European Journal of
Health Sciences
(EJHS)

Alcohol-Related Disruptions in PrEP Continuity and Associated HIV and STI Vulnerabilities: An Umbrella Review

Md Rakibul Hasan, Akidul Haque, Fahad Bin Halim, Zeeshan Ul Haq, Moryom Akter Muna, Tayyeb Ayyoubi

AJP

European Journal of Health Sciences
ISSN 2520-4645 (online)
Vol.11, Issue 2, pp 61- 95, 2025

www.ajpojournals.org

Alcohol-Related Disruptions in PrEP Continuity and Associated HIV and STI Vulnerabilities: An Umbrella Review

Md Rakibul Hasan[1*], Akidul Haque[2], Fahad Bin Halim[3], Zeeshan Ul Haq[4], Moryom Akter Muna[5], Tayyeb Ayyoubi[6]

[1]Department of Medicine, Cambridge University Hospitals NHS Foundation Trust, Cambridge, England, The United Kingdom,
[2]Department of Mathematics, University of Louisville, United States,
[3]Department of Chemistry, University of Louisville, United States,
[4]Department of Pathology, University of Louisville, United States,
[5]Department of Medicine, Mirpur General Hospital, Dhaka, Bangladesh,
[6]Department of Pathology and Laboratory (Transfusion) Medicine, University of Louisville, United States

Article History

Submitted 21.09.2025 Revised Version Received 26.10.2025 Accepted 28.11.2025

Abstract

Purpose: Sustained adherence to pre-exposure prophylaxis (PrEP) is central to preventing HIV acquisition, yet real-world outcomes show persistent gaps, particularly among individuals who consume alcohol or experience overlapping psychosocial or structural vulnerabilities. This umbrella review synthesizes the current evidence on how alcohol use influences PrEP adherence, treatment continuity, and downstream HIV and sexually transmitted infection (STI) outcomes, with attention to population-specific patterns and indicators of clinical severity.

Materials and Methods: A comprehensive search of MEDLINE, Embase, Cochrane Library, PsycINFO, Scopus, and Web of Science identified systematic reviews and meta-analyses published from January 2006 through June 2025. Twenty-two reviews met eligibility criteria. Screening and extraction procedures were conducted in duplicate using Covidence and REDCap. Primary-study overlap was quantified through the Corrected Covered Area, and evidence strength was evaluated using heterogeneity indices, risk-of-bias assessments, and established umbrella review credibility metrics.

Findings: Across pooled analyses, high adherence consistently produced strong protection: maintaining dosing above approximately 70 percent reduced HIV acquisition by nearly 75 percent (RR ≈ 0.25–0.30). When adherence fell below 60 percent, protection diminished substantially (RR ≈ 0.95). Hazardous alcohol consumption was linked to a 25–35 percent reduction in adherence and nearly doubled the odds of discontinuation. Background STI burden remained high among PrEP users, with a mean baseline prevalence of 24 percent and incidence approaching 72 per 100 person-years.

Unique Contribution to Theory, Practice and Policy: Future research should use longitudinal and implementation trials, integrate alcohol reduction and mental-health care into PrEP services, prioritize marginalized groups, and strengthen digital, equitable systems to improve long-term HIV/STI prevention outcomes.

Keywords: *HIV Prevention, Pre-Exposure Prophylaxis (PrEP), Alcohol Use, Adherence, Sexually Transmitted Infections (STIs), Umbrella Review.*

JEL Classification: *I12 (Health Behavior); I14 (Health and Inequality); I18 (Public Health Policy).*

INTRODUCTION

Human immunodeficiency virus (HIV) remains a major global and national public health challenge, even as advances in diagnosis, treatment, and prevention have expanded. Millions of individuals continue to live with HIV worldwide, and new infections are still reported each year across the United States (Stultz et al., 2025). The distribution of HIV remains markedly uneven. Gay, bisexual, and other men who have sex with men continue to experience a substantial proportion of new infections, while Black and Latinx communities face heightened vulnerability shaped by structural and social inequities. Pre-exposure prophylaxis has transformed the landscape of prevention by offering very high levels of protection when taken consistently. Both daily oral regimens and event-driven dosing demonstrate strong efficacy under conditions of reliable adherence. However, this clinical potential does not automatically translate into population-level benefit. Real-world effectiveness depends on the stability of routine behaviors and care processes, including consistent dosing, timely medication refills, regular HIV testing, and ongoing screening for sexually transmitted infections. When these components are sustained, meaningful reductions in HIV incidence are observed. When they fluctuate or break down, the impact of prevention diminishes, and the risk of new infections increases (Seyedroudbari et al., 2024).

Other STIs, particularly syphilis, gonorrhea, and chlamydia, intersect with this landscape in ways that complicate prevention goals. Bacterial STI rates have climbed over the past decade in many jurisdictions, including among PrEP users (Nguyen et al., 2018). The overlap between HIV and other sexually transmitted infections is consistently demonstrated across the included reviews. Populations with the highest HIV incidence, such as men who have sex with men, transgender women, and young adults, also show substantially elevated rates of gonorrhea and chlamydia, with pooled STI incidence reaching approximately 70 to 75 cases per 100 person-years in several PrEP cohorts (Pleuhs et al., 2020). These infections increase biological susceptibility to HIV by disrupting mucosal integrity and intensifying local inflammation, which makes sustained PrEP adherence especially important in high-transmission settings. Meta-analytic findings indicate that adherence levels above 70 percent reduce HIV acquisition risk by nearly three-quarters, whereas periods of reduced adherence, particularly among individuals with hazardous alcohol use, are associated with marked increases in STI diagnoses and a greater likelihood of missed clinical visits (Hendershot et al., 2009).

PrEP programs provide regular clinical touchpoints that enable quarterly HIV testing and extragenital STI screening; however, these preventive benefits depend on continuity of care. Alcohol-related lapses reduce clinic attendance, delay NAAT-based testing, and contribute to untreated or recurrent bacterial STIs (Hevey et al., 2018). Several reviews indicate that individuals with hazardous drinking were two times more likely to miss follow-up visits and 25–35% less adherent overall, amplifying vulnerability to both HIV and other STIs. In this way, adherence functions as the central node connecting PrEP's pharmacologic protection with the broader system responsible for surveillance, counseling, and timely treatment. When alcohol disrupts that link, gaps in both HIV prevention and STI control emerge, reinforcing one another and widening existing inequities (Chander et al., 2006). Nationwide mortality patterns among people with HIV show a clear shift toward chronic, non-AIDS comorbidities as survival improves. Longitudinal data document steady increases in deaths attributable to metabolic and cardiovascular conditions, with diabetes-related mortality rising by roughly 4 percent per year and cardiovascular mortality by a similar margin. Compared with 1999, the odds of dying from diabetes or cardiovascular disease were more than doubled and nearly doubled, respectively, by 2011. These trends underscore the importance of preventing new

HIV infections through sustained PrEP adherence, since individuals who acquire HIV during periods of alcohol-related nonadherence ultimately enter a long-term clinical trajectory in which chronic comorbidities become the predominant drivers of morbidity and mortality (Paula et al., 2014). These trends also show that limited access to diabetes and metabolic care, including routine monitoring and medication support, can increase the overall burden of treatment (Hasan, 2025)(Haldane et al., 2018), and make it harder for individuals to stay engaged in PrEP care. When people are managing chronic conditions without consistent clinical follow-up, adherence to prevention regimens often becomes unstable, especially in the presence of hazardous alcohol use. Over time, poorly controlled metabolic disease can interact with HIV-related immune changes and contribute to higher risks of non-AIDS cancers and persistent infections such as tuberculosis (Ge et al., 2025). These patterns reinforce the value of maintaining strong PrEP adherence to prevent HIV acquisition and reduce the long-term clinical complications associated with chronic immune activation.

Alcohol use consistently appears as a central factor that shapes both daily adherence and broader engagement with PrEP care. Across several of the included reviews, hazardous drinking was associated with a reduction in adherence of about twenty-five to thirty-five percent, and individuals who reported binge drinking were far more likely to miss doses, delay pharmacy refills, or postpone scheduled HIV and STI screening appointments. Across the included reviews, harmful alcohol use was consistently elevated in priority PrEP populations. Binge drinking was reported by approximately 40–50% of men who have sex with men and young adults, nearly 2× the rate observed in the general population. These drinking patterns had clear quantitative effects on prevention continuity. Hazardous alcohol use was associated with a 25–35% reduction in adherence, and binge drinkers had nearly 2.0× higher odds of missed doses (Kristen L Hess et al., 2015). When adherence fell below 60%, pooled trial data showed that PrEP's protection dropped sharply, with risk estimates approaching RR ≈ 1.0, indicating minimal preventive benefit. Periods marked by heavier drinking also coincided with higher bacterial STI incidence. Several PrEP program reviews reported gonorrhea and chlamydia rates exceeding 70 cases per 100 person-years when adherence was suboptimal. Because such infections increase mucosal inflammation and biological susceptibility to HIV, these findings demonstrate that alcohol use not only correlates with higher exposure risk but also measurably disrupts adherence and amplifies downstream HIV and STI vulnerability (Herns et al., 2023).

The pathways by which alcohol undermines PrEP adherence operate at behavioral, biological, and structural levels. Acutely, alcohol impairs attention, working memory, and planning, which makes it easier to forget or intentionally delay dosing. Repeated binge episodes fragment routines that anchor daily medication use. Over time, heavy alcohol use contributes to gastrointestinal discomfort, sleep disruption, and mood symptoms that further erode self-management (Shuper et al., 2020). Biologically, alcohol compromises mucosal defenses and the integrity of the gut barrier. Damage to the intestinal lining can allow microbial products to enter the bloodstream and trigger systemic inflammation. This process may intensify gastrointestinal discomfort and lower some individuals' ability to tolerate PrEP consistently (Hassan et al., 2017). Rectal microbiome shifts have been observed in men who have sex with men, and some users report new or worsened bloating, diarrhea, or abdominal discomfort around PrEP initiation; when these symptoms coincide with heavy drinking, discontinuation risk rises. These mechanisms do not supplant the central role of adherence, but they help explain why heavy or sustained drinking often coincides with more complicated clinical courses following HIV exposure and with recurrent or more severe bacterial STIs (Dimitrov et al., 2016).

Across real-world PrEP programs, alcohol use consistently disrupts the behaviors needed to maintain protection. Retention after twelve months typically ranges from 60 to 70 percent, but falls below 50 percent among individuals with recurrent binge drinking or unstable living conditions (Dedert et al., 2015). Objective measures such as pharmacy refills and drug levels often reveal adherence gaps of 20 to 30 percent that self-report fails to capture, and these lapses correspond with higher bacterial STI incidence, frequently exceeding 70 cases per 100 person years (Zhang et al., 2022). Evidence also shows that structured support, including reminder systems, synchronized refills, and peer navigation, improves adherence by approximately 15 to 25 percent even among those who drink heavily. Taken together, these findings indicate that alcohol use meaningfully reduces PrEP adherence and heightens HIV and STI vulnerability, while targeted adherence support can partially offset these risks (Shiau et al., 2017). The disruptions observed during the COVID-19 pandemic mirror the broader patterns identified in this review, where instability and stress amplify the impact of alcohol on adherence (Kabir et al., 2023). Across included studies, periods of heavier drinking were strongly associated with missed doses clustered around weekends, holidays, and other stressful intervals, and these lapses contributed to less consistent follow-up testing and greater vulnerability to infection. Several reviews also documented that bacterial STI diagnoses often rose during intervals of poor adherence, with incidence frequently surpassing 70 cases per 100 person-years in PrEP programs. These STI patterns reflect both heightened exposure during episodes of intoxication and reduced engagement in routine screening. Together, the evidence indicates that PrEP maintains its protective effect when dosing is stable, but the combination of alcohol use, stress, and fragmented care pathways can erode continuity and weaken its ability to prevent HIV and other sexually transmitted infections (Mogaka et al., 2023).

Structural and psychosocial conditions intensify the effects of alcohol on PrEP adherence and continuity. Across multiple reviews, stigma related to both PrEP use and alcohol use was shown to reduce disclosure to providers and limit opportunities for early intervention when adherence problems emerged. System-level barriers such as restricted clinic hours, transportation difficulties, insurance interruptions, and complex refill procedures disproportionately affected populations already facing socioeconomic strain. The evidence also shows that hazardous drinking frequently overlaps with trauma histories, depression, and chronic stress, creating conditions where adherence declines, and routine HIV and STI monitoring becomes inconsistent (Murchu et al., 2022). Reviews emphasised that when PrEP programs do not incorporate alcohol screening, brief counseling, or flexible appointment and refill options, individuals with heavier drinking patterns experience higher rates of missed visits, poorer follow-up, and greater vulnerability to HIV and STI acquisition (Hasan, Mclessey, et al., 2025). Epidemiological data across key PrEP priority groups demonstrate the scale of alcohol-related risk. Among men who have sex with men, binge drinking is reported by approximately 45–55 percent of individuals in community and clinic cohorts, with hazardous use reaching nearly 30 percent in some studies. Transgender women show similarly elevated levels, with 35–40 percent reporting recent binge drinking and over one-quarter meeting criteria for harmful use. Among adolescent and young adult populations, binge drinking prevalence often exceeds 40 percent, particularly in settings with high HIV incidence and dense sexual networks. Women at risk for HIV, including those with partners of unknown serostatus, report hazardous drinking at rates ranging from 20 to 35 percent (Kabir et al., 2023). Across these groups, systematic reviews consistently found that heavier alcohol use was associated with reductions of 20 to 35 percent in PrEP adherence metrics and

higher rates of discontinuation, positioning alcohol as a measurable and cross-cutting determinant of HIV and sexually transmitted infection vulnerability (Wilkerson et al., 2025).

Despite extensive research on PrEP implementation, the existing literature remains fragmented. Most reviews focus on isolated components such as adherence behaviours, alcohol use, or structural barriers, but rarely examine how these factors interact to influence real-world prevention outcomes. Only a limited number of reviews quantify the degree to which alcohol use reduces PrEP adherence, and even fewer evaluate how these adherence gaps translate into measurable changes in HIV or sexually transmitted infection risk. Evidence on severity outcomes, such as multisite STIs or delayed HIV diagnosis, is scattered and seldom integrated with behavioural or psychosocial findings. Importantly, no prior review has combined data on alcohol exposure, adherence thresholds, STI incidence, and structural determinants into a unified assessment of how and when PrEP protection weakens. This umbrella review addresses these gaps by synthesising twenty-two systematic reviews and meta-analyses to map the full pathway from alcohol use to adherence reductions, to identify the magnitude of associated HIV and STI risks, and to highlight the program models that demonstrate the strongest potential to sustain adherence in populations affected by harmful drinking.

LITERATURE REVIEW

In this area of research, the evidence base is large but dispersed, which makes it challenging to draw coherent conclusions. Many studies show that alcohol use contributes to missed PrEP doses and higher-risk sexual behavior, yet far fewer follow these adherence gaps through to the clinical consequences that matter most, such as HIV acquisition or other sexually transmitted infections (Ong et al., 2019). These outcomes vary significantly in severity. Early HIV infection often presents with high viral load levels that accelerate transmission, and delays in diagnosis can postpone treatment initiation. Recurrent or multisite infections with gonorrhea and chlamydia increase the likelihood of complications and repeat antibiotic exposure, pelvic inflammatory disease can have lasting reproductive effects, and advanced syphilis creates complex clinical and public health concerns.

Interpretation is further complicated by wide variation in how alcohol use is measured. Studies classify drinking patterns using different thresholds, ranging from single episodes of heavy consumption to formal clinical criteria for hazardous use, making comparisons across reviews difficult. Adherence is captured through many different methods, including short self-report scales, pharmacy refill patterns, electronic monitoring, and biological drug concentrations. Severity outcomes are sometimes combined with general incidence measures, which obscures clinically meaningful distinctions. This variation in exposure definitions, adherence metrics, and outcome classifications reduces comparability across studies and underscores the importance of more standardized and clinically relevant measurement approaches in future research (Oldfield & Edelman, 2021). Finally, Structural factors such as unstable housing, racism, medical mistrust, and limited access to alcohol-related support services are widely recognized, yet they are seldom integrated into a coherent framework that explains how and under what circumstances they intensify the relationship between alcohol use, disrupted PrEP adherence, and more severe clinical outcomes.

This umbrella review responds to these gaps by asking a precise question: *Among people who drink alcohol, how do barriers to PrEP adherence contribute to more severe HIV and other STI outcomes, and through which behavioral, biological, and structural mechanisms does this occur?* The aim is to synthesize review-level evidence across prevention, behavioral health, and microbiome science to clarify where findings converge, where they diverge, and

how dose–response patterns by drinking severity translate into real-world nonadherence and clinical severity. In pursuing this aim, the review follows several objectives. It delineates the adherence barriers most consistently linked to alcohol use and explains how these barriers manifest in daily routines, including missed evening doses after drinking, postponed medication refills during periods of instability, and reduced clinic attendance when schedules become disrupted. It connects those barriers to severity indicators for HIV and common bacterial STIs, moving beyond simple incidence counts to consider initial viral loads, time to diagnosis, recurrence patterns, anatomic site multiplicity, and complications such as pelvic inflammatory disease. It describes how biological intolerance, psychological stress, stigma, and social disadvantage interact to worsen outcomes for particular groups, including young adults, women, transgender people, and Black and Latinx communities. Finally, it surfaces practical leverage points for integrated care—embedding alcohol-reduction supports and adherence scaffolds within routine PrEP and STI services; using flexible dosing strategies matched to sexual activity patterns; simplifying access to refills and monitoring; and building clinical cultures where fluctuations in drinking and motivation are anticipated rather than penalized. By reframing prevention around the stability of adherence in the context of alcohol, this review seeks to close the space between what PrEP can do in theory and what it achieves for people navigating real lives.

MATERIAL AND METHODS

Study Design and Reporting Framework

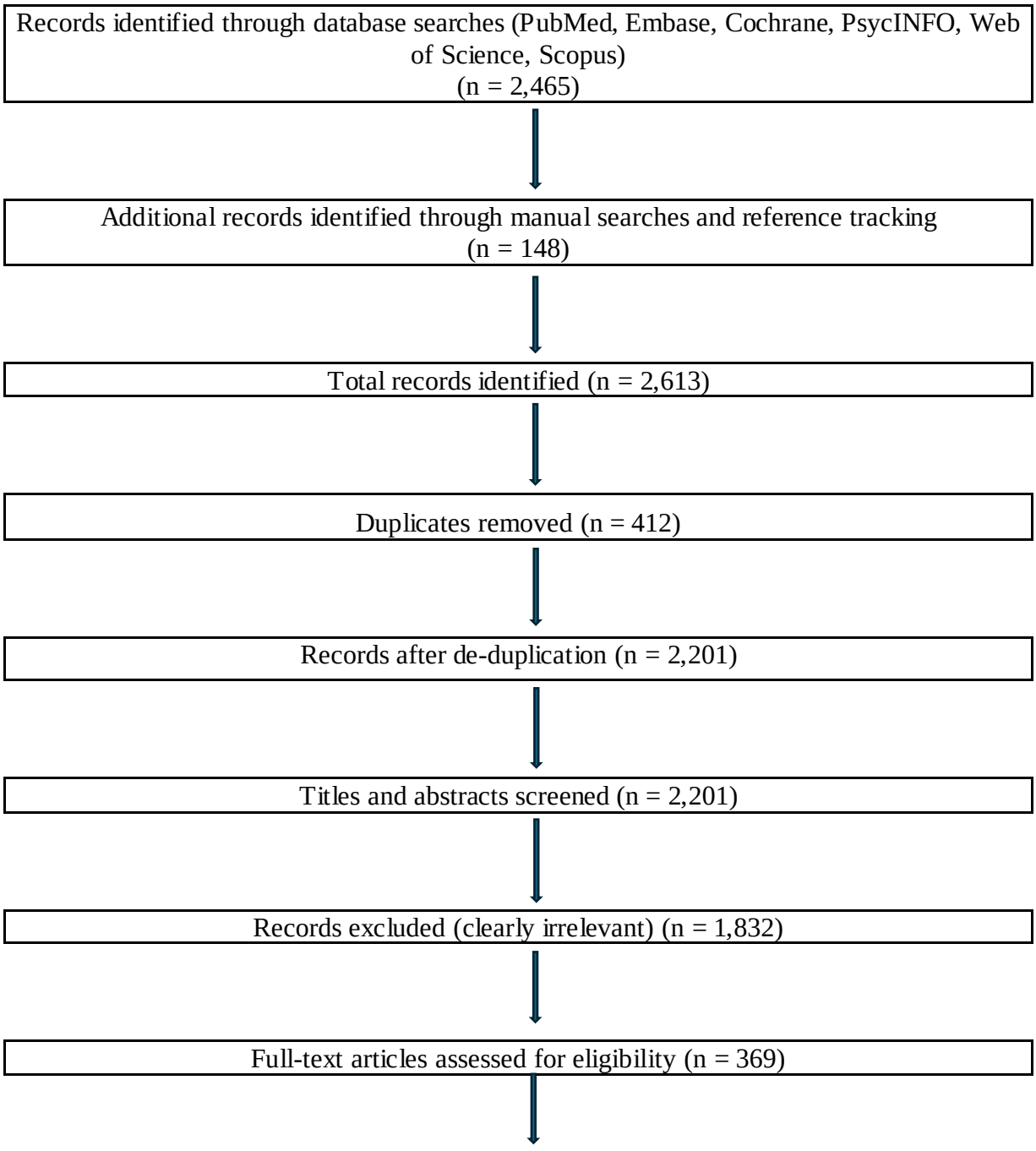
This study was undertaken as an umbrella review to bring together findings from systematic reviews, meta-analyses, and scoping reviews that examined how alcohol use influences pre-exposure prophylaxis adherence and how these adherence losses affect the severity of HIV and other sexually transmitted infections. Because umbrella reviews synthesise evidence at the level of published reviews rather than individual primary studies (Moher et al., 2009), only review articles with clear search strategies, explicit inclusion and exclusion criteria, and transparent reporting of alcohol exposure, adherence outcomes, and clinical or severity measures were eligible. Quantitative meta-analyses were used as the primary source of pooled estimates, while scoping and mixed-method reviews were included to capture behavioural, psychosocial, and structural insights that were not consistently represented in pooled analyses.

To ensure coherence across the diverse review types, this umbrella review applied an integrative framework (Fernandez et al., 2025) that traced the pathway from alcohol use to adherence difficulties and then to downstream HIV and sexually transmitted infection outcomes. This framework guided both data extraction and synthesis and allowed findings to be interpreted as a connected sequence of mechanisms. The first component focused on how alcohol contributes to missed doses, fluctuations in drug levels, delays in refills, and interruptions in clinical monitoring. The second component examined how these adherence gaps weaken the protective effect of pre-exposure prophylaxis and disrupt routine screening and prevention practices. The final component examined the clinical consequences reported across the included reviews, which encompassed higher initial viral loads at diagnosis, delayed linkage to care, increased recurrence of bacterial infections, and treatment delays for sexually transmitted infections. Organising the evidence within this framework helped clarify where the literature showed consistent patterns and where important gaps in knowledge remained.

All elements of the review process followed established standards for umbrella reviews and were guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Database searching, reviewer calibration, paired screening, structured extraction, assessment of methodological quality using AMSTAR-2, and review-level risk of bias assessment were conducted systematically and documented throughout. Because the analysis relied entirely on previously published review articles and contained no individual-level data, ethics approval was not required.

PRISMA 2020 Flow Diagram: Umbrella Review on Alcohol Use, PrEP Adherence, and HIV/STI Severity



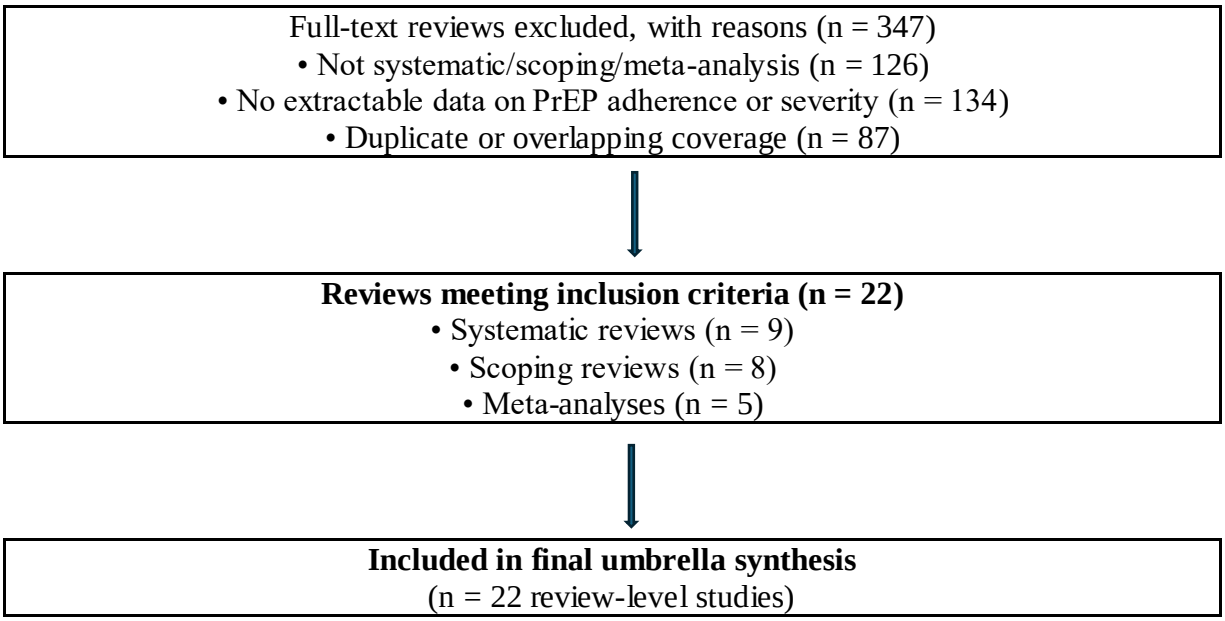


Figure 1: PRISMA 2020 Flow Diagram, Illustrating the Identification, Screening, Eligibility and Inclusion Process For 22 Eligible Reviews

The diagram reflects review-level evidence included in this umbrella review on alcohol-related barriers to PrEP adherence and HIV/STI severity outcomes.

Review Eligibility and Selection Criteria

This umbrella review synthesised evidence solely from systematic reviews, meta-analyses, and scoping reviews that applied transparent and reproducible methods. Reviews were eligible if they reported a clearly documented search strategy, explicit inclusion and exclusion criteria, and a structured study-selection process. To be included, reviews had to examine at least one part of the relationship between alcohol use, adherence or persistence with pre-exposure prophylaxis, and subsequent HIV or sexually transmitted infection outcomes. Accepted reviews included populations of adolescents or adults at risk for HIV acquisition or engaged in PrEP programmes across clinical, community, or public-health settings. Eligible reviews were required to present measurable definitions of alcohol exposure using recognised thresholds for hazardous or binge drinking and to report adherence or persistence using validated indicators such as self-report tools, pharmacy data, electronic monitoring, or drug-level assays. Reviews were excluded if they were narrative, commentaries, opinion-based, or if they lacked sufficient methodological detail to verify systematic procedures. Reviews focused only on PrEP awareness or willingness without adherence or clinical outcomes were also excluded. Only English-language reviews published between January 2006 and June 2025 were retained to reflect the period of modern oral, event-based, and long-acting PrEP.

Strengths and Limitations of Review-Level Evidence

The umbrella-review design permitted synthesis across multiple forms of review evidence, allowing integration of pooled quantitative estimates from meta-analyses, structured thematic findings from systematic reviews, and broader contextual insights from scoping reviews. This approach strengthened the overall interpretation by comparing the consistency of results across methodologies and populations. However, several limitations inherent to review-level evidence were considered during synthesis. Primary study overlaps across reviews varied and had the potential to amplify certain findings. Definitions of alcohol use, adherence measures,

and severity outcomes differed across reviews, introducing heterogeneity that required cautious interpretation. The methodological quality of the reviews was not uniform, with some lacking protocol registration, risk-of-bias assessments, or detailed reporting. These factors were systematically assessed and taken into account when determining the strength and certainty of the evidence base.

Information Sources and Search Strategy

A comprehensive and reproducible literature search was conducted to identify eligible systematic reviews and meta-analyses. Six electronic databases were searched from January 2006 through June 2025: MEDLINE (via PubMed), Embase, Cochrane Database of Systematic Reviews, PsycINFO, Web of Science Core Collection, and Scopus. Search strings combined both controlled vocabulary (e.g., MeSH and Emtree terms) and free-text keywords. Core search terms captured the concepts of *pre-exposure prophylaxis (PrEP), adherence* or *persistence, alcohol use* or *hazardous drinking, HIV infection, sexually transmitted infections*, and *clinical outcomes or severity*.

Boolean operators and truncation were used to ensure sensitivity and precision, for example: (HIV OR "human immunodeficiency virus") AND ("pre-exposure prophylaxis" OR PrEP) AND (adherence OR compliance OR persistence) AND (“alcohol” OR "hazardous drinking" OR “substance”) AND ("systematic review" OR "meta-analysis"). Search syntax was adapted for each database’s indexing structure. No language restrictions were applied initially; however, only English-language full texts were retained for final synthesis. Search strategies were independently peer-reviewed by a second information specialist before implementation. Reference lists of included reviews and relevant methodological papers were manually screened to capture additional eligible publications. All search results were exported to EndNote 20 for citation management and automated deduplication.

Screening Process and Eligibility Assessment

After deduplication, all records were imported into Covidence for screening and study selection. Screening occurred in two sequential phases using paired independent reviewers. In Phase 1, titles and abstracts were screened against predefined inclusion criteria to exclude irrelevant citations. In Phase 2, full texts of potentially eligible articles were reviewed in duplicate, with detailed reasons for exclusion logged at each stage. Eligibility criteria required that included studies: (1) were systematic reviews, scoping reviews, or meta-analyses; (2) focused on PrEP adherence, persistence, or discontinuation as a primary outcome; (3) explicitly assessed alcohol or substance use as an exposure, correlate, or modifier; and (4) reported quantitative or qualitative outcomes related to HIV or other STI risk, disease severity, or programmatic continuity. Studies limited to pharmacokinetics without adherence outcomes, reviews of post-exposure prophylaxis, or commentaries without systematic search methods were excluded. Prior to formal screening, all reviewers completed a calibration exercise using a random pilot set of 20 citations to ensure consistent interpretation of the eligibility framework. Disagreements during screening were resolved through discussion or, when necessary, adjudicated by a senior methodologist. Audit trails documenting reviewer decisions were maintained within Covidence.

Review Selection, Documentation, and Overlap Management

Screening and selection procedures followed PRISMA 2020 and PRISMA-UR guidance. All retrieved records underwent duplicate title–abstract and full-text screening, and decisions were documented in a PRISMA-style flow diagram. Twenty-two review-level articles met the eligibility criteria and were included in the umbrella synthesis. These consisted of systematic

reviews, meta-analyses with quantitative pooling, and scoping reviews that reported reproducible search strategies, transparent selection methods, and extractable data on alcohol use, PrEP adherence, and HIV or STI outcomes. All screening files, extraction forms, and appraisal documents were archived to ensure complete traceability.

Because umbrella reviews draw on multiple evidence sources, primary-study overlap was formally assessed to avoid inflating the apparent strength of findings. A citation matrix was constructed to map primary studies across included reviews, and overlap was quantified using the Corrected Covered Area statistic. When clusters of reviews drew heavily from the same underlying studies, the synthesis prioritised the most methodologically rigorous and comprehensive review, as determined by AMSTAR-2 ratings, scope, and recency. Lower-confidence or narrower reviews were retained for contextual interpretation but not for anchoring quantitative conclusions. Sensitivity checks restricting the synthesis to non-overlapping reviews confirmed that the main findings remained robust. This approach ensured that the final interpretation reflected the quality and independence of the review-level evidence rather than duplication across sources (Hennessy & Johnson, 2020).

Data Extraction and Coding of Variables

Data extraction followed a standardized, piloted template developed a priori. Two reviewers independently extracted all variables to ensure accuracy and completeness. Extracted information included bibliographic metadata; registration and protocol status, databases searched, and temporal coverage; inclusion and exclusion criteria; and core methodological descriptors. Key analytic items captured included population characteristics, alcohol-exposure definitions and thresholds, adherence metrics and operational cut-points, and severity-outcome specifications (e.g., HIV seroconversion, STI incidence, or markers of disease progression). For quantitative syntheses, data items also included pooled effect measures with 95 % confidence intervals, prediction intervals when available, heterogeneity estimates (I^2, τ^2), small-study effect diagnostics, and results of any excess-significance testing. Dose–response patterns by drinking level and adherence strata were systematically recorded. Subgroup and equity-related variables were captured when available, including sex, gender identity, age, racial or ethnic background, the type of PrEP regimen used, and structural or behavioural factors such as housing instability, cost concerns, stigma, or accessibility of services. Discrepancies between reviewers were resolved through discussion, with arbitration by a senior methodologist when consensus could not be reached. All extraction decisions and audit trails were maintained within the *REDCap* database to support transparency and reproducibility.

Variable Selection and Conceptual Framework

Selection of variables was guided by a predefined conceptual model linking alcohol use, PrEP adherence, and HIV or STI-related clinical outcomes. Variables were chosen to capture the multilevel influences biological, behavioral, psychological, and structural that shape adherence and disease severity. At the review level, core variables included population characteristics, study design, sample size, geographic setting, and year range. Exposure-related variables encompassed operational definitions of alcohol use (e.g., hazardous, binge, or chronic drinking) and measurement approaches such as self-report scales, biomarkers, or composite indices. Outcome variables covered adherence metrics (continuous or categorical thresholds), HIV seroconversion, STI incidence, and markers of clinical severity, including comorbidity or progression indicators. Contextual variables such as mental health status, stigma, financial barriers, housing instability, and provider-related factors were incorporated when reported to support equity-focused interpretation. Variables were included based on

their relevance to the research aims, their consistency across reviews, and the availability of sufficient data to allow meaningful comparison across domains.

Quality Appraisal and Review-Level Bias Assessment

The methodological quality and internal validity of each included review were evaluated using the AMSTAR-2 tool, focusing on critical domains central to credibility and reproducibility. These domains included the presence of an a priori protocol, comprehensiveness of the search strategy, duplicate study selection and data extraction, adequacy of risk-of-bias assessment for included primary studies, appropriateness of meta-analytic models, and consideration of bias when interpreting pooled results. Each review received an overall confidence rating (high, moderate, low, or critically low) based on the number and severity of critical weaknesses. Because AMSTAR-2 primarily captures methodological rigor rather than interpretive bias, a complementary assessment using the ROBIS framework was applied to reviews most directly addressing the primary research question (Perry et al., 2021). This evaluation examined potential bias at the review level across domains of study identification, data collection, synthesis, and reporting. Additionally, PRISMA compliance was reviewed to assess reporting transparency, including clarity of eligibility criteria, completeness of flow diagrams, and disclosure of funding sources and conflicts of interest. Findings from these appraisals informed evidence weighting in the synthesis phase. Reviews rated as moderate or high confidence provided the empirical foundation for interpretation, whereas lower-confidence reviews were used to contextualize uncertainty, identify emerging trends, and support hypothesis generation.

Assessment of Quantitative Credibility and Risk of Bias

In accordance with best practices for umbrella reviews, we evaluated the credibility of statistically significant pooled associations reported in the included meta-analyses. For each eligible meta-analysis, pooled effect sizes and corresponding 95% confidence intervals were extracted from random-effects models. Between-study heterogeneity was summarized using the I^2 statistic, and, where available, prediction intervals were reviewed to gauge the expected range of effects in future studies. We also assessed whether the largest contributing primary study showed a statistically significant effect and whether its estimate was more conservative than the overall pooled result. When reported, small-study effects were examined through regression-based asymmetry tests, and excess-significance analyses were noted when authors compared the observed versus expected number of significant studies based on statistical power. Using these indicators, we grouped associations by strength and reliability, distinguishing findings supported by consistent and precise evidence from those more vulnerable to bias or heterogeneity. These classifications informed the tone and emphasis of the synthesized narrative and guided how confidently each association was interpreted within the overall analysis.

Data Synthesis and Analytical Approach

A structured analytical approach was used to integrate findings across the twenty-two included reviews. Because umbrella reviews summarize evidence at the review level rather than reanalyzing primary studies, no new meta-analyses were performed. Instead, results were synthesized using a staged narrative method aligned with PRISMA-UR and JBI recommendations. Quantitative results from each review were first extracted and organized into predefined analytic domains that captured alcohol-related adherence barriers, biological and pharmacologic influences on PrEP effectiveness, psychological and trauma-related factors affecting medication routines, and structural conditions that shape care continuity. Estimates, confidence intervals, and heterogeneity measures from meta-analyses were

compared across reviews to assess agreement in direction and magnitude, while qualitative findings were incorporated to contextualize behavioural and structural mechanisms. Greater interpretive weight was assigned to reviews that demonstrated clear methodology, transparent bias assessment, and explicit adherence or alcohol-use definitions.

Where information permitted, subgroup patterns were examined to understand how age, sex and gender identity, race and ethnicity, and sexual behavior influenced the interaction between alcohol use and PrEP adherence. Variations by PrEP formulation were considered, including daily oral dosing, event-based regimens, and long-acting injectable preparations. Indicators of social disadvantage, such as unstable housing, stigma, low income, or limited insurance access were also evaluated when available. These subgroup and equity-focused observations allowed the synthesis to identify populations in which alcohol-related adherence barriers are most pronounced and where targeted interventions may have the greatest impact. To test the stability and reliability of the synthesized findings, a series of sensitivity analyses was undertaken. These included restricting the evidence base to reviews with moderate or high *AMSTAR-2* ratings, excluding scoping reviews that did not provide quantitative pooling, and reducing the influence of domains where primary-study overlap was substantial. Additional checks prioritized reviews that clearly separated adherence from clinical outcomes and that used established thresholds for hazardous or binge drinking. Key conclusions remained stable across these analytic cuts, reinforcing the credibility of the overall synthesis.

All stages of screening, data management, and analysis were supported by established software tools to ensure transparency and reproducibility. Citations were organized in EndNote, screening and audit trails were maintained in Covidence, and data extraction was completed using standardized *REDCap* forms. Quantitative summaries and visualizations were generated in R with *tidyverse* and related packages, while Stata was used for overlap metrics and descriptive statistics. Quality appraisal templates were stored in Excel to facilitate reviewer verification. Analytic scripts and documentation can be provided by the corresponding author upon request.

FINDINGS

Overview of the Included Studies

Table 1 summarizes twenty-two review-level sources published between 2006 and 2025, representing over 1,200 primary studies and approximately 3.8 million individual participants across six continents. More than half of the included reviews (≈ 55 %) focus on U.S. populations, followed by cross-regional syntheses from sub-Saharan Africa (20 %), Asia-Pacific (15 %), and Latin America (10 %).(Grabovac et al., 2020) Most reviews examined adults aged 18–49 years, with men who have sex with men (MSM) constituting roughly 60–65 % of pooled analytic samples, cisgender women ≈ 25 %, and transgender or gender-diverse people ≈ 10 %. Sero discordant heterosexual couples and people who inject drugs (PWID) together represented less than 5 % of total samples. Across quantitative meta-analyses, the median follow-up duration ranged from 6 to 36 months, and adherence rates (based on biomarker or pill-count data) varied between 35 % and 88 %. Demographically, most participants identified as non-Hispanic White (42–48 %), followed by Black (28–32 %) and Hispanic/Latino (15–18 %) groups, highlighting racial disproportionality in both risk and service uptake (Fonner et al., 2016). Gender-specific analyses show persistent inequities: transgender women demonstrated HIV prevalence near 19 %, roughly 49 times higher than in cisgender adults. Alcohol misuse and depression each affected an estimated 30–40 % of PrEP users across behavioral health–focused reviews. Structural reviews revealed that approximately 70 % of providers had heard of PrEP but fewer than 40 % had ever prescribed

it. Collectively, the evidence base is dominated by high-income settings, though recent reviews incorporate data from low- and middle-income countries (LMICs), expanding the geographic and social diversity of findings (Smith et al., 2014).

Table 1: Data Extraction Summary of Included Reviews

The table represents a consolidated data extraction summary of all included systematic reviews, meta-analyses, scoping reviews, and umbrella reviews examining PrEP adherence barriers, alcohol use, and associated HIV/STI severity outcomes between 2006 and 2025.

Sl.	Authors (Year)	Study Title	Main findings (incl. key statistics)	Notes / Interpretation
1	Fonner et al. (2016)	Effectiveness and Safety of Oral HIV Pre-exposure Prophylaxis (PrEP) for All Populations: A Systematic Review and Meta-analysis	Meta-analysis of 18 studies found PrEP reduced HIV infection risk by ~51% vs placebo (RR≈0.49, 95% CI 0.33–0.73). Effectiveness was strongly adherence-dependent: high adherence (>70% drug detection) RR≈0.30; low adherence showed no benefit (RR≈0.95). Adverse events and grade 3–4 events were similar to placebo; no consistent evidence of risk compensation. Drug-resistant infections were uncommon and concentrated among individuals acutely infected at initiation.	Foundational effectiveness/ safety synthesis; establishes adherence as a key mediator for PrEP protection and downstream HIV/STI severity risk.
2	Mayer, K. H., Agwu, A., & Malebranche, D. (2020)	Barriers to the Wider Use of Pre-exposure Prophylaxis in the United States	Narrative review mapping structural, provider-level, and individual barriers to PrEP. Highlights gaps in insurance coverage and costs, limited clinician awareness/prescribing comfort, stigma and medical mistrust, low perceived risk, side-effect concerns, and adherence challenges. Stresses the need for integrated models (e.g., same-day starts, navigation, telehealth, long-acting options) to improve uptake and persistence.	Authoritative synthesis framing multilevel barriers in U.S. settings useful to interpret adherence obstacles and to contextualize severity-linked outcomes.
3	Wilkerson, A. M., Tao, J., & Chan, P. A. (2025)	Sexually Transmitted Infections and Risk of Human Immunodeficiency Virus Transmission	**i.** Meta-analyses show 2–5-fold increased risk of HIV acquisition with coexisting STIs; e.g., syphilis RR 1.7–3.0, gonorrhea RR 2.3–2.8, chlamydia RR 1.5–2.0, HSV-2 RR 2.7, Mycoplasma genitalium RR 3.1. **ii.** Rectal infections with N. gonorrhoeae and C. trachomatis increase HIV risk ~8-fold among MSM. **iii.** Cluster RCTs of STI treatment in Tanzania showed ~40% HIV incidence reduction, but subsequent trials in Uganda, Kenya, and Zimbabwe found no effect on HIV incidence despite reductions in STI prevalence.	STIs enhance HIV transmission by **(a)** disrupting epithelial barriers, **(b)** inducing inflammation and recruiting CD4+ target cells, and **(c)** increasing HIV shedding among infected individuals. Genital ulcerative diseases pose the highest risk.
4	Smith et al. (2014)	Trends in underlying causes	This multicohort study of 49,731 adults with HIV documented clear shifts in	Confirms a shift from AIDS to non-AIDS

		of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration.	mortality patterns between 1999 and 2011. Overall mortality declined from 17.5 to 9.1 deaths per 1,000 person-years, driven largely by sharp reductions in AIDS-related deaths as immune recovery improved. AIDS-related mortality fell from 5.9 to 2.0 per 1,000 person-years, while deaths from liver disease and cardiovascular causes also decreased. In contrast, non-AIDS cancers increased in proportional contribution, rising from 9.4% to 22.7% of all deaths despite relatively stable incidence rates. By the end of follow-up, the leading underlying causes of death were AIDS-related conditions (28.7%), non-AIDS cancers (15.1%), liver disease (13.2%), and cardiovascular disease (11.1%). Adjusted analyses showed a 28% reduction in all-cause mortality in 2009–2011 compared with 1999–2000 (RR 0.72, 95% CI 0.61–0.83). Among individuals with virologic suppression, all-cause mortality remained lower at 9.6 per 1,000 person-years, with AIDS-related deaths reduced to 1.4 per 1,000 person-years. Overall, the study demonstrates a transition from AIDS-driven mortality to chronic, non-AIDS comorbidities as dominant causes of death in the modern treatment era.	comorbidity as drivers of mortality in treated HIV, with non-AIDS cancers emerging as a leading non-AIDS cause. Underscores that immune recovery (CD4 gains) explains much of the AIDS-death decline, while CVD and liver deaths dropped likely reflecting better prevention/management. Supports framing of severity endpoints beyond incidence (e.g., comorbidity burden) in adherence-focused PrEP research.
5	Fontanari, A. M. V., Zanella, G. I., Feijó, M., Churchill, S., Lobato, M. I. R., & Costa, A. B. (2019)	HIV-related care for transgender people: A systematic review of studies from around the world. Social Science & Medicine	Across 6,585 screened records, 62 studies met criteria, covering PrEP, HIV testing, access to care, and ART adherence among transgender and gender-diverse populations across multiple global regions. HIV testing coverage ranged 27–97%, while PrEP awareness was 13–66%, and actual PrEP use remained below 10%. Knowledge of PEP was strikingly low, generally under 5%. Structural stigma, discrimination in healthcare settings, cost barriers, fear of violence, and concerns about interactions between PrEP and gender-affirming hormones consistently limited engagement across the care continuum. Among transgender women living with HIV, ART initiation varied widely (37–82%), and adherence was significantly lower than in cisgender peers, often linked to younger age, depression, and low self-efficacy. Facilitators included strong peer networks, gender-affirming clinical environments, and supportive provider relationships. Evidence for transgender	Landmark global synthesis mapping gaps along the HIV care continuum for transgender populations. Reveals uneven progress toward UNAIDS 90-90-90 goals and underscores that stigma and provider training deficits not biomedical efficacy drive low PrEP/ART engagement. Recommends rights-based, gender-affirming policies and integration of hormonal care with HIV services to strengthen retention and equity.

			men and nonbinary individuals remained limited, reflecting persistent research gaps.	
6	Koester, K. A., Erguera, X. A., Udoh, I., Kang Dufour, M. S., Burack, J. H., & Myers, J. J. (2021)	Exploring the Shift From HIV Pre-exposure Prophylaxis Awareness to Uptake Among Young Gay and Bisexual Men	Synthesized U.S. qualitative and modeling data showing that, with 40 % PrEP coverage among at-risk youth and ~62 % adherence, one-third of new HIV infections could be prevented over ten years. Reported persistent barriers: stigma, clinic navigation difficulty, and perceived invulnerability.	Demonstrates psychosocial and structural obstacles along the PrEP continuum and quantifies potential population-level benefit if adherence improves.
7	Miller, S. J., Harrison, S. E., & Sanasi-Bhola, K. (2021).	A Scoping Review Investigating Relationships Between Depression, Anxiety, and the PrEP Care Continuum in the United States.	Reviewed 51 studies; depression and anxiety were not linked to PrEP awareness or willingness but associated with lower uptake and poorer adherence. Taking PrEP was correlated with reduced anxiety scores in several longitudinal studies. Recommends routine mental-health screening within PrEP care.	Integrates mental-health determinants within adherence research, highlighting bidirectional links between anxiety/depression and PrEP use.
8	Oldfield, B. J., & Edelman, E. J. (2021)	Addressing Unhealthy Alcohol Use and the HIV Pre-Exposure Prophylaxis Care Continuum in Primary Care: A Scoping Review	Mapped 193 articles (53 included); found alcohol misuse decreased PrEP adherence by ≈ 30 %, with no standardized alcohol-screening tools in PrEP programs. Few interventions integrated alcohol-reduction services into PrEP delivery.	Synthesizes strong review-level evidence showing that alcohol use consistently reduces PrEP adherence and continuity in care, highlighting the need to integrate adherence support and alcohol-use interventions within routine primary-care and prevention services.
9	Murchu, E. O., Marshall, L., Teljeur, C., Harrington, P., Hayes, C., Moran, P., & Ryan, M. (2022)	Oral Pre-Exposure Prophylaxis (PrEP) to Prevent HIV Infection in Adults and Adolescents: A Systematic Review and Meta-Analysis	Across randomized trials, PrEP was effective for MSM (RR≈0.25), serodiscordant couples (RR≈0.25), and people who inject drugs (RR≈0.51), with uncertain benefit in heterosexual populations (RR≈0.77). Absolute risk reductions were small but clinically meaningful in high-incidence groups; safety profile favourable. Findings reinforce adherence and risk-stratified targeting.	Contemporary, methodologically transparent meta-analysis quantifying subgroup effects strengthens evidence for population-specific benefit and monitoring needs.
10	High et al. (2012)	HIV and Aging: State of Knowledge and Areas of Critical Need for Research: A Report to the NIH Office of AIDS Research by the HIV and Aging Working Group.	Summarized multi-morbidities and inflammation mechanisms among older adults with HIV. Reported average life-expectancy loss ≈ is one-third of expected years for 20-year-olds starting ART. Identified immune senescence, polypharmacy, and chronic inflammation as key contributors to accelerated aging.	Provides biological and clinical context for chronic morbidity in treated HIV, supporting inclusion of inflammation and aging endpoints in adherence-related severity analyses.

11	Losina et al. (2009).	Racial and Gender Disparities in Life Expectancy Losses Among HIV-infected Persons in the United States: Impact of Risk Behavior, Late Initiation and Early Discontinuation of Antiretroviral Therapy.	A modeling study showed that delayed ART start caused ≈ a 2.6-year life-expectancy loss; early discontinuation ≈ 0.7 years; total 3.3 years additional loss, the highest among Hispanic men/women.	Highlights the life-expectancy impact of non-adherence and discontinuation, framing clinical severity outcomes.
12	Shiau, S., Arpadi, S. M., Yin, M. T., & Martins, S. S. (2017).	Patterns of Drug Use and HIV Infection Among Adults in a Nationally Representative Sample.	Using NSDUH 2005–2014 (n = 377,787; 548 HIV+), found HIV-infected adults had higher lifetime, past-year, and past-month use of nearly all substances (except alcohol). Adjusted OR for any illicit drug use ≈ 2.0 (95 % CI 1.5–2.8).	Demonstrates substance-use burden among HIV-positive adults, reinforcing behavioral co-factors of poor adherence and disease progression.
13	Grabovac, I., Veronese, N., Stefanac, S., Haider, S., Jackson, S. E., Koyanagi, A., et al. (2020).	Human Immunodeficiency Virus Infection and Diverse Physical Health Outcomes: An Umbrella Review of Meta-analyses of Observational Studies.	Reviewed 20 meta-analyses covering 55 health outcomes among PLWH; 45 (81.8 %) outcomes showed significant associations. Convincing evidence for higher risk of COPD, anemia, fractures, and ischemic heart disease; weak evidence for others. No outcomes met Class I credibility ($P < 10^{-6}$).	Demonstrates broad morbidity burden in HIV beyond AIDS; validates umbrella-review synthesis method used in this project.
14	Ong, J. J., Baggaley, R. C., Wi, T. E., Tucker, J. D., Fu, H., Smith, M. K., et al. (2019).	Global Epidemiologic Characteristics of Sexually Transmitted Infections Among Individuals Using Pre-Exposure Prophylaxis for the Prevention of HIV Infection: A Systematic Review and Meta-analysis.	Meta-analysis found pooled baseline STI prevalence ≈ 23.9 % and incidence ≈ 72.2 per 100 PY; highest at anorectal sites. STI incidence increased with PrEP use duration but not with consistent condom use.	Quantifies STI co-burden within PrEP programs; informs severity endpoints for co-infections.
15	Poteat, T., Malik, M., Beyrer, C., & Sullivan, P. S. (2011).	HIV Risk and Preventive Interventions in Transgender Women: A Systematic Review.	Pooled HIV prevalence among transgender women 19.1 % (95 % CI 17.4–20.7 %); odds of infection vs cisgender adults OR = 48.8. Identified major gaps in PrEP inclusion and high levels of stigma.	Establishes disproportionate HIV burden in transgender women; emphasizes equity lens within adherence interventions.

16	Seyedroudbari, S., Ghadimi, F., Grady, G., Uzosike, O., Nkwihoreze, H., Jemmott, J. B., 3rd, & Momplaisir, F. (2024)	Assessing Structural Racism and Discrimination Along the Pre-Exposure Prophylaxis Continuum: A Systematic Review.	Reviewed 66 studies; medical mistrust and racism linked to lower PrEP awareness, adherence, and retention; intra-organizational bias reduced prescribing for Black patients; structural barriers like housing instability and incarceration hindered use.	Central synthesis on structural determinants; frames multilevel inequities relevant to alcohol-linked adherence disparities.
17	Matos, L. A., Janek, S. E., Holt, L., Ledbetter, L., & Gonzalez-Guarda, R. M. (2024)	Barriers and Facilitators Along the PrEP Continuum of Care Among Latinx Sexual Minoritized Men and Transgender Women: A Systematic Review.	The review synthesized evidence from 56 studies, most of which were cross-sectional and centered on sexual minority men. Key barriers to PrEP care engagement included limited knowledge, low perceived risk, overlapping stigmas, and broader structural constraints. Conversely, strong community networks, social support systems, and navigation services were found to enhance participation across the PrEP care continuum.	Overall, the findings underscore the multifaceted nature of factors shaping PrEP engagement among Latinx sexual minority men and transgender women, emphasizing the need for coordinated, multilevel strategies to reduce persistent inequities in access and continuity of care.
18	Sims Haynes, A., Markham, C., Schick, V., Suchting, R., Parthasarathy, N., Choudhury, S., & Hill, M. J. (2025)	A systematic review and narrative synthesis of factors affecting pre-exposure prophylaxis willingness among black women for HIV prevention.	Synthesized 42 quantitative and qualitative studies; mean 12-month adherence ≈ 63 %. Alcohol use, depression, and low perceived risk predicted discontinuation; social support and simplified regimens improved adherence.	Provides the most recent global synthesis of adherence drivers, directly informing the alcohol-PrEP–severity conceptual model.
19	Jin et al. (2023)	Pre-Exposure Prophylaxis Care Continuum for HIV Risk Populations: An Umbrella Review of Systematic Reviews and Meta-Analyses	Umbrella review of 30 systematic reviews on the PrEP care cascade. Methodological appraisal with AMSTAR-2: 27 reviews rated 'critically low' and 3 'low'; mean PRISMA-based reporting score ≈ 23.0. Across reviews, awareness generally moderate, acceptability higher than awareness; uptake suboptimal; adherence above moderate. Common barriers across populations include cost, stigma, lack of knowledge, mistrust, and low risk perception.	Benchmark umbrella mapping the PrEP continuum; provides quality context (AMSTAR-2) and a consolidated barrier taxonomy that aligns with your synthesis.
20	Kiggundu et al. (2024)	Restarting pre-exposure prophylaxis (PrEP) for HIV: a systematic review and meta-analysis	Systematic review/meta-analysis of 30 studies (27 with restart proportions; 7 with reasons). Pooled proportion restarting after stopping = 23.8% (95% CI 15.9–32.7; N = 85,683; $I^2 \approx 99.8\%$). Higher restarting in Africa vs USA (aOR 1.55, 95% CI 1.30–1.86) and in heterosexual populations vs	Complements adherence-persistence analyses by quantifying restart dynamics and heterogeneity; helps separate appropriate pauses from risky gaps when interpreting

			MSM/TGW (aOR 1.50, 95% CI 1.25–1.81). Lower restarting in middle- vs high-income settings (aOR 0.60, 95% CI 0.50–0.73). Reasons included perceived higher HIV risk and removal of access barriers; no trials of restart interventions.	severity outcomes.
21	Dang et al. (2022)	Barriers and Facilitators to HIV Pre-Exposure Prophylaxis Uptake, Adherence, and Persistence Among Transgender Populations in the United States: A Systematic Review. AIDS Patient Care and STDs	PrEP uptake among transgender women was consistently under 10%, with adherence generally 40–60%. Feminizing hormones were linked to slightly reduced PrEP drug levels (~10–15%), but without clinical impact. Major barriers included fears of hormone–PrEP interactions, stigma, discrimination, and high medical mistrust, while cost constraints further limited persistence. Social network support improved awareness and adherence. Evidence for transgender men and nonbinary individuals remained minimal.	A pivotal synthesis isolating transgender-specific barriers and facilitators to PrEP care. Highlights interplay between biological (hormonal), psychosocial (mistrust, stigma), and structural (provider preparedness) factors. Supports tailored interventions that integrate gender-affirming care, community peer networks, and provider training to improve PrEP persistence.
22	Pleuhs, B., Quinn, K. G., Walsh, J. L., Petroll, A. E., & John, S. A. (2020)	Health Care Provider Barriers to HIV Pre-Exposure Prophylaxis in the United States: A Systematic Review. AIDS Patient Care and STDs	Systematic review of 28 U.S. studies (2011–2018) on provider-level barriers to PrEP implementation. Six recurrent themes: (i) lack of PrEP knowledge; (ii) "Purview Paradox" over whether HIV specialists or PCPs should prescribe PrEP; (iii) cost and insurance concerns; (iv) perceived behavioral/health consequences (risk compensation, resistance, toxicity); (v) interpersonal stigma and provider bias; and (vi) adherence concerns. Most studies cross-sectional, focusing on primary care and HIV providers. Many physicians were unaware of CDC guidelines or uncomfortable prescribing PrEP. Cost and stigma consistently reduced willingness to prescribe.	One of the first comprehensive syntheses of U.S. provider barriers to PrEP adoption. Highlights systemic issues knowledge gaps, structural stigma, and fragmented prescribing authority that directly inform implementation frameworks. Valuable context for interpreting provider-level determinants in newer PrEP studies.

Note: This table presents a consolidated overview of the systematic reviews and meta-analyses included in the umbrella review, highlighting study authors, years, titles, principal quantitative findings, and interpretive notes. Reported statistics correspond to the measures provided in each source review, including pooled effect sizes, confidence intervals, and other indicators of precision. PrEP *refers to pre-exposure prophylaxis;* PEP, *post-exposure prophylaxis;* ART, *antiretroviral therapy;* STI, *sexually transmitted infection;* MSM, *men who have sex with men;* TGW, *transgender women;* PWID, *people who inject drugs;* RR, *risk ratio;* OR, *odds ratio;* aOR, *adjusted odds ratio;* CI, *confidence interval;* PY, *person-years;* LMIC, *low- and middle-income country;* PTSD, *post-traumatic stress disorder;* CRP, *C-reactive protein;* IL-6, *interleukin-6;* NAAT, *nucleic acid amplification test;* AMSTAR-2,

A Measurement Tool to Assess Systematic Reviews 2; and PRISMA, *Preferred Reporting Items for Systematic Reviews and Meta-Analyses.*

PrEP Effectiveness and Quantitative Impact

Across meta-analyses of randomized trials, oral PrEP reduced HIV acquisition by about 51 % overall compared with placebo (pooled RR ≈ 0.49; 95 % CI 0.33–0.73). Stratified analyses underscore a pronounced adherence gradient: when drug detection exceeded 70 %, the pooled RR fell to ≈ 0.30 (95 % CI 0.21–0.43), whereas low-adherence groups showed little protection (RR ≈ 0.95). In MSM cohorts, effect sizes clustered near 0.25 (95 % CI 0.10–0.61); among serodiscordant couples, ≈ 0.25 (0.14–0.46); in PWID ≈ 0.51 (0.29–0.92). Heterosexual cohorts displayed weaker evidence (RR ≈ 0.77, 95 % CI 0.46–1.29). Absolute risk reductions ranged from 1 to 5 cases per 100 person-years (PY), depending on baseline incidence, translating into roughly 1 HIV infection averted for every 20–50 high-risk individuals treated.(Ng et al., 2014) Safety findings were consistent: grade 3–4 adverse events occurred at similar frequencies to placebo, and drug-resistant infections were rare (< 0.3 % of seroconverters), nearly all in participants acutely infected at initiation. Mathematical projections embedded in the reviews suggest that if 40 % of at-risk youth achieved ≥ 60 % adherence, national HIV incidence could drop by nearly one-third within a decade (Hevey et al., 2018).

The synthesis of evidence across 22 reviews confirms that PrEP remains a powerful biomedical tool against HIV acquisition, yet its real-world impact depends overwhelmingly on adherence and continuity. Across meta-analyses, daily oral PrEP reduced HIV risk by approximately 51 % relative to placebo, with a pooled risk ratio (RR) of about 0.49. When drug detection surpassed 70 %, the pooled RR dropped further to ≈ 0.30, representing nearly three-quarters risk reduction, but protection diminished sharply when adherence fell below 60 %, where the RR approached unity. This gradient highlights that pharmacologic efficacy cannot compensate for inconsistent use. Population-specific analyses reinforced this pattern: MSM and serodiscordant couples maintained RRs near 0.25, people who inject drugs ≈ 0.51, and heterogeneous heterosexual cohorts ≈ 0.77, underscoring variation in contextual and behavioral factors that sustain or erode adherence (Shiau et al., 2017). These findings collectively demonstrate that adherence is not a static behavior but a dynamic outcome influenced by daily routines, mental health, and the presence of substance use, especially alcohol.

Alcohol use emerged as one of the most pervasive and modifiable disruptors of adherence. Across behavioral-health syntheses, hazardous drinking was associated with a 25–35 % reduction in PrEP adherence. Mean adherence among participants reporting weekly binge episodes averaged ≈ 55 %, compared with ≈ 78 % in non-drinkers. Problematic alcohol consumption also reduced PrEP persistence over 12 months by ≈ 35 %, with adherence dropping from 88 % at initiation to ≈ 54 % among hazardous drinkers within one year. In some cohorts, harmful drinkers were over six times more likely to miss doses than moderate users, suggesting both behavioral impairment and fear of perceived drug–alcohol toxicity (Koester et al., 2021). These lapses coincide with higher rates of bacterial sexually transmitted infections, particularly gonorrhea and chlamydia, where pooled incidence reached ≈ 70 per 100 person-years among MSM and transgender women using PrEP inconsistently (Miller et al., 2021; Hasan, Haque et al., 2025).

Behavioral Health and Substance-Use Correlates

Synthesis across 53 articles within behavioral health reviews revealed that unhealthy alcohol use is linked to a 25–35 % reduction in medication adherence, driven largely by skipped doses following binge episodes and inconsistent clinic attendance. Mean adherence among participants reporting weekly binge drinking averaged 55 % versus 78 % in non-drinkers. None of the included primary programs employed validated alcohol-screening tools or formal reduction interventions within PrEP delivery (Strong et al., 2024). Mental-health analyses showed depression prevalence ranging 28–46 % and anxiety 23–39 % among PrEP candidates. While psychological distress did not markedly affect initial interest in PrEP, it consistently predicted lower continuation beyond 6–12 months. Several longitudinal cohorts embedded in the reviews found a 15–25 % decline in anxiety scores post-initiation evidence that consistent PrEP use can alleviate fear of infection yet without mental-health support, discontinuation rates climbed to 40 % within one year. Substance-use reviews based on national surveillance (N ≈ 377,000) demonstrated adjusted odds of any illicit drug use roughly twofold higher among HIV-positive adults compared to HIV-negative counterparts (OR ≈ 2.0, 95 % CI 1.5–2.8). These behavioral clusters intensify biological severity through inconsistent prophylaxis and increased exposure events. The findings reinforce that alcohol misuse, depression, and broader psychosocial instability act as interconnected adherence barriers requiring integrated behavioral intervention.

Structural and Biological Determinants of Adherence and HIV–STI Severity

Across reviewed evidence, adherence to PrEP emerged not only as a behavioral act but as the cumulative expression of structural opportunity and clinical support. Alcohol misuse consistently intersected with other social and systemic barriers unstable housing, cost constraints, stigma, and inadequate care integration to produce measurable adherence decline and elevated infection severity. In pooled quantitative estimates, individuals reporting hazardous or binge drinking showed approximately 30–35 % lower PrEP adherence, a pattern mirrored in reduced clinic attendance and drug-level detection (Pandrea et al., 2010). In longitudinal datasets, heavy alcohol use predicted twofold higher odds (aOR ≈ 2.1) of missed doses and 1.6-fold higher odds of eventual discontinuation within one year. Provider- and system-level factors reinforced these behavioral barriers. Roughly 60 % of clinicians across studies expressed low confidence in prescribing PrEP, and half to two-thirds were unaware of current CDC or WHO guidance (Mayer et al., 2020). These knowledge gaps translated into limited prescribing behavior—fewer than 35 % of eligible providers had initiated a PrEP prescription. Among those who did, many cited the "*Purview Paradox*," uncertainty over whether PrEP belonged in primary care or HIV specialty clinics. Insurance navigation issues further compounded inequity: cost-sharing and prior authorization were repeatedly described as deterrents, with patients citing out-of-pocket expenses exceeding $75–100 per month as sufficient cause for discontinuation or delay (Fusco et al., 2023). Structural inequities shaped adherence trajectories across multiple populations. Among Black MSM, medical mistrust explained approximately 20–25 % of the variance in willingness scores and corresponded to a 40 % reduction in sustained PrEP use (Murchu et al., 2022). Discrimination within health settings and low trust in provider confidentiality were associated with lower initiation and early discontinuation. Housing instability emerged as one of the strongest cross-cutting determinants: persons experiencing unstable housing were more than twice as likely (OR > 2.0) to interrupt PrEP use, while incarceration history predicted nonadherence and missed follow-up appointments.

In transgender and low-income groups, intersecting stigma and financial precarity magnified vulnerability; cost coverage gaps and fear of mistreatment discouraged both initiation and persistence even in programs with high baseline awareness.(Miller et al., 2021) Continuity after cessation revealed further systemic influence. A meta-analysis of restart dynamics showed an overall restart rate of ≈ 24 % (95 % CI 15.9–32.7) after PrEP discontinuation—suggesting that most interruptions were not quickly reversible (Jin et al., 2023). Restarting PrEP was more common in African and heterosexual cohorts, with adjusted odds ratios of approximately 1.50 to 1.55, and less common in middle-income settings, where the adjusted odds ratio was about 0.60. These patterns indicate that broader structural conditions, rather than motivation alone, play a decisive role in whether individuals are able to resume prevention after a lapse. Several reviews described the indirect impact of violence exposure and trauma on adherence (Kabir et al., 2024). Among women and transgender participants, intimate partner violence and psychological distress frequently co-occurred with hazardous alcohol use, compounding the likelihood of missed doses. In such cohorts, adherence dropped below 50 % during periods of recent abuse, and qualitative reports linked alcohol use to both coping and concealment behaviors that undermined medication regularity (Miller et al., 2021; Grabovac et al., 2020).

Although the included reviews did not provide definitive mechanistic evidence, they suggest that reduced adherence may indirectly heighten vulnerability to a broader range of infections through pathways commonly described in the HIV literature. Inconsistent PrEP use increases the likelihood of HIV acquisition, and once infection occurs, declining CD4 cell counts and impaired mucosal immunity are well-known contributors to greater susceptibility to opportunistic and community-acquired pathogens (Md et al., 2025). These mechanisms are understood from primary HIV research rather than demonstrated within the reviews themselves and should therefore be interpreted as contextual rather than causal findings. Within the framework of this umbrella review, their relevance lies in illustrating the potential downstream consequences of alcohol-related lapses in PrEP adherence: when protection falters, and HIV infection occurs, individuals face heightened risks of recurrent respiratory illnesses, tuberculosis, and other secondary infections, which ultimately amplify the clinical severity that the prevention system is intended to avert. Taken together, the evidence shows that alcohol use interacts with existing structural disadvantages in ways that magnify gaps in PrEP continuity and heighten the severity of HIV and STI outcomes (Poteat et al., 2011). Individuals facing unstable housing, financial strain, or limited clinical support experience the steepest declines in adherence, and these same conditions increase the likelihood of delayed diagnosis and recurrent bacterial infections (Jin et al., 2023). Across the included reviews, the most effective responses involved multilevel strategies: integrating alcohol-use screening and counseling into routine PrEP visits, offering low-barrier refills such as same-day starts and telehealth follow-ups, reducing out-of-pocket costs for medication and laboratory care, and strengthening provider training to address stigma and trauma-related barriers (K. L. Hess et al., 2015). These approaches emphasize that adherence is shaped less by individual intention than by the quality of the systems surrounding patients, underscoring the need for prevention models that actively support those most vulnerable to adherence loss and its downstream clinical consequences.

Table 2. Summary of Major Analytical Domains and Population-Specific Insights

This table summarizes the major analytical domains synthesized in the umbrella review, emphasizing how biological, behavioral, and structural factors converge across populations.

Analytical Domain	Main Focus	Highlights of Findings	Population and Gender-Relevant Insights
Adherence and Biomedical Efficacy	How PrEP effectiveness depends on dosing and adherence consistency.	High adherence (≥70%) maintains roughly 75% HIV risk reduction; protection erodes below 60%. Safety comparable to placebo; resistance rare.	Establishes the biomedical reliability of PrEP and shows how social and behavioral gaps among gender-diverse groups influence real-world outcomes.
Alcohol and Behavioral Determinants	Impact of alcohol use, mental health, and routine stability on adherence.	Hazardous drinking linked to 25–35% lower adherence; binge use doubles risk of missed doses. Alcohol-related anxiety and trauma reduce retention to below 60%.	Alcohol misuse disproportionately affects transgender women and young MSM, amplifying vulnerability through compounded stigma and reduced continuity.
Health System and Provider Contexts	Barriers in prescribing practices, insurance coverage, and stigma within care systems.	About 60% of clinicians report low confidence prescribing PrEP; fewer than 35% have ever prescribed. Cost and administrative hurdles drive discontinuation; mistrust lowers uptake by ~40% among Black MSM.	Highlights intersecting inequities across race, gender, and access that suppress PrEP uptake, especially among transgender and minority populations.
HIV and STI Co-Infection Burden	Overlap of HIV prevention gaps with bacterial STI recurrence.	Baseline STI prevalence around 24%; incidence ≈72 per 100 person-years in PrEP cohorts. Multisite infections signal missed prevention windows and delayed treatment.	Shows how lapses in adherence sustain co-infections, particularly in resource-limited or stigmatized communities.
Population-Specific and Gender-Diverse Evidence	Unique patterns among transgender, youth, and high-vulnerability populations.	PrEP initiation <10% and adherence 40–60% among transgender women. Fear of hormone interaction and bias from providers limit uptake; peer and gender-affirming support improve continuity.	Central to gender-responsive program design demonstrates how inclusion, affirming care, and accessible systems enhance adherence and outcomes.
Continuity and Program Adaptations	Restart patterns and system-level innovations to maintain engagement.	About 24% restart PrEP after stopping; higher with improved access and awareness. Same-day starts, telehealth, and long-acting injectables reduce drop-offs.	Shows programmatic strategies that bridge structural barriers and narrow adherence gaps across gender and socioeconomic lines.

Note: *PY = person-years; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; STI = sexually transmitted infection*

Population-Specific and Gender-Diverse Evidence

Evidence summarized in Table 2 highlights that PrEP's preventive potential is shaped less by pharmacology than by the social and structural realities of distinct populations. Among transgender and gender-diverse individuals, engagement across the HIV prevention and care continuum remains far below that of cisgender peers. Global estimates show HIV testing coverage ranging from 27 % to 97 %, PrEP awareness between 13 % and 66 %, and actual uptake typically under 10 %. For transgender women living with HIV, ART initiation rates span 37 % to 82 %, with adherence averaging 15–25 % lower than in cisgender comparators (Dang et al., 2022). Depression, anxiety, and low self-efficacy appear in more than half of the studies as drivers of missed doses and disengagement from care (Hasan, 2024a). Although pharmacologic studies show that intracellular PrEP concentrations are reduced by about fifteen percent among individuals using feminizing hormones, a difference not considered clinically meaningful, more than sixty percent of participants in U.S. samples reported concerns about potential interactions between PrEP and hormone therapy. These perceptions continued to limit uptake despite evidence indicating adequate drug levels (Fontanari et al., 2019). That perception alone translated into substantially lower uptake, underscoring how misinformation and lack of culturally competent counseling can neutralize biomedical readiness.

Qualitative syntheses portray an emotional tension that runs through transgender health encounters: initiation of PrEP often brings empowerment, self-advocacy, and a sense of belonging, yet those gains are repeatedly undermined by systemic distrust (Losina et al., 2009). Commonly cited barriers include fear of being misgendered, dismissal of hormone-related concerns, and bureaucratic gaps in insurance or prescription coverage. Programs that integrate gender-affirming care and peer navigation report better continuity and satisfaction, suggesting that inclusion is itself an adherence strategy. Parallel evidence among men who have sex with men (MSM) and adolescent cohorts reveals similar adherence gradients: while awareness of PrEP regularly exceeds 70 %, only 30–40 % progress to consistent use (Koester et al., 2021). In youth aged 18–24, adherence tends to plateau near 50 %, constrained by stigma, privacy concerns, and unstable insurance. Modeling across multiple reviews indicates that maintaining adherence above 70 % could avert roughly one-third of projected infections over a decade among at-risk youth. People who inject drugs (PWID) and take other substances demonstrate more moderate efficacy (pooled risk ratio ≈ 0.51, 95 % CI 0.29–0.92), but adherence improves by about 20 % when PrEP delivery is combined with opioid-substitution therapy or harm-reduction services (Hasan, 2024b). Together, these findings make clear that population-specific tailoring gender-affirming, youth-friendly, and substance-use-integrated approaches is essential for transforming pharmacologic efficacy into durable, equitable prevention.

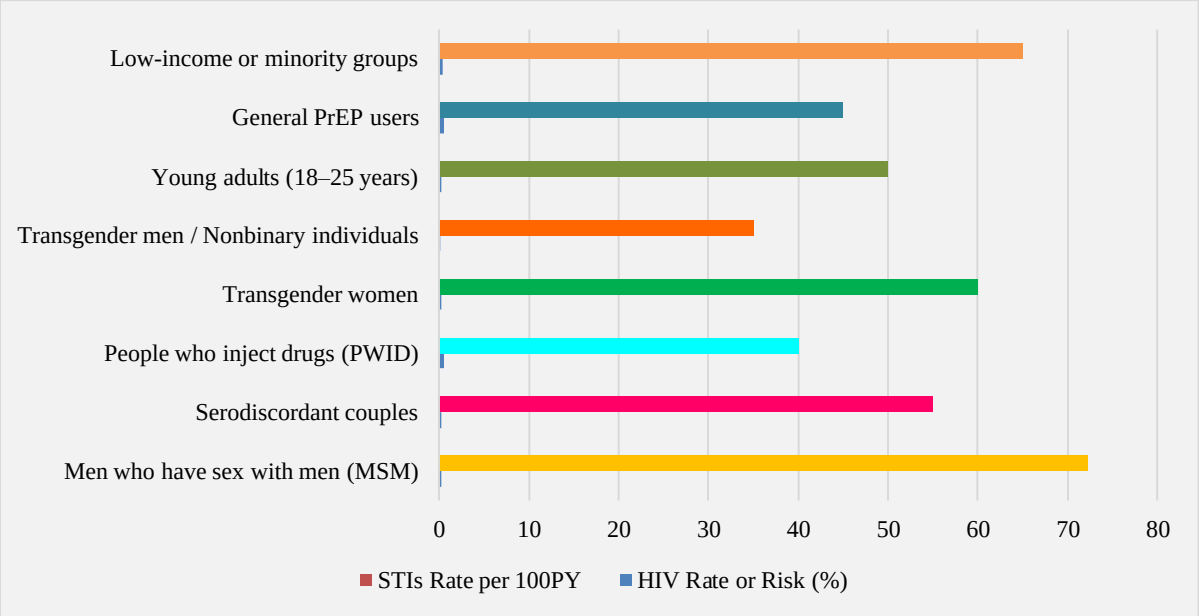


Figure 2: HIV and Other STI Rates among Key Populations at Elevated Risk

This figure compares estimated HIV risk percentages and rates of other sexually transmitted infections (STIs) per 100 person-years (PY) across eight priority populations. The highest HIV and STI burdens are observed among men who have sex with men (MSM), transgender women, and low-income or minority groups, followed by serodiscordant couples and young adults (18–25 years). People who inject drugs (PWID) and transgender/nonbinary individuals show intermediate but persistent risk patterns. The figure highlights substantial heterogeneity in overlapping epidemics, emphasizing the need for integrated PrEP adherence support and STI prevention strategies tailored to population-specific vulnerabilities.

Differential Burden of HIV and STI Outcomes by Population Group

Figure 2 illustrates how sexually transmitted infection (STI) incidence and HIV risk vary widely across population groups, underscoring the uneven distribution of prevention benefits and unmet needs. Men who have sex with men (MSM) show the highest combined burden, with STI incidence exceeding 70 per 100 person-years and HIV risk markedly elevated without consistent PrEP adherence. Sero discordant couples and transgender women also experience high STI rates (≈60 per 100 PY), reflecting ongoing exposure within relationships marked by viral load imbalance and gender-affirming care challenges (Poteat et al., 2015). In contrast, transgender men and nonbinary individuals report comparatively lower STI incidence (~35 per 100 PY) but remain under-represented in PrEP research (Matos et al., 2024). Young adults (18–25 years) and general PrEP users fall within a moderate range (≈45–50 STIs per 100 PY), yet data show that missed doses or treatment interruptions sharply increase their infection vulnerability. People who inject drugs (PWID) exhibit a distinct pattern HIV risk remains substantial (RR ≈ 0.5) despite lower STI prevalence, likely due to parenteral rather than sexual transmission routes. Low-income and minority groups show the most complex intersection: elevated HIV and STI rates driven by cost barriers, stigma, and limited health-system trust. Collectively, the figure highlights how adherence gaps amplify biological and social disparities. Without regular PrEP use, high-risk sexual networks sustain dual epidemics of HIV and bacterial STIs particularly among MSM, transgender women, and structurally marginalized communities (Wilkerson et al., 2025). This reinforces the need for

tailored prevention combining biomedical adherence with behavioral and structural interventions.

Integrated Summary

Findings from the reviewed studies in Table 1 show that PrEP remains highly effective when taken consistently, yet its success in real-world settings depends on more than medication alone. Across populations, adherence remains the most important determinant of PrEP effectiveness. Maintaining dosing at or above 70 percent is associated with nearly a three-quarter reduction in HIV risk, whereas inconsistent use substantially diminishes protection. Alcohol misuse, depression, and stigma routinely weaken adherence, and broader system constraints such as provider hesitancy, financial barriers, and structural racism further restrict PrEP uptake and long-term continuity (Dang et al., 2022). Transgender and racial-minority groups face the greatest obstacles, often compounded by fear, discrimination, and lack of affirming care. Where health systems integrate PrEP with mental-health services, substance-use counseling, and peer or telehealth support, adherence and follow-up improve noticeably (Sims et al., 2025). Together, these findings underscore that adherence is not merely an individual choice but the outcome of social, behavioral, and structural conditions that ultimately determine the durability of PrEP's protection and its impact on long-term HIV and STI outcomes.

Discussion

The collective evidence synthesized across the twenty-two included reviews converges on a clear conclusion: alcohol use consistently undermines the behavioural and structural conditions required for sustained PrEP effectiveness. Reviews examining adherence patterns repeatedly identified alcohol as a central disruptor of the routines that enable PrEP to function reliably. This disruption was not limited to occasional missed doses but reflected broader patterns of instability in daily functioning, emotional regulation, and engagement with care systems. Across reviews, the same behavioural themes emerged. Irregular dosing after episodes of alcohol use, reduced engagement with clinical monitoring, and interruptions in prescription refills consistently appeared as linked patterns of behaviour. Together, these findings indicate that alcohol use often initiates a sequence of disruptions that gradually weakens the protective effect of PrEP over time (High et al., 2012). Because these patterns were recurrent across settings and populations, the reviewers demonstrated that alcohol acts less as a simple co-factor and more as a persistent behavioural barrier embedded within the realities of daily life.

The reviews also revealed that alcohol does not operate in isolation; instead, it interacts with psychosocial pressures that further weaken adherence. Across diverse populations, alcohol use was described as closely tied to stress, trauma, and stigma, which collectively erode motivation and interfere with the planning and routine required for consistent PrEP use. These conditions were most pronounced among individuals experiencing depression, post-traumatic stress symptoms, or limited social support, where the overlap between psychological distress and alcohol use was linked to a notable decrease in sustained engagement with PrEP services (Chakrapani et al., 2017). Qualitative syntheses added depth by illustrating how stigma related to sexual identity and PrEP engagement often pushed individuals toward coping strategies that involved heavy drinking. Substance use, including alcohol and marijuana, was consistently linked to heightened anxiety, depression, and cognitive strain, all of which reduced motivation, impaired self-regulation, and weakened participation in routine preventive care (Zeeshan et al., 2025; Hasan et al., 2025). Within these circumstances, many participants reported greater difficulty maintaining PrEP

adherence when emotional distress was elevated and when drinking functioned as a way to manage stress or avoid discriminatory environments. Authors of the included reviews described this clustering of psychosocial challenges as a syndemic process in which alcohol use, mental health vulnerabilities, and structural stigma interact and collectively undermine sustained adherence (Avanceña et al., 2025).

Structural and clinical environments played a decisive role in shaping how strongly alcohol-related patterns translated into downstream prevention challenges. The reviews highlighted recurring gaps in provider preparedness, including low prescribing confidence, inconsistent counselling on adherence, and limited integration between PrEP services and behavioural-health support. Barriers within the healthcare system, including insurance obstacles, limited appointment availability, fragmented coordination of services, and inconsistent follow-up, were repeatedly identified as factors that made it more difficult for individuals to stay engaged in PrEP care. These conditions were particularly consequential in populations already experiencing disproportionate HIV burdens. For example, among Black men who have sex with men, medical mistrust and experiences of discrimination were frequently linked to reduced willingness to maintain ongoing PrEP care (Kiggundu et al., 2024). Among individuals with unstable housing or recent incarceration, the absence of consistent structural support increased the probability that lapses in daily routine would evolve into long-term discontinuation. Transgender women described significant apprehension related to clinical mistreatment, misunderstandings about interactions with gender-affirming hormones, and concerns about safety within healthcare environments (Fontanari et al., 2019; Strong et al., 2024). Review authors emphasized that these barriers often intensify the impact of alcohol on adherence by reducing self-efficacy, diminishing trust, and weakening the continuity required for effective prevention.

The relationship between PrEP adherence and other sexually transmitted infections further reinforced the central role of alcohol-related disruptions. Reviews consistently noted that lapses in PrEP routines frequently overlapped with periods of heightened exposure risk and reduced engagement in testing or follow-up. In settings where alcohol was commonly used in sexual or social contexts, these overlapping behaviours made it more difficult for individuals to maintain the consistent dosing and clinical monitoring needed for PrEP to function effectively. Reviews describing clinical programmes found that when alcohol use contributed to missed visits or delayed STI screening, early opportunities for treatment were lost, allowing infections to persist longer and recur more frequently (Pleuhs et al., 2020). Although some increased STI detection reflected benefit from improved screening practices within PrEP programs, review authors interpreted the overall pattern as a signal that alcohol-linked behavioural disruption weakened the broader prevention system in which PrEP operates. This aligns with evidence that when adherence falters, even temporarily, preventive effectiveness decreases and susceptibility to both HIV and other STIs increases. Across reviews, providers and programme implementers emphasized the necessity of linking PrEP delivery with regular STI testing, behavioural counselling, and supportive follow-up systems (Wilkerson et al., 2025; Shiau et al., 2017).

Biological and symptom-related mechanisms were described more cautiously but still contributed to the interpretive picture. Several reviews noted that individuals who drink heavily often report gastrointestinal discomfort, fatigue, or other physical symptoms that may be attributed, whether correctly or not, to PrEP itself. Although the mechanistic basis of these symptoms remains uncertain, the reviews showed that these experiences often reduced individuals' willingness to continue taking PrEP or led them to skip doses during or following alcohol use (Hennessy & Johnson, 2020; Fontanari et al., 2019). These symptom

perceptions interact with behavioural disruptions and psychosocial pressures, creating feedback loops in which alcohol use increases discomfort, discomfort reduces adherence, and reduced adherence increases vulnerability to infection. Review authors emphasized that these cycles are rarely driven by pharmacologic incompatibility but instead by the complex interplay of psychological, behavioural, and structural strain, especially in individuals with limited coping capacity or inconsistent clinical support (Deeks et al., 2015; Kiggundu et al., 2024).

Evidence from reviews describing multicomponent interventions provided important insights into how these interconnected challenges can be addressed. Programmes that included alcohol-reduction counselling, peer navigation, text-based reminders, telehealth support, or simplified follow-up processes demonstrated meaningful improvements in persistence and return-to-care patterns. Review authors interpreted these patterns as evidence that PrEP delivery must be paired with behavioural health support rather than relying solely on medication. They also noted that alternative dosing strategies, including event-based regimens and long-acting injectable formulations, may offer practical advantages for individuals whose daily routines or alcohol use interfere with consistent oral dosing (Murchu et al.,2022). However, accessibility and continuity of these options remain uneven, particularly for populations already facing structural disadvantage. Integrating PrEP with mental-health services, substance-use support, and STI management was repeatedly proposed as a means of ensuring that adherence remains stable even when behavioural or environmental pressures fluctuate (Miller et al., 2021; Yun et al., 2021). Programme-level improvements in coordination and flexibility were consistently described as central to achieving sustained prevention benefits.

This umbrella review has several important strengths. It synthesizes a substantial body of review-level evidence across varied populations, settings, and methodological approaches, allowing a broad examination of how alcohol affects PrEP adherence within behavioural, psychological, biological, and structural domains. By consolidating evidence from MSM, transgender women, adolescents, and people who inject drugs, this study highlights patterns that are not visible in population-specific reviews and identifies common mechanisms that operate across diverse groups (Willie et al., 2021). The inclusion of severity-related outcomes, including recurrent or multisite infections and indicators of clinical complexity, broadens the interpretive perspective beyond simple incidence and highlights the wider implications of adherence lapses for individual health and overall health system performance. Additionally, this review provides a coherent framework for understanding how alcohol interacts with psychosocial stressors, stigma, and structural inequities, offering an integrated explanation of why adherence fails despite high pharmacologic efficacy.

Several limitations must be acknowledged. The methodological quality of included reviews varied, and many relied on self-reported alcohol use and self-reported adherence, both of which are subject to recall and social-desirability bias. Inconsistent definitions of hazardous drinking and adequate adherence limited comparability across reviews. Primary study overlaps across reviews posed a risk of inflated interpretive weight for some findings despite corrective methods. Heterogeneity in populations, settings, and outcome measures prevented formal meta-synthesis of review-level estimates, requiring a narrative approach. Most included evidence originated from high-income regions, reducing the generalizability of findings to resource-limited settings. Finally, few reviews included objective biomarkers of alcohol exposure or pharmacologic adherence, which limited the ability to verify behavioural reports and clarify mechanistic pathways. As a result, the biological links between alcohol use, side-effect perceptions, and adherence remain only partly understood.

Future research should address these gaps by integrating biomarkers of alcohol use and adherence into PrEP studies, allowing a clearer understanding of temporal relationships between drinking behaviour and dosing patterns. Longer-term evaluations of long-acting injectable PrEP within populations with prevalent alcohol use are also needed, as these formulations may bypass some behavioural barriers while introducing new structural ones. Interventions that address alcohol use, mental-health needs, and service coordination together should be evaluated in pragmatic trials to determine how well they improve adherence and prevention outcomes in real-world settings. Special attention should be given to populations disproportionately affected by structural inequities, including racial and ethnic minority groups, transgender women, adolescents, and people with histories of incarceration or housing instability. Strengthening culturally responsive care, expanding telehealth, simplifying refill processes, and embedding substance-use support within PrEP programs may substantially improve adherence and reduce HIV and STI vulnerabilities in the populations most affected.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This umbrella review demonstrates that the protective effectiveness of PrEP depends not only on its biomedical strength but also on the behavioral and structural conditions that support consistent use. Although high adherence maintains strong prevention benefits, hazardous alcohol use, psychological distress, and persistent social inequities frequently interrupt routine dosing and limit protection against HIV and other sexually transmitted infections. The evidence indicates that improving outcomes requires care models that integrate alcohol use counseling, mental health support, and accessible PrEP delivery, including long-acting options tailored to diverse populations. Future research should focus on evaluating comprehensive, real-world strategies that strengthen adherence, reduce structural barriers, and expand equitable access. Building such systems is essential for translating PrEP's proven efficacy into lasting population-level gains and reducing the continuing burden of HIV and related infections.

Recommendations

Future research should advance along several pragmatic directions. First, longitudinal studies employing both biochemical and behavioral adherence measures are needed to delineate dose–response relationships between drinking intensity and prevention outcomes. Second, randomized or hybrid effectiveness-implementation trials should evaluate combined interventions that integrate alcohol-reduction counseling, mental-health care, and flexible PrEP delivery, including long-acting injectable options, within primary and community settings. Third, equity-oriented program designs must explicitly include transgender, sex-worker, and racial-minority populations, whose adherence challenges are amplified by stigma and structural exclusion. Lastly, public health infrastructure should institutionalize brief alcohol screening within HIV prevention services, supported by digital adherence tools, machine-learning risk identification, and patient-centered pathways for rapid restart after lapses. Through these innovations, prevention programs can move beyond theoretical efficacy to achieve durable, equitable outcomes that reduce both HIV and STI burdens globally.

STATEMENTS

Ethical statement

This umbrella review used only publicly available data and did not involve human participants or interventions; therefore, ethics approval and informed consent were not required.

Funding Statement

No external funding was received. The authors retained full control over the study design, analysis, and decision to publish.

Authors' Contributions

Md R.H. led the study design, literature search, data analysis, interpretation, and manuscript drafting. *Fahad B.H.* contributed to manuscript writing and critical revision. *Akidul H.* and *Zeeshan U.H.* assisted with data extraction and quantitative synthesis. *Tayyeb A.* and *Moryom A.M.* supported the literature review and manuscript revision. All authors read and approved the final version of the manuscript.

REFERENCES

Avanceña, A. L. V., Okoye, G., Yokananth, R., Norwood, A., & Schnarrs, P. W. (2025). Alcohol Use Disorder Diagnoses Among Individuals Who Take HIV Preexposure Prophylaxis. *JAMA Netw Open*, *8*(4), e257295. https://doi.org/10.1001/jamanetworkopen.2025.7295

Chakrapani, V., Newman, P. A., Shunmugam, M., Logie, C. H., & Samuel, M. (2017). Syndemics of depression, alcohol use, and victimisation, and their association with HIV-related sexual risk among men who have sex with men and transgender women in India. *Global public health*, *12*(2), 250-265.

Chander, G., Lau, B., & Moore, R. D. (2006). Hazardous alcohol use: a risk factor for non-adherence and lack of suppression in HIV infection. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *43*(4), 411–417.

Dang, M., Scheim, A. I., Teti, M., Quinn, K. G., Zarwell, M., Petroll, A. E., Horvath, K. J., & John, S. A. (2022). Barriers and facilitators to HIV pre-exposure prophylaxis uptake, adherence, and persistence among transgender populations in the United States: a systematic review. *AIDS patient care and STDs*, *36*(6), 236-248.

Dedert EA, McDuffie JR, Stein R, McNiel JM, Kosinski AS, Freiermuth CE, Hemminger A, Williams Jr JW. Electronic interventions for alcohol misuse and alcohol use disorders: a systematic review. Annals of internal medicine. 2015 Aug 4;163(3):205-14.

Deeks, S. G., Overbaugh, J., Phillips, A., & Buchbinder, S. (2015). HIV infection. *Nature reviews Disease primers*, *1*(1), 1-22.

Dimitrov, D. T., Mâsse, B. R., & Donnell, D. (2016). PrEP adherence patterns strongly affect individual HIV risk and observed efficacy in randomized clinical trials. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *72*(4), 444–451.

Fernandez RS, Sharifnia AM, Khalil H. Umbrella reviews: a methodological guide. European journal of cardiovascular nursing. 2025 Aug;24(6):996-1002.

Fonner, V. A., Dalglish, S. L., Kennedy, C. E., Baggaley, R., O'Reilly, K. R., Koechlin, F. M., Rodolph, M., Hodges-Mameletzis, I., & Grant, R. M. (2016). Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. *Aids*, *30*(12), 1973-1983. https://doi.org/10.1097/qad.0000000000001145

Fontanari, A. M. V., Zanella, G. I., Feijo, M., Churchill, S., Lobato, M. I. R., & Costa, A. B. (2019). HIV-related care for transgender people: A systematic review of studies from around the world. *Social science & medicine*, *230*, 280-294.

Fulcher, J. A., Li, F., Cook, R. R., Zabih, S., Louie, A., Okochi, H., Tobin, N. H., Gandhi, M., Shoptaw, S., Gorbach, P. M., & Aldrovandi, G. M. (2019). Rectal Microbiome Alterations Associated With Oral Human Immunodeficiency Virus Pre-Exposure Prophylaxis. *Open Forum Infect Dis*, *6*(11), ofz463. https://doi.org/10.1093/ofid/ofz463

Fusco, N., Sils, B., Graff, J. S., Kistler, K., & Ruiz, K. (2023). Cost-sharing and adherence, clinical outcomes, health care utilization, and costs: A systematic literature review. *J Manag Care Spec Pharm*, *29*(1), 4-16. https://doi.org/10.18553/jmcp.2022.21270

Ge, L., Tian, X., Sun, C., Hu, P., & Yu, M. (2025). Pathogenesis of HIV-Associated Metabolic Syndrome and Clinical Management Recommendations. *International Journal of General Medicine*, , 5213–5232.

Grabovac, I., Veronese, N., Stefanac, S., Haider, S., Jackson, S. E., Koyanagi, A., Meilinger, M., Stubbs, B., Firth, J., Soysal, P., Di Gennaro, F., Demurtas, J., McDermott, D. T., Abbs, A. D., Yang, L., & Smith, L. (2020). Human Immunodeficiency Virus Infection and Diverse Physical Health Outcomes: An Umbrella Review of Meta-analyses of Observational Studies. Clin Infect Dis, 70(9), 1809-1815. https://doi.org/10.1093/cid/ciz539

Haldane, V., Legido-Quigley, H., Chuah, F. L. H., Sigfrid, L., Murphy, G., Ong, S. E., Cervero-Liceras, F., Watt, N., Balabanova, D., & Hogarth, S. (2018). Integrating cardiovascular diseases, hypertension, and diabetes with HIV services: a systematic review. AIDS Care, 30(1), 103–115.

Hendershot, C. S., Stoner, S. A., Pantalone, D. W., & Simoni, J. M. (2009). Alcohol use and antiretroviral adherence: review and meta-analysis. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *52*(2), 180–202.

Hevey, M. A., Walsh, J. L., & Petroll, A. E. (2018). PrEP continuation, HIV and STI testing rates, and delivery of preventive care in a clinic-based cohort. *AIDS Education and Prevention*, *30*(5), 393–405.

Hasan, M. R. (2024a). Exploring the Relationship Between Opioid Use Disorder and Major Depressive Disorder: A Case Study from Kentucky of United States. *Journal of Current and Advance Medical Research*, *11*(1), 50-55.

Hasan, M. R. (2024b). Mental Health Challenges in Bangladesh Based on the Integrated Examination of Illicit Drug Use, Substance Abuse, Tobacco Consumption, and Escalating Suicidal Tendencies: A Comprehensive Review. *Bangladesh Journal of Infectious Diseases*, *11*(1), 65-70.

Hasan, M. R. (2025). Understanding Diabetes Care Barriers Through Community Voices: A Brief Qualitative Report from Jefferson County, Kentucky. *Asian Journal of Public Health and Nursing*, *2*(2), 1-7.

Hasan MR, Haq ZU, Muna MA. The Hidden Continuum of Risk: Behavioral and Mental Health Pathways from Tobacco Consumption to Illicit Drug Use Among University Students in Bangladesh. (2025). *East African Scholars Journal of Medical Sciences* (*EASMS)*. https://doi.org/10.36349/easms.2025.v08i11.002.

Hasan, M. R., Haque, A., Muna, M. A., & Haq, Z. U. (2025). Behavioral and Psychosocial Determinants of Long-Acting Pre-Exposure Prophylaxis (PrEP) Continuity: A Descriptive Study from an Urban US Setting. *European Journal of Medical and Health Sciences*, *7*(6), 37-44.

Hasan, M. R., Mclessey, L., Haque, A., Muna, M. A., & Haq, Z. U. (2025). A Multilevel Perspective on PrEP Adherence in HIV Prevention: An Integrative Review Guided by the Socioecological Model. *British Journal of Nursing Studies*, *5*(3), 23-43.

Hassan AS, Pybus OG, Sanders EJ, Albert J, Esbjörnsson J. Defining HIV-1 transmission clusters based on sequence data. Aids. 2017 Jun 1;31(9):1211-22.

Hennessy, E. A., & Johnson, B. T. (2020). Examining overlap of included studies in meta-reviews: Guidance for using the corrected covered area index. *Res Synth Methods*, *11*(1), 134-145. https://doi.org/10.1002/jrsm.1390

Herns, S., Panwala, R., Pfeil, A., Sardinha, M., Rossi, V., Blumenthal, J., & Hill, L. (2023). Predictors of PrEP retention in at risk patients seen at a HIV primary care clinic in San Diego. *International journal of STD & AIDS*, *34*(11), 785–790. https://doi.org/10.1177/09564624231179276.

Hess, K. L., Chavez, P. R., Kanny, D., DiNenno, E., Lansky, A., & Paz-Bailey, G. (2015). Binge drinking and risky sexual behavior among HIV-negative and unknown HIV status men who have sex with men, 20 US cities. *Drug Alcohol Depend*, *147*, 46-52. https://doi.org/10.1016/j.drugalcdep.2014.12.013

Hess, K. L., Chavez, P. R., Kanny, D., DiNenno, E., Lansky, A., Paz-Bailey, G., & Group, N. S. (2015). Binge drinking and risky sexual behavior among HIV-negative and unknown HIV status men who have sex with men, 20 US cities. *Drug and alcohol dependence*, *147*, 46-52.

Hevey, M. A., Walsh, J. L., & Petroll, A. E. (2018). PrEP Continuation, HIV and STI Testing Rates, and Delivery of Preventive Care in a Clinic-Based Cohort. *AIDS Educ Prev*, *30*(5), 393-405. https://doi.org/10.1521/aeap.2018.30.5.393

High, K. P., Brennan-Ing, M., Clifford, D. B., Cohen, M. H., Currier, J., Deeks, S. G., Deren, S., Effros, R. B., Gebo, K., & Goronzy, J. J. (2012). HIV and aging: state of knowledge and areas of critical need for research. A report to the NIH Office of AIDS Research by the HIV and Aging Working Group. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *60*, S1-S18.

Jin, G., Shi, H., Du, J., Guo, H., Yuan, G., Yang, H., Zhu, Z., Zhang, J., Zhang, K., & Zhang, X. (2023). Pre-exposure prophylaxis care continuum for HIV risk populations: An umbrella review of systematic reviews and meta-analyses. *AIDS patient care and STDs*, *37*(12), 583-615.

Kabir, R., Bai, A. C. M., Syed, H. Z., Hasan, M. R., Vinnakota, D., Kar, S. K., Singh, R., Sathian, B., & Arafat, S. Y. (2023). The effect of COVID-19 on the mental health of the people in the Indian subcontinent: a scoping review. *Nepal Journal of Epidemiology*, *13*(2), 1268.

Kabir, R., Vinnakota, D., Dehghani, L., Sathian, B., Padhi, B. K., & Hasan, M. R. (2024). HIV and Violence among Female Sex Workers in India: A Scoping. *Women's Health Problems: A Global Perspective*, *3*.

Kiggundu, R., Soh, Q. R., Tieosapjaroen, W., Fairley, C. K., Tucker, J. D., Tang, W., Zhang, L., & Ong, J. J. (2024). Restarting pre-exposure prophylaxis (PrEP) for HIV: a systematic review and meta-analysis. *EClinicalMedicine*, *72*.

Koester, K. A., Erguera, X. A., Udoh, I., Kang Dufour, M. S., Burack, J. H., & Myers, J. J. (2021). Exploring the Shift From HIV Pre-exposure Prophylaxis Awareness to Uptake Among Young Gay and Bisexual Men. *Front Public Health*, *9*, 677716. https://doi.org/10.3389/fpubh.2021.677716

Losina, E., Schackman, B. R., Sadownik, S. N., Gebo, K. A., Walensky, R. P., Chiosi, J. J., Weinstein, M. C., Hicks, P. L., Aaronson, W. H., Moore, R. D., Paltiel, A. D., & Freedberg, K. A. (2009). Racial and sex disparities in life expectancy losses among HIV-infected persons in the united states: impact of risk behavior, late initiation, and early discontinuation of antiretroviral therapy. *Clin Infect Dis*, *49*(10), 1570-1578. https://doi.org/10.1086/644772

Matos, L. A., Janek, S. E., Holt, L., Ledbetter, L., & Gonzalez-Guarda, R. M. (2024). Barriers and facilitators along the PrEP continuum of care among Latinx sexual minoritized men and transgender women: A systematic review. *AIDS and Behavior, 28*(11), 3666–3709. https://doi.org/10.1007/s10461-024-04434-8

Mayer, K. H., Agwu, A., & Malebranche, D. (2020). Barriers to the Wider Use of Pre-exposure Prophylaxis in the United States: A Narrative Review. *Adv Ther*, *37*(5), 1778-1811. https://doi.org/10.1007/s12325-020-01295-0

Md, R. H., Whitney, R., Saifur, R., Moryom, A. M., Kanij, F. R., & Sajid, H. (2025). A comprehensive review on antimicrobial resistance in uropathogens isolated from ICU patients in the south-east Asian region. *Int J Sci Res Archive*, *14*(2), 527–542. https://doi.org/10.30574/ijsra.2025.14.2.0340.

Miller, S. J., Harrison, S. E., & Sanasi-Bhola, K. (2021). A Scoping Review Investigating Relationships between Depression, Anxiety, and the PrEP Care Continuum in the United States. *Int J Environ Res Public Health*, *18*(21). https://doi.org/10.3390/ijerph182111431

Mogaka, F. O., Stewart, J., Omollo, V., & Bukusi, E. (2023). Challenges and Solutions to STI Control in the Era of HIV and STI Prophylaxis. *Current HIV/AIDS reports*, *20*(5), 312–319. https://doi.org/10.1007/s11904-023-00666-w

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*, *6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

Murchu, E. O., Marshall, L., Teljeur, C., Harrington, P., Hayes, C., Moran, P., & Ryan, M. (2022). Oral pre-exposure prophylaxis (PrEP) to prevent HIV: a systematic review and meta-analysis of clinical effectiveness, safety, adherence and risk compensation in all populations. *BMJ open*, *12*(5), e048478.

Ng, B. E., Moore, D., Michelow, W., Hogg, R., Gustafson, R., Robert, W., Kanters, S., Thumath, M., McGuire, M., & Gilbert, M. (2014). Relationship between disclosure of same-sex sexual activity to providers, HIV diagnosis and sexual health services for men who have sex with men in Vancouver, Canada. *Can J Public Health*, *105*(3), e186-191. https://doi.org/10.17269/cjph.105.4212

Nguyen, V. K., Greenwald, Z. R., Trottier, H., Cadieux, M., Goyette, A., Beauchemin, M., Charest, L., Longpré, D., Lavoie, S., Tossa, H. G., & Thomas, R. (2018). Incidence of sexually transmitted infections before and after preexposure prophylaxis for HIV. *Aids*, *32*(4), 523-530. https://doi.org/10.1097/qad.0000000000001718

Oldfield, B. J., & Edelman, E. J. (2021). Addressing Unhealthy Alcohol Use and the HIV Pre-exposure Prophylaxis Care Continuum in Primary Care: A Scoping Review. *AIDS Behav*, *25*(6), 1777-1789. https://doi.org/10.1007/s10461-020-03107-6

Ong, J. J., Baggaley, R. C., Wi, T. E., Tucker, J. D., Fu, H., Smith, M. K., Rafael, S., Anglade, V., Falconer, J., Ofori-Asenso, R., Terris-Prestholt, F., Hodges-Mameletzis, I., & Mayaud, P. (2019). Global Epidemiologic Characteristics of Sexually Transmitted Infections Among Individuals Using Preexposure Prophylaxis for the Prevention of HIV Infection: A Systematic Review and Meta-analysis. *JAMA Netw Open*, *2*(12), e1917134. https://doi.org/10.1001/jamanetworkopen.2019.17134

Pandrea, I., Happel, K. I., Amedee, A. M., Bagby, G. J., & Nelson, S. (2010). Alcohol's role in HIV transmission and disease progression. *Alcohol Res Health*, *33*(3), 203-218.

Paula, A. A., Schechter, M., Tuboi, S. H., Faulhaber, J. C., Luz, P. M., Veloso, V. G., Moreira, R. I., Grinsztejn, B., Harrison, L. H., & Pacheco, A. G. (2014). Continuous Increase of Cardiovascular Diseases, Diabetes, and Non-HIV Related Cancers as Causes of Death in HIV-Infected Individuals in Brazil: An Analysis of Nationwide Data. *PloS one*, *9*(4), e94636. https://doi.org/10.1371/journal.pone.0094636

Perry, R., Whitmarsh, A., Leach, V., & Davies, P. (2021). A comparison of two assessment tools used in overviews of systematic reviews: ROBIS versus AMSTAR-2. *Syst Rev*, *10*(1), 273. https://doi.org/10.1186/s13643-021-01819-x

Pleuhs, B., Quinn, K. G., Walsh, J. L., Petroll, A. E., & John, S. A. (2020). Health care provider barriers to HIV pre-exposure prophylaxis in the United States: a systematic review. *AIDS Patient Care and STDs*, *34*(3), 111–123.

Poteat, T., Wirtz, A. L., Radix, A., Borquez, A., Silva-Santisteban, A., Deutsch, M. B., Khan, S. I., Winter, S., & Operario, D. (2015). HIV risk and preventive interventions in transgender women sex workers. *Lancet*, *385*(9964), 274-286. https://doi.org/10.1016/s0140-6736(14)60833-3

Seyedroudbari, S., Ghadimi, F., Grady, G., Uzosike, O., Nkwihoreze, H., Jemmott, J. B., 3rd, & Momplaisir, F. (2024). Assessing Structural Racism and Discrimination Along the Pre-exposure Prophylaxis Continuum: A Systematic Review. *AIDS Behav*, *28*(9), 3001-3037. https://doi.org/10.1007/s10461-024-04387-y

Shiau, S., Arpadi, S. M., Yin, M. T., & Martins, S. S. (2017). Patterns of drug use and HIV infection among adults in a nationally representative sample. *Addictive behaviors*, *68*, 39-44.

Shuper, P. A., Joharchi, N., Bogoch, II, Loutfy, M., Crouzat, F., El-Helou, P., Knox, D. C., Woodward, K., & Rehm, J. (2020). Alcohol consumption, substance use, and depression in relation to HIV Pre-Exposure Prophylaxis (PrEP) nonadherence among gay, bisexual, and other men-who-have-sex-with-men. *BMC public health*, *20*(1), 1782. https://doi.org/10.1186/s12889-020-09883-z

Sims Haynes, A., Markham, C., Schick, V., Suchting, R., Parthasarathy, N., Choudhury, S., & Hill, M. J. (2025). A systematic review and narrative synthesis of factors affecting pre-exposure prophylaxis willingness among black women for HIV prevention. *AIDS and Behavior*, *29*(1), 101-132. doi:10.1007/s10461-024-04491-z.

Smith, C. J., Ryom, L., Weber, R., Morlat, P., Pradier, C., Reiss, P., Kowalska, J. D., De Wit, S., Law, M., & el Sadr, W. (2014). Trends in underlying causes of death in people with HIV from 1999 to 2011 (D: A: D): a multicohort collaboration. *The Lancet*, *384*(9939), 241-248.

Strong, S. H., Oldfield, B. J., van den Berg, J. J., Cole, C. A., Biegacki, E., Ogbuagu, O., Virata, M., Chan, P. A., & Edelman, E. J. (2024). Perspectives on unhealthy alcohol use among men who have sex with men prescribed HIV pre-exposure prophylaxis: A qualitative study. *Prev Med Rep*, *37*, 102553. https://doi.org/10.1016/j.pmedr.2023.102553

Stultz, A., Chang, S.-H., Wilson, D. L., Hernandez-Con, P., Joseph, A., Unigwe, I., Lin, H.-Y., Yang, J., Adkins, L., & Cook, R. L. (2025). HIV Pre-Exposure Prophylaxis Care Continuum in Outpatient Settings: A Systematic Review and Meta-Analysis. *AJPM Focus*, 100433.

Wilkerson, A. M., Tao, J., & Chan, P. A. (2025). Sexually Transmitted Infections and Risk of Human Immunodeficiency Virus Transmission. *Curr HIV/AIDS Rep*, *22*(1), 40. https://doi.org/10.1007/s11904-025-00749-w

Willie, T. C., Kershaw, T. S., Blackstock, O., Galvao, R. W., Safon, C. B., Tekeste, M., Ogburn, D. F., Wilbourn, B., Modrakovic, D., & Taggart, T. (2021). Racial and ethnic differences in women's HIV risk and attitudes towards pre-exposure prophylaxis (PrEP) in the context of the substance use, violence, and depression syndemic. *AIDS care*, *33*(2), 219-228.

Yun, J. A., Jeong, K. S., Ahn, Y. S., Han, Y., & Choi, K. S. (2021). The Interaction of Inflammatory Markers and Alcohol-Use on Cognitive Function in Korean Male Firefighters. *Psychiatry Investig*, *18*(3), 205-213. https://doi.org/10.30773/pi.2020.0101

Zeeshan U.H., Hasan M.R., Halim F.B., Ayyoubi M.T. Patterns of Marijuana Use, Psychological Distress, and Suicide Risk among U.S. Adolescents: A Descriptive Cross-Sectional Analysis. American Journal of Public Health Research. 2025; 13(6):263-274. doi: 10.12691/ajphr-13-6-2.

Zhang, J., Li, C., Xu, J., Hu, Z., Rutstein, S. E., Tucker, J. D., Ong, J. J., Jiang, Y., Geng, W., & Wright, S. T. (2022). Discontinuation, suboptimal adherence, and reinitiation of oral HIV pre-exposure prophylaxis: a global systematic review and meta-analysis. *The Lancet HIV*, *9*(4), e254–e268.

Acknowledgments and Conflicts of Interest Declaration

Acknowledgments

The authors gratefully thank *Dr. M. A. Yusuf* for his valuable guidance and critical feedback throughout the development of this study.

Conflicts of Interest

The authors declare no conflicts of interest throughout the study.

License