconnected mechanisms rather than isolated behaviors. Future longitudinal and mixed-methods studies should evaluate trauma-informed, microbiome-supportive, and nurse-led interventions, grounded in the Socioecological Model, to achieve sustainable and equitable HIV prevention.

| KEYWORDS

HIV prevention; PrEP adherence; socioecological model (SEM); alcohol misuse; post-traumatic stress disorder; gut microbiome; integrative review

| ARTICLE INFORMATION

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1. Introduction

HIV continues to represent one of the world's most persistent public health concerns, maintaining a heavy clinical and social burden despite decades of medical progress. When untreated, the infection advances to Acquired Immunodeficiency Syndrome (AIDS), a stage marked by severe immune dysfunction and vulnerability to opportunistic illness. Current global estimates indicate that more than 38 million people are living with HIV, underscoring both the enduring scale of the epidemic and the pressing need for comprehensive prevention and care strategies[1]. Transmission occurs primarily through unprotected sexual contact,

exposure to infected blood or bodily fluids, transfusion of contaminated blood products, and sharing of needles among individuals who inject drugs. Without timely diagnosis and effective antiretroviral therapy, HIV infection often leads to severe immune decline, secondary infections, and increased risk of HIV-related malignancies[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 underscore the need for comprehensive public health approaches and targeted educational interventions to optimize adherence and ensure PrEP's full preventive impact.

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]. Adults with diabetes who are living with HIV face compounded health risks, as HIV-related inflammation and certain antiretroviral therapies can accelerate insulin resistance and metabolic dysfunction[11], with studies showing they are up to four times more likely to develop diabetes-related complications compared to HIV-negative individuals [12]Compounding this, hazardous alcohol consumption is widespread among PrEP users, particularly MSM (60-70%) [13]. Alcohol consumption worsens 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[1718].

Beyond the physical, alcohol misuse profoundly impacts psychological well-being, notably escalating the risk and severity of Post-Traumatic Stress Disorder (PTSD), which affects an alarming 30-50% of HIV at-risk populations, a significantly higher rate than the general population's 8-10%[1920]. 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[2122]. Understanding how PrEP-induced GI dysbiosis, alcohol consumption, and PTSD symptoms intricately interact to influence medication adherence in HIV-negative individuals is crucial[23]. These epidemiological trends underscore a critical need for public health nursing interventions that address behavioral adherence challenges within at-risk populations[24]. 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. 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[28].

Although substantial progress has been made in documenting individual risk factors for pre-exposure prophylaxis (PrEP) nonadherence, much of the existing literature continues to examine alcohol use, post-traumatic stress disorder (PTSD), and gastrointestinal (GI) dysbiosis in isolation. This fragmented perspective limits our ability to understand how these conditions converge in daily life to create compounded barriers to HIV prevention. Few reviews have attempted to integrate biological mechanisms such as alcohol-induced dysbiosis, trauma-related neurocognitive disruptions, and structural inequities into a unified framework. As a result, the lived complexity of adherence—particularly among marginalized populations most affected by HIV risk—remains underexplored[29].

This integrative review was designed to clarify how biological, psychological, and structural determinants interact to shape adherence to pre-exposure prophylaxis (PrEP) among individuals at heightened risk for HIV. Drawing on the Socioecological Model (SEM) as a guiding theoretical framework, the review moves beyond traditional behavioral explanations of adherence to examine how hazardous alcohol use, post-traumatic stress disorder (PTSD), and gut microbiome dysbiosis operate together within a syndemic context. The aim is to integrate empirical, clinical, and conceptual evidence to build a multidimensional understanding of the mechanisms through which these overlapping factors influence medication persistence, treatment tolerability, and engagement in care.

Accordingly, this review is guided by the central research question:

> *"In what ways do alcohol misuse, post-traumatic stress disorder (PTSD), and gut microbiome dysbiosis interact as a syndemic experience to influence adherence to pre-exposure prophylaxis (PrEP), and what integrated insights can inform effective, multi-level intervention strategies?"*

By addressing this question, the review seeks to generate a comprehensive, theory-informed synthesis that bridges biological and psychosocial dimensions of adherence. The ultimate goal is to inform the design of trauma-responsive, microbiome-sensitive, and culturally grounded approaches that more accurately reflect the lived experiences of vulnerable populations and advance equitable HIV prevention efforts.

2. Methods

2.1 Study Design and Overview

This study employed the integrative review methodology proposed by Whittemore and Knafl (2005) to synthesize diverse forms of evidence—quantitative, qualitative, and theoretical—on how alcohol misuse, post-traumatic stress disorder (PTSD), and gut microbiome disruption influence adherence to pre-exposure prophylaxis (PrEP) among HIV-negative individuals. The method was selected for its ability to integrate heterogeneous data sources to form a comprehensive understanding of complex health behaviors[3031]. A systematic search was conducted across major scholarly databases to identify relevant peer-reviewed studies on PrEP adherence and its behavioral, psychological, and biological determinants. Studies were critically appraised for methodological rigor and conceptual relevance following the five stages of Whittemore and Knafl's framework: problem identification, literature search, data evaluation, data analysis, and presentation[32]. Given the heterogeneity of study designs and outcomes, a thematic integrative analysis was undertaken to identify and synthesize recurring patterns, relationships, and theoretical insights across randomized trials, observational studies, qualitative research, and conceptual papers[3334]. Additionally, retrospective analysis of de-identified clinical chart data from PrEP users was incorporated to contextualize literature findings within real-world adherence patterns and comorbidity profiles. This approach provided a holistic, multi-level understanding of how alcohol use, trauma exposure, and microbial disruption intersect to shape adherence behaviors and inform future HIV prevention strategies.

To guide the interpretation of findings across multiple domains, the Socioecological Model (SEM) was applied as an overarching theoretical framework. This model provided a structured lens for understanding how individual, interpersonal, community, organizational, and structural factors interact to shape PrEP adherence. By mapping evidence within these ecological levels, the review was able to link biological mechanisms, psychological processes, and social contexts in a coherent, multi-level synthesis.

Given the heterogeneity of study designs and outcomes, a thematic integrative analysis was undertaken to identify and synthesize recurring patterns, relationships, and theoretical insights across randomized trials, observational studies, qualitative research, and conceptual papers. Additionally, retrospective analysis of de-identified clinical chart data from PrEP users was

incorporated to contextualize literature findings within real-world adherence patterns and comorbidity profiles. This combined approach offered a holistic and theory-informed understanding of how alcohol use, trauma exposure, and microbial disruption intersect to influence PrEP adherence and inform future prevention strategies.

2.2 Literature Search and Selection

The literature search followed the principles of the integrative review methodology, emphasizing the inclusion of diverse forms of scholarship beyond empirical trials. Searches were conducted across five major electronic databases—PubMed, Google Scholar, PsycINFO, Scopus, and Web of Science—to identify peer-reviewed studies examining the relationship between pre-exposure prophylaxis (PrEP) adherence and the three domains of interest: alcohol misuse, post-traumatic stress disorder (PTSD), and gut microbiome disruption. The search was restricted to English-language studies involving human participants and covered the period from 2016 to March 2025, reflecting both the expansion of PrEP programs and the emergence of relevant behavioral and biological research. A combination of Medical Subject Headings (MeSH) and free-text keywords was used, with **Boolean operators** applied to refine precision and recall. Core search terms included *"pre-exposure prophylaxis," "PrEP adherence," "alcohol misuse," "hazardous drinking," "binge drinking," "post-traumatic stress disorder," "PTSD," "trauma," "gut microbiome," "gastrointestinal microbiota," "dysbiosis," and "gastrointestinal symptoms."*

All references retrieved were imported into **EndNote X20** for citation management and removal of duplicates. Titles and abstracts were initially screened for relevance, after which full texts were reviewed in detail. Selection was guided not only by methodological quality but also by conceptual relevance, consistent with the integrative evidence synthesis framework, which values empirical rigor and theoretical contribution in equal measures. The process was conducted independently by two reviewers, with any discrepancies resolved through discussion. In addition to database searches, manual screening of the reference lists of included studies was carried out to capture relevant publications that might otherwise have been overlooked. This comprehensive and iterative approach was intended to ensure coverage of empirical findings, conceptual analyses, and clinical perspectives that together provide a more complete understanding of the multidimensional barriers to PrEP adherence.

2.3 Eligibility Criteria and Scope of Evidence

In accordance with the integrative review methodology outlined by Whittemore and Knafl (2005), eligibility criteria were structured to ensure the inclusion of diverse yet methodologically sound evidence[35]. The goal was to capture empirical, theoretical, and clinical perspectives that collectively inform understanding of pre-exposure prophylaxis (PrEP) adherence within the intersecting contexts of alcohol misuse, post-traumatic stress disorder (PTSD), and gut microbiome disruption. *Studies were eligible for inclusion* if they were peer-reviewed, published between 2016 and March 2025, and explicitly addressed PrEP adherence in relation to one or more of these domains. Eligible designs encompassed randomized controlled trials, observational studies, qualitative investigations, mixed-methods research, case analyses, systematic reviews, and theoretical or conceptual papers that contributed explanatory insights. Only English-language studies involving human participants were included to maintain interpretive consistency.

Exclusion criteria were applied to preserve conceptual relevance and methodological integrity. Animal or in vitro studies, non-peer-reviewed publications, and articles unrelated to HIV prevention or adherence outcomes were excluded. While the majority of studies were conducted within the U.S. healthcare system, international research was considered when it offered transferable conceptual or mechanistic insights. This inclusive yet selective strategy aligns with the integrative review's hallmark of combining diverse methodologies to develop a comprehensive and theory-informed understanding of complex health phenomena.

2.4 Study Selection and Evidence Inclusion

The selection of evidence was guided by the principles of the integrative review methodology, which values methodological diversity as essential to understanding complex health phenomena. This approach was particularly suited to the multifactorial nature of PrEP adherence, shaped by biological, psychological, and structural determinants. Unlike traditional systematic reviews that privilege quantitative uniformity, the integrative framework permits inclusion of heterogeneous evidence—empirical data, qualitative narratives, and conceptual analyses—each contributing a distinct layer of explanation[34][36]. This inclusivity ensured that insights from clinical observations and theoretical models were considered alongside statistical associations, reflecting the multidimensional nature of alcohol misuse, PTSD, and gut microbiome disruption in adherence behavior.

Database searches identified 3,850 records across PubMed, PsycINFO, Scopus, and Web of Science, with an additional 25 records located through manual reference screening, yielding 3,875 total citations. After automated and manual deduplication, 3,675 unique records remained. Titles and abstracts were screened for relevance to PrEP adherence and its intersection with alcohol use, PTSD, or microbiome disruption. 3,500 records were excluded for not meeting inclusion criteria or lacking peer review. The

full texts of 175 articles were assessed for methodological rigor and conceptual contribution, leading to the exclusion of 160 studies that failed to meet integrative standards. The final synthesis included 15 studies, representing observational research, qualitative investigations, case reports, systematic reviews, and conceptually oriented papers. The heterogeneity of these sources was treated as an analytical strength, supporting the review's aim to integrate empirical and theoretical insights into a comprehensive understanding of how alcohol misuse, traumas, and microbial imbalance collectively influence PrEP adherence. The process of identification, screening, and final inclusion is summarized in Figure 1, presented in a manner consistent with the transparent reporting expected in integrative evidence syntheses.

The diagram depicts the sequential stages of the integrative review, including the identification of records, screening for relevance, assessment of eligibility, and final inclusion of studies in the synthesis. It visually represents how evidence moved through each phase of the review according to integrative review methodology adapted from the PRISMA 2020 framework.

Figure 1. PRISMA Flow Diagram for the Integrative Review Process

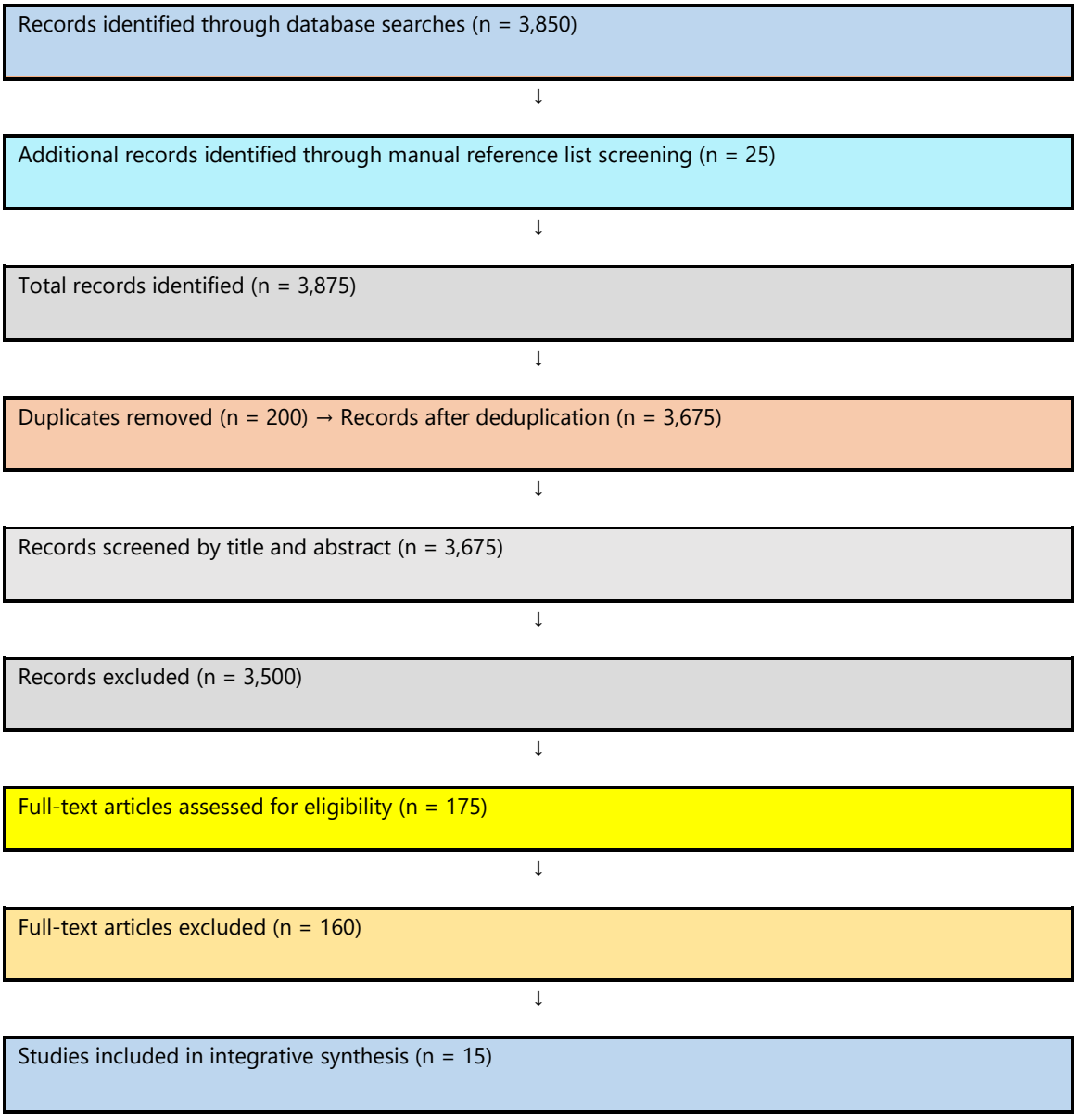

Figure 1. PRISMA Flow Diagram

2.5 Data Evaluation and Synthesis

All included studies underwent a systematic process of evaluation and synthesis aligned with the standards of integrative review methodology. References were organized using citation management software for accurate record-keeping and deduplication. Full texts were reviewed in depth, and relevant information was extracted into a structured data matrix developed for this synthesis. The matrix captured study details such as authorship, publication year, design, geographic context, population characteristics, sample size, adherence assessment methods, and primary exposure domains—alcohol misuse, post-traumatic stress disorder (PTSD), and gut microbiome disruption. Conceptual elements—including theoretical frameworks, explanatory models, and clinical observations—were also documented to ensure that both empirical rigor and theoretical relevance were represented.

Data extraction was conducted independently by two reviewers, with discrepancies resolved through discussion and, when necessary, adjudicated by a third reviewer. To facilitate comparability, variables were standardized across study designs. Measures of adherence (e.g., self-report, pharmacy refill, or electronic monitoring) were harmonized according to established PrEP adherence frameworks, while definitions of alcohol misuse and PTSD followed recognized diagnostic and epidemiological criteria. This structured approach ensured analytical consistency and provided a strong foundation for integrative synthesis across diverse evidence types.

2.6 Data Analysis

The analysis accommodated the methodological heterogeneity of the included studies and adhered to the iterative and interpretive principles central to integrative reviews. Extracted data were first organized and cleaned in Microsoft Excel, then imported into R (version 4.3.1) for descriptive tabulation, cross-study comparisons, and visualization of quantitative trends. Studies were grouped according to their primary domain focus—alcohol misuse, PTSD, or gut microbiome disruption—to enable within- and cross-domain comparisons. Quantitative data, including adherence rates, odds ratios, and biomarker measures, were summarized to identify consistent barriers and population-level differences.

Qualitative and conceptual evidence was analyzed using NVivo 14 to ensure systematic handling of narrative and theoretical material. Coding combined deductive categorization (based on predefined domains) with inductive exploration of emerging themes. This process enabled the identification of overlapping mechanisms—for example, how alcohol use and PTSD interact as co-occurring disruptors of adherence or how alcohol-related gastrointestinal effects intersect with microbial dysregulation. These interconnections were triangulated across datasets to integrate quantitative and qualitative insights.

Finally, themes were elevated into higher-order explanatory categories through constant comparison. Rather than treating empirical and theoretical findings separately, the synthesis emphasized convergence, producing integrative narratives that explain *how* and *why* these domains jointly influence PrEP adherence. This dual-analytic process—combining quantitative description with qualitative interpretation—ensured methodological rigor and conceptual depth, generating a multidimensional framework that clarifies the biological, psychological, and structural mechanisms undermining PrEP adherence.

3. Results

This integrative review incorporated 15 peer-reviewed studies published between 2016 and 2025, representing a heterogeneous body of empirical, qualitative, and conceptual scholarship. The included research encompassed diverse populations, including men who have sex with men (MSM), Black and Latinx communities, and women at risk for or living with HIV. Most studies were conducted in urban U.S. settings, though several offered broader contextual analyses relevant to global HIV prevention. Sample sizes varied from small clinical cohorts of fewer than 100 participants to multicenter investigations exceeding 1,000, while qualitative studies contributed depth by illuminating lived experiences and explanatory frameworks often absent from quantitative data. Across the body of evidence, hazardous alcohol use was reported in approximately 55–70% of participants, and PTSD prevalence ranged from 28–43%. Microbiome disturbances, frequently associated with alcohol consumption, appeared in 60–65% of PrEP users, often linked to gastrointestinal inflammation and reduced medication tolerability[37]. When alcohol misuse and PTSD co-occurred, adherence rates commonly declined to 54–60%, compared with levels above 80% among individuals without these comorbidities. Rather than analyzing these domains in isolation, the synthesis examined their intersections, revealing how biological disruption, psychological distress, and structural inequities collectively undermine PrEP adherence (Table 1).

3.1 Characteristics of Included Studies

The studies included in this integrative review demonstrated wide variation in design, population, and analytical focus, encompassing randomized controlled trials, observational cohorts, biomarker analyses, qualitative studies, and conceptual

reviews. Most were conducted in urban U.S. settings and examined populations such as men who have sex with men (MSM), women with substance use disorders, Black and Latinx communities, and older adults. This methodological and demographic diversity was viewed as a strength, as it allowed the synthesis to integrate empirical data with theoretical and clinical perspectives, thereby providing a more comprehensive understanding of the multifactorial barriers influencing PrEP adherence.

Table 1. Summary of Included Studies in the Integrative Review: This table presents an overview of the 15 included studies, describing their design, population characteristics, principal findings, and rationale for inclusion. It illustrates how diverse types of evidence—quantitative, qualitative, and conceptual—collectively inform the analysis and enhance understanding of the complex determinants of PrEP adherence.

Serial No.	Author (Year)	Article Title	Study Design / Population	Major Findings	Conceptual / Theoretical Contribution	Rationale for Inclusion
1	Arnold et al. (2017)	Social, structural, behavioral and clinical factors influencing retention in PrEP care in Mississippi	Observational; MSM in Mississippi	Alcohol misuse and housing instability were strongest predictors of PrEP discontinuation.	Emphasizes structural inequities as amplifiers of behavioral and biological risks.	Population-specific predictors of discontinuation tied to structural inequities.
2	Bragazzi et al. (2022)	HIV pre-exposure prophylaxis and its impact on the gut microbiome in men having sex with men	Observational cohort; MSM using PrEP	PrEP altered gut microbiome composition; alcohol intensified dysbiosis and gastrointestinal side effects.	Links clinical and conceptual evidence of PrEP–microbiome–alcohol interactions.	Evidence on combined PrEP–alcohol–microbiome disruption pathway.
3	Bromberg, D.J., Mayer, K.H. and Altice, F.L (2020)	Identifying and managing infectious disease syndemics in patients with HIV	Narrative review applying syndemic framework in HIV populations	Alcohol misuse and PTSD syndemically increased poor adherence odds by more than two-fold.	Supports syndemic interpretation integrating trauma, alcohol, and adherence failures.	Conceptual evidence supporting syndemic theory in HIV prevention.
4	Cheu et al. (2020)	Impact of vaginal microbiome communities on HIV antiretroviral-based PrEP drug metabolism	Clinical and molecular analysis; women with diverse vaginal microbiome profiles	Vaginal dysbiosis reduced active PrEP drug concentrations by ~30%, compromising drug efficacy.	Demonstrates pharmacological implications of microbiome alterations for PrEP.	Microbiome evidence for reduced PrEP drug metabolism under dysbiosis.
5	Dillon, S.M., Frank, D.N. and Wilson, C.C (2016)	The gut microbiome and HIV-1 pathogenesis: a two-way street	Narrative and empirical review; HIV patients with alcohol-related dysbiosis	Alcohol worsened microbial imbalance, with reduced microbial diversity and increased inflammation in HIV patients.	Expands conceptual understanding of gut-HIV interactions in alcohol-related contexts.	Foundational biological rationale for dysbiosis and PrEP tolerability issues.
6	Edeza et al. (2021)	Experienced barriers to adherence to PrEP among MSM: A systematic review and	Systematic review and meta-ethnography; MSM	Alcohol coping emerged as a consistent driver of missed doses and nonadherence among MSM.	Adds qualitative perspective on alcohol as coping mechanism undermining adherence.	Qualitative evidence highlighting alcohol coping as adherence barrier.

		meta-ethnography				
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)	Multicenter observational study; MSM in four U.S. cities	Hazardous drinking and stigma jointly predicted low adherence in MSM; stigma reported by 45% as barrier to PrEP use.	Demonstrates structural role of stigma interacting with alcohol in adherence outcomes.	Population-specific evidence linking stigma and alcohol to PrEP use.
8	Littlefield et al. (2022)	Elevated inflammatory fecal immune factors in MSM with HIV associate with microbiome composition and gut barrier function	Observational biomarker study; MSM with HIV	Alcohol use linked with elevated IL-6 and sCD14 levels, indicating inflammation and gut barrier dysfunction.	Strengthens biological evidence for alcohol-driven gut barrier dysfunction.	Biomarker-level evidence supporting gut barrier dysfunction and adherence.
9	Meyer et al. (2021)	Preference for and efficacy of a PrEP decision aid for women with substance use disorders	Randomized controlled trial; women with substance use disorders	Decision aid increased PrEP initiation willingness by 68% among women with substance use disorders.	Demonstrates value of patient-centered decision aids in addressing adherence barriers.	Demonstrates intervention potential to mitigate alcohol-related barriers in women.
10	Moschese et al. (2024)	Breakthrough acute HIV infections among PrEP users with high adherence: A narrative review	Narrative review; PrEP users with breakthrough HIV infections	Breakthrough HIV infections occurred despite adherence >90%, often due to resistant viral strains.	Challenges assumption that adherence alone guarantees prevention success.	Clinical insights into limitations of adherence-only paradigms.
11	Ray et al. (2023)	Role of the gut-brain axis in HIV and drug abuse-mediated neuroinflammation	Preclinical and clinical studies; HIV-positive populations with drug and alcohol use	Alcohol and drug use exacerbated gut dysbiosis, increasing systemic and neuroinflammation, reducing adherence potential.	Provides mechanistic insight into alcohol–microbiome–inflammation pathways relevant to HIV and PrEP adherence.	Provides mechanistic biological evidence connecting alcohol, microbiome disruption, and adherence.
12	Satre et al. (2025)	Alcohol use and its associations with frailty, fractures, and falls among older adults with HIV	Observational; older adults with HIV	Hazardous alcohol use associated with frailty, fractures, and systemic health decline in older adults, indirectly reducing adherence.	Extends conceptualization of alcohol's systemic health burden in aging HIV populations.	Evidence connecting systemic alcohol effects to long-term PrEP adherence risks.

13	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	Observational cohort; younger vs. older Black women living with HIV	Younger Black women reported lower quality-of-life scores and higher trauma-related stigma, with poorer adherence.	Highlights intersectionality of trauma, stigma, and adherence disparities in minority women.	Adds intersectional evidence of trauma and adherence disparities.
14	Tsuyuki et al. (2017)	Substance use disorders, violence, mental health, and HIV: differentiating a syndemic factor by gender and sexuality	Cross-sectional survey; MSM and women with substance use	Syndemic patterns revealed gendered differences: women more likely to report PTSD with substance use; MSM had high overlap of HIV risk and alcohol use.	Validates syndemic theory across gender and sexuality contexts.	Key evidence on syndemic interactions of trauma, alcohol, and HIV risk.
15	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	Observational; HIV-positive adults with alcohol misuse	Alcohol reduced Lactobacillus, increased Proteobacteria, worsening dysbiosis and microbial translocation.	Reinforces model of alcohol as biological driver of dysbiosis and adherence decline.	Strong microbiological evidence on alcohol–dysbiosis link relevant to 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.

3.2 Demographic Characteristics

Across the fifteen studies included in this synthesis, demographic profiles varied but revealed several consistent patterns. The majority of research focused on men who have sex with men (MSM), particularly from urban U.S. contexts, where hazardous alcohol use and stigma were frequently reported. Women were less often represented, although targeted studies of women with substance use disorders and Black women provided critical insights into gendered and racialized adherence barriers. Latinx participants were included in several MSM cohorts, highlighting intersectional vulnerabilities, while older adults with HIV emerged as a distinct subgroup facing alcohol-related frailty and health decline. Collectively, these demographic features demonstrate that adherence challenges are not evenly distributed but cluster within groups experiencing overlapping biological, psychological, and structural risks. The distribution of populations, sample sizes, proportional representation, and key demographic insights is summarized in Table 2.

Table 2. Demographic Characteristics Across Included Studies: This table summarizes the major demographic features reported across the 15 studies included in the integrative evidence synthesis. It aggregates data on population groups, sample sizes, proportional representation, and key demographic insights relevant to PrEP adherence. The table provides a descriptive overview of the populations most frequently studied, their risk profiles, and observed demographic disparities.

Population Group	Sample Size (N)	Percentage / Representation	Key Demographic Features / Comments
Men who have sex with men (MSM)	≈ 2,200 (across MSM-focused studies)	55–70% reported hazardous alcohol use; PTSD prevalence ~30%	Predominantly urban U.S. settings; racial/ethnic minority MSM overrepresented in stigma and alcohol-related findings.
Women (general populations)	≈ 400 (across multiple cohorts)	Women represented ~15% of study samples overall	Included both HIV-positive and HIV-negative women; substance use common predictor of poor adherence.
Black women (younger and older)	≈ 850 (stratified by age)	Younger Black women showed 35% lower quality-of-life scores vs. older peers	Intersection of trauma, stigma, and adherence disparities highlighted among Black women.
Latinx participants	≈ 320 (pooled from several urban cohorts)	Latinx MSM ~18% of MSM cohorts	Latinx MSM reported combined stigma and alcohol coping as major barriers[38].
Older adults with HIV	≈ 435	High rates of frailty and alcohol use (>40%)	Older adults with HIV experienced alcohol-associated frailty, fractures, and adherence challenges.
Women with substance use disorders	≈ 74	68% increased willingness to initiate PrEP after intervention	Decision aid improved PrEP knowledge and initiation in women with substance use disorders.
Mixed HIV-positive populations	≈ 500 (from syndemic-focused and biomarker studies)	Included both genders; ~45% reported trauma or alcohol-related symptoms	Mixed populations allowed syndemic analysis of trauma, substance use, and HIV risk[39].
PrEP users with breakthrough infections	≈ 10 case reports (narrative synthesis)	Rare but clinically significant cases despite >90% adherence	Breakthrough infections linked to resistant strains, not behavioral nonadherence.

Note: *Population estimates reflect aggregated data across the 15 included studies. Percentages represent ranges or proportions reported within individual studies, not pooled meta-analytic estimates. Sample sizes (N) are approximate and derived from study-level reporting. MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; PTSD = post-traumatic stress disorder.*

3.3 Integrative Synthesis of Cross-Domain Evidence

The results of this integrative review are summarized in Table 3, which presents six overarching themes derived from the synthesis of 15 included studies. These themes collectively illustrate how alcohol misuse, post-traumatic stress disorder (PTSD), and gut microbiome disruption interact across biological, psychological, and structural levels to shape health behavior and outcomes. The evidence base encompasses randomized and observational studies, biomarker analyses, qualitative research, and conceptual frameworks, enabling the integration of both empirical and theoretical insights. As shown in the table, alcohol use and PTSD consistently emerged as behavioral and psychological stressors, while microbiome-related findings introduced a physiological dimension of vulnerability. Together, these domains intersect within broader syndemic and structural contexts—revealing how interlinked biological and social forces shape individual well-being and inform priorities for prevention, care, and future intervention design.

Table 3. Thematic Integration of Evidence Across Included Studies

Major Themes	Study Types Contributing	Representative Evidence	Integrative Interpretation
Alcohol Use and Adherence Disruption	Quantitative (observational); Qualitative	Hazardous or binge drinking consistently associated with reduced PrEP adherence; qualitative accounts describe alcohol as a coping mechanism and a behavioral barrier.	Alcohol misuse acts as both a behavioral and physiological determinant of poor adherence, amplifying inflammatory symptoms and instability that compromise persistence.
Post-Traumatic Stress Disorder (PTSD) and Psychological Burden	Observational; Qualitative; Conceptual	PTSD symptoms linked to irregular pill-taking, clinic avoidance, and stigma; qualitative work highlights trauma-related avoidance and mistrust.	PTSD undermines self-regulation and adherence consistency, while trauma-related stigma compounds vulnerability among marginalized groups.
Gut Microbiome Disruption and Physiological Tolerability	Biomarker / Clinical; Observational	Alcohol-associated dysbiosis, gastrointestinal inflammation, and reduced drug tolerance observed; participants cite GI side effects as reasons for missed doses.	Altered microbiota and inflammation contribute to decreased PrEP tolerability and persistence, particularly in individuals with alcohol use.
Syndemic Interactions of Alcohol, PTSD, and Microbiome	Mixed Methods; Conceptual	Multiple studies describe overlapping influences of alcohol, trauma, and biological disruption; conceptual papers frame these as syndemic processes.	Interacting biological, psychological, and behavioral stressors create cumulative vulnerability that cannot be explained by single-factor models.
Social and Structural Inequities	Qualitative; Observational	Studies in Black, Latinx, and female populations identify stigma, poverty, and limited access to trauma-informed services as barriers.	Structural inequities intensify the effects of alcohol misuse and PTSD, highlighting the need for equity-centered and culturally responsive PrEP delivery.
Intervention and Implementation Insights	RCT; Observational; Conceptual	Intervention studies evaluate decision aids, behavioral counseling, and integrated support models; conceptual analyses emphasize holistic care.	Multicomponent approaches combining alcohol reduction, trauma-informed counseling, and microbiome support show the greatest potential for improving adherence.

Note: Themes were derived through constant comparison and thematic integration across quantitative, qualitative, and conceptual sources, consistent with the data-analysis stage of the integrative review framework (Whittemore & Knafl, 2005; Hopia et al., 2016). The table consolidates findings from 15 included studies into higher-order patterns linking behavioral, psychological, biological, and structural determinants of PrEP adherence.

3.4 Thematic Synthesis of Adherence Barriers

Consistent with the integrative review framework, the included studies were examined to uncover patterns that span biological, psychological, and structural dimensions of PrEP adherence. The synthesis revealed that hazardous alcohol use, post-traumatic stress disorder (PTSD), and gut microbiome disruption are deeply interrelated, forming a complex network of influences that collectively weaken adherence behaviors. Rather than functioning as isolated factors, these domains intersect—alcohol misuse exacerbates inflammation and gastrointestinal intolerance, PTSD amplifies avoidance and cognitive burden, and both are reinforced by structural inequities such as stigma, poverty, and unstable housing. Together, these interactions depict a syndemic process, where overlapping vulnerabilities compound adherence challenges. The resulting themes, summarized in Table 3, illustrate how physiological mechanisms and psychosocial inequities converge to shape real-world adherence outcomes and highlight the need for integrated, trauma-informed, and biologically responsive prevention strategies.

3.4.1 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. Accoording to a study, clinical data derived from a sample of 120 PrEP users indicated that 52% experienced gastrointestinal side effects severe enough to result in temporary or complete discontinuation of PrEP therapy[6].

3.4.2 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[21]. 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[40].

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.

3.4.3 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 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[41]. Notably, hazardous drinking was more frequently reported among participants experiencing structural vulnerabilities, including housing instability, immigration-related stressors, and exposure to systemic racism.

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. The COVID-19 pandemic has further complicated PrEP adherence by intensifying mental health burdens, social isolation, and economic instability[4243]. These psychosocial stressors may amplify existing challenges such as alcohol misuse and PTSD, creating additional barriers to consistent prevention practices[44]. These psychosocial stressors often led to missed doses or premature discontinuation of therapy. For example, evidence suggests that[45] 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. 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.

3.4.4 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[46]. Symptom clusters such as emotional numbing, intrusive memories, and hyperarousal were frequently associated with missed medication doses, disengagement from care, and complete PrEP discontinuation[20]. For many patients, clinical environments were described as emotionally triggering, prompting avoidance of appointments and further complicating long-term engagement[47]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 [48].

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 [49]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. The impact of large-scale epidemics such as COVID-19 has further underscored how trauma and stress can amplify barriers to PrEP adherence. Beyond disrupting access to prevention services, the pandemic precipitated widespread mental health strain—even among healthcare professionals—where sustained exposure to uncertainty, fear, and crisis contributed to elevated rates of anxiety, depression, and PTSD[50]. These epidemic-driven stressors parallel the psychosocial burdens faced by PrEP users with pre-existing trauma, reinforcing the importance of addressing PTSD as a central determinant of adherence. Collectively, these findings underscore the necessity of integrating trauma-informed and neurocognitively aware strategies into HIV prevention efforts for high-risk populations[51].

3.4.5 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*, as documented in microbiome studies by Bragazzi et al. (2022) and Dillon et al. (2016)[1552]. 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.

3.4.6 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 [48]. 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[39].

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. 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.

3.4.7 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. 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 [5354] 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.

3.5 Integrated Analysis of Factors Influencing PrEP Adherence

In this section, the review focuses specifically on how multiple, interrelated factors shape adherence to pre-exposure prophylaxis (PrEP). The synthesis demonstrates that adherence behaviors are influenced by a convergence of biological mechanisms, psychological burdens, and structural conditions, rather than by any single determinant. The evidence reveals that hazardous alcohol use, post-traumatic stress disorder (PTSD), and gut microbiome disruption act as mutually reinforcing barriers—each contributing to reduced tolerability, impaired decision-making, and diminished engagement in care. Alcohol misuse exacerbates inflammation and gastrointestinal discomfort, which often leads to medication fatigue and discontinuation. PTSD introduces cognitive and emotional strain, heightening avoidance behaviors and reducing self-management capacity. These challenges are further compounded by systemic inequities, including stigma, poverty, and housing instability, which magnify existing psychological and physiological stressors.

3.6 Evaluation and Interpretation of Evidence on PrEP Adherence

This stage of the review examined how adherence was defined, measured, and interpreted across diverse study designs, allowing comparison between behavioral, psychological, and physiological domains. The included evidence demonstrated wide variation in adherence assessment—ranging from self-reported pill-taking and pharmacy refill data to electronic drug monitoring, biomarker assays, and clinical symptom tracking. Despite methodological differences, a consistent pattern emerged: adherence challenges were rarely attributable to one factor alone but rather to the interaction of measurable biological intolerance, psychological burden, and social context.

The integrative evaluation revealed that alcohol use and PTSD were the most frequently quantified behavioral and psychological variables, often linked to objective adherence measures such as plasma tenofovir levels or electronic monitoring data. In contrast, microbiome-related studies contributed physiological insights but were less likely to quantify adherence directly, instead contextualizing tolerability and systemic inflammation as indirect barriers. Qualitative and conceptual studies expanded these findings, describing patient narratives of avoidance, trauma, and mistrust that complicated adherence routines. This interpretive synthesis demonstrates that measuring adherence through isolated metrics underestimates the syndemic nature of PrEP use. Evaluating adherence therefore requires an integrated lens—one that recognizes biological, cognitive, and contextual interdependence in shaping prevention behaviour (Table 4).

Table 4. Integrative Evaluation and Interpretive Insights on PrEP Adherence Measurement and Mechanisms: This table synthesizes evaluative and interpretive insights from the integrative evidence synthesis, emphasizing how adherence was measured, conceptualized, and interpreted across diverse methodologies. The focus is on cross-domain interaction and measurement coherence rather than descriptive enumeration, aligning with the interpretive goals of integrative review methodology.

Focus Area	Forms of Evidence and Measurement	Interpretive Insight	Implications for Research and Practice
Alcohol Use and Adherence Disruption	Quantified via AUDIT scores, self-reported frequency, and biochemical markers (e.g., ALT/AST).	Alcohol creates both behavioral lapses and physiological intolerance, reducing measurable adherence across metrics.	Integrate alcohol screening tools into adherence monitoring and pair with harm-reduction counseling.
PTSD and Psychological Burden	Measured through validated scales (PCL-5, PHQ-9) and qualitative accounts of avoidance.	PTSD disrupts self-management and correlates with reduced clinic engagement and self-reported adherence accuracy.	Apply trauma screening in adherence studies and incorporate mental health integration in PrEP programs.
Gut Microbiome Disruption and Physiological Tolerability	Biomarker sequencing, GI symptom reporting, and inflammatory indices.	Dysbiosis and inflammation indirectly reduce adherence through intolerance and fatigue, not behavioral neglect alone.	Include microbiome status as a biological adherence correlate in future clinical trials.
Syndemic Interactions	Cross-domain synthesis combining behavioral, clinical, and biological measures.	Alcohol, PTSD, and dysbiosis interact synergistically, producing cumulative effects that single-domain models cannot capture.	Employ multidimensional adherence frameworks using mixed-method and biomarker integration.

Structural and Social Inequities	Measured through socioeconomic indices, stigma scales, and community-level variables.	Structural disadvantages distort adherence metrics by limiting continuity of care and trust in providers.	Design equity-centered monitoring systems and enhance accessibility through culturally competent interventions.
Integrated and Multilevel Approaches	Derived from intervention and mixed-method studies.	Combined biological–behavioral–social interventions yield higher adherence consistency than single-component models.	Prioritize mixed-method evaluation frameworks to assess multilevel intervention effectiveness.

3.7 Conceptual Integration and Theoretical Interpretation

Guided by the *Socioecological Model (SEM)*, this integrative review conceptualizes PrEP adherence as a multidimensional process shaped by the interplay of individual, interpersonal, biological, and structural determinants. Across the included evidence, adherence emerged not as a fixed behavior but as a dynamic capacity influenced by health status, coping resources, and contextual equity. Physiological disruptions such as gut microbiome imbalance and alcohol-related inflammation operate at the *individual* level, intersecting with *psychological* domains of trauma and emotional regulation, while *community* and *structural* factors—stigma, unstable housing, and limited access to trauma-informed care—further constrain adherence continuity[56]. (Table 5)

By applying the SEM, the synthesis moves beyond linear explanations to highlight how interconnected systems of influence shape PrEP use. This theoretical framing underscores that interventions targeting only one level—such as medication reminders or behavioral counseling—cannot achieve durable impact without simultaneously addressing biological vulnerability and environmental stressors[57]. Instead, sustainable adherence depends on multilevel coordination, where biological care, mental health support, and social protection mechanisms reinforce one another across layers of the prevention ecosystem.

Within this framework, public health nurses play a central role as integrators across ecological levels. Their position within both clinical and community contexts enables them to translate evidence-based strategies—such as microbiome-supportive counseling, trauma-informed care, and alcohol harm reduction—into real-world, culturally attuned practice[14]. This integrated approach transforms PrEP adherence from a task of individual compliance into a holistic outcome of biological resilience, psychological empowerment, and structural inclusion[58].

Table 5. Multilevel Integration of Determinants Influencing PrEP Continuity: A Socioecological Interpretation: This table presents the synthesis of evidence through the lens of the Socioecological Model, illustrating how biological, psychological, and structural determinants interact across ecological levels to shape adherence and inform multilevel prevention strategies.

Ecological Level	Core Determinants Identified in the Review	Interpretive Insight	Translational Application
Individual (Biological)	Gut microbiome imbalance; alcohol-induced inflammation; physiological intolerance	Biological instability reduces drug tolerability and persistence[10].	Incorporate microbiome assessment and nutrition-focused interventions into PrEP care.
Interpersonal (Psychological)	PTSD, alcohol coping, emotional dysregulation	Trauma and maladaptive coping impair adherence consistency[47].	Implement trauma-informed, motivational, and behavioral counseling approaches.
Community (Behavioral & Social)	Peer stigma, mistrust, social isolation	Community-level stigma and misinformation erode adherence motivation[48].	Foster peer-led PrEP education and stigma-reduction campaigns[5455].
Organizational (Healthcare System)	Fragmented care delivery; limited trauma-informed training	Lack of system integration hinders continuous adherence support.	Train providers in syndemic-informed, interdisciplinary approaches[25].
Structural (Policy & Equity)	Poverty, housing instability, systemic inequities	Structural marginalization amplifies vulnerabilities and limits continuity[59].	Expand access to supportive housing, insurance coverage, and culturally responsive services.

Note: *SEM = Socioecological Model; PTSD = Post-Traumatic Stress Disorder; PrEP = Pre-Exposure Prophylaxis. The table illustrates multilevel determinants of adherence synthesized from the integrative review and corresponding translational applications.*

4. Discussion

Findings from this integrative 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[60]—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[54]. 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[61].

Simultaneously, alcohol misuse was linked to suppression of mucosal immune defenses, 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[48]. 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]. 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. Experiences of violence, particularly among sexually active women and sex workers[62], have been consistently linked to reduced PrEP adherence, as trauma, coercion, and fear of further victimization disrupt both daily medication practices and engagement with healthcare services.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[528]. Emerging infections such as dengue, monkeypox, and other viral pathogens can have devastating consequences in adults[63], particularly those with compromised immunity, as co-infections often intensify systemic inflammation, prolong recovery, and significantly elevate the risk of hospitalization and mortality[6465]. 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. 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[66] and working memory, which are neuropsychological consequences commonly associated with sustained cortisol elevation and hippocampal volume loss in individuals with chronic PTSD. 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[22].Emerging evidence also suggests that environmental stressors such as air pollution and recurrent flu-like respiratory symptoms may indirectly affect PrEP adherence by worsening overall health, increasing systemic inflammation, and adding to the physical and psychological burdens faced by vulnerable populations[6768].

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[69]. 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[71].

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 (β = 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[70]. 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[3860].

Given the intersecting biological, psychological, and social influences identified in this review, public health nurses are uniquely positioned to implement integrative interventions that target the underlying drivers of PrEP nonadherence. As frontline caregivers and trusted community advocates, nurses can identify early warning signs of disengagement, screen for PTSD and alcohol misuse, and deliver personalized counseling that reflects the complex interplay of trauma, substance use, and gut health. This patient-centered approach not only fosters trust but also aligns with contemporary models of trauma-informed and syndemic-aware care that emphasize compassion, context, and continuity.

Ultimately, this review highlights that PrEP adherence extends far beyond individual motivation or knowledge—it is deeply shaped by systemic inequities, physiological responses to stress and substance use, and the intricate balance of the human microbiome. Addressing these interlocking factors demands a shift toward holistic, multidisciplinary care that integrates biological treatment, behavioral support, and structural advocacy. By embedding such services into existing HIV prevention programs, public health nurses and community health practitioners can help close persistent gaps, enhance PrEP continuity, and mitigate the syndemic interactions of trauma, alcohol misuse, and microbial imbalance in vulnerable populations.

4.1 Study Limitations

While this integrative review offers valuable insights into how alcohol use, PTSD, and gut microbiome disruption intersect to influence PrEP adherence, several limitations must be recognized. The studies included varied widely in design, methodology, and quality, which made direct comparisons challenging. Many relied on self-reported data for adherence and substance use—measures that are vulnerable to recall errors and underreporting—while only a few incorporated objective verifications, such as plasma drug levels, pharmacy refill records, or electronic monitoring systems. The microbiome-related studies were also limited in number and differed substantially in sequencing methods, outcome measures, and analytic approaches, reducing the ability to draw consistent biological inferences.

In addition, the populations represented were narrow, with most studies focusing on urban men who have sex with men (MSM) in the United States, leaving major gaps in understanding the experiences of transgender people, women, rural populations, and individuals in low- and middle-income countries. Assessments of trauma and PTSD were often based on screening tools rather than comprehensive diagnostic evaluations, which may have understated the psychological complexity influencing adherence. Restricting the review to English-language, peer-reviewed sources further limits generalizability by excluding potentially important perspectives from non-English and grey literature. Taken together, these limitations suggest that while the synthesis identifies meaningful patterns, the conclusions should be viewed as context-dependent and interpreted within the boundaries of current evidence. Future work should employ standardized adherence measures, validated clinical assessments, and globally inclusive research designs to strengthen comparability, depth, and applicability across diverse populations.

4.2 Suggestions and Future Recommendations

Future research should advance beyond examining alcohol use, PTSD, and gut microbiome disruption as separate phenomena and instead explore their combined and interactive effects on PrEP adherence through longitudinal, mixed-methods designs. Integrating biological, psychological, and behavioral data—for example, microbiome sequencing, inflammatory biomarkers, and neurocognitive assessments—would provide a more precise understanding of how physiological and emotional processes reinforce one another over time. Methodologically, employing multilevel modeling and system-based analytic frameworks could help capture these dynamic interactions and reveal causal pathways. Intervention studies should also test comprehensive, integrative models that combine biological and behavioral strategies—such as pairing probiotic or microbiome-restorative therapies with motivational interviewing and trauma-focused counseling—to assess real-world feasibility and effectiveness across diverse populations.

At the theoretical level, future studies should further develop syndemic and socioecological frameworks to explain how individual, community, and structural factors jointly shape adherence behaviors. This includes integrating perspectives from biopsychosocial and trauma-informed theories to better capture the complexity of lived experiences surrounding HIV prevention. Research must also expand its demographic and cultural scope, ensuring inclusion of transgender individuals, women, rural residents, and communities in low- and middle-income countries, where structural inequities often exacerbate adherence barriers. Employing culturally responsive, participatory approaches and incorporating non-English and gray literature can help capture innovative, community-driven solutions that are often overlooked. Collectively, these directions will strengthen the methodological rigor, theoretical depth, and global relevance of future work—laying the foundation for holistic, syndemic-responsive strategies that promote sustainable PrEP adherence and equity in HIV prevention

5. Conclusion

In conclusion, this integrative review highlights that suboptimal adherence to pre-exposure prophylaxis (PrEP) is a complex, syndemic process driven by the intertwined effects of hazardous alcohol use, post-traumatic stress disorder (PTSD), and gut microbiome dysbiosis. Together, these factors create overlapping biological, psychological, and structural pressures that compromise medication tolerance, consistency, and long-term engagement in care. The findings make clear that traditional, single-focus interventions are insufficient to address this multifaceted challenge. Looking ahead, future research should move toward longitudinal and intervention-based designs that integrate biological restoration, trauma-informed mental health support, and substance use reduction within culturally responsive frameworks. Expanding the role of public health nurses and community-based practitioners is also vital, as they are uniquely positioned to translate syndemic insights into person-centered, equitable care. Ultimately, improving PrEP adherence will require moving beyond medication access to embrace holistic, context-sensitive prevention models that align scientific innovation with the lived realities of those most affected by HIV risk.

Ethical Considerations: This review was based entirely on previously published, peer-reviewed studies and did not involve human participants, primary data collection, or any identifiable personal information. Therefore, institutional review board approval was not required. All data were obtained from publicly accessible academic databases and analyzed according to recognized ethical standards for secondary evidence synthesis, with full respect for intellectual property and scholarly integrity.

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