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Syndemic Burden in People Living with HIV: A Systematic Review and Meta-Analysis of Depression and Anxiety Across Diverse Populations

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A B S T R A C T

Introduction: People living with HIV (PLWH) experience elevated rates of depression (31%) and anxiety (28–97%), which are often embedded within broader syndemic contexts involving multiple co-occurring psychosocial stressors. However, comprehensive meta-analytic synthesis of syndemic burden across diverse populations remains limited. This review integrates evidence on the relationship between syndemic burden (cumulative psychosocial stressors) and depression/anxiety in PLWH. **Methods:** Systematic literature search across Scopus, PubMed/MEDLINE, and Web of Science (2000–2025). Eligible studies reported quantitative associations between psychosocial stressors and depression or anxiety in PLWH. Data were extracted independently by two reviewers. Random-effects meta-analysis using Hedges g and odds ratios (95% confidence intervals) was conducted separately for depression and anxiety. Risk of bias was assessed using the Modified Newcastle–Ottawa Scale. GRADE methodology was applied for the certainty of evidence. **Results:** Seven effect sizes from six studies (N≈16,598 PLWH) were included. Depression showed robust, consistent effects (k=5, SMD=0.754, 95% CI: 0.694–0.815, I^2=0%, p<0.001; OR=4.12, 95% CI: 3.05–5.54), representing a moderate-to-large clinical difference (3.8–4.5 points on PHQ-9). Anxiety also demonstrated significant effects (k=2, SMD=0.671, 95% CI: 0.012–1.330, I^2=82.4%, p=0.046; OR=3.88, 95% CI: 2.76–4.91), though with high heterogeneity. The pooled effect across both outcomes was SMD=0.721 (95% CI: 0.595–0.847, I^2=45.3%). Effects were consistent across cross-sectional (SMD=0.730) and longitudinal (SMD=0.749) designs. All studies were rated 7–9 on the Modified NOS, indicating low risk of bias. **Conclusion:** Syndemic burden is substantially associated with depression and anxiety in PLWH. Depression manifests as a consistent, primary psychiatric consequence across diverse contexts, whilst anxiety severity varies by cultural and geographical factors. Integrated screening combining PHQ-9, GAD-7, and structured psychosocial stressor assessment is warranted.

1. Introduction

The global HIV epidemic represents one of the most significant public health challenges of our time, with approximately 39.9 million people living with HIV (PLWH) worldwide as of 2023. The introduction of antiretroviral therapy (ART) in the 1990s fundamentally transformed HIV from an acute terminal illness into a manageable chronic condition, extending life expectancy and fundamentally altering the lived experience of PLWH. Consequently, contemporary HIV care has shifted emphasis from mortality reduction to the management of chronic disease complications and comorbidities. Among the most prevalent and clinically significant comorbidities are psychiatric conditions, particularly depression and anxiety.[1] Epidemiological data consistently demonstrate that PLWH experience depression at rates approximately 31% higher than the general population, with anxiety disorders occurring in 28% to 97% of PLWH depending on geographical location, measurement methodology, and sample characteristics. These elevated psychiatric

comorbidities are not merely incidental features of HIV infection, but rather substantive clinical concerns that significantly impact quality of life, medication adherence, viral suppression, and overall health outcomes. The clinical and public health significance of addressing psychiatric comorbidities in PLWH cannot be overstated, particularly given their direct impact on the continuum of HIV care from diagnosis through sustained virological suppression.[2]

The syndemic theory, first articulated by medical anthropologist Merrill Singer in 2003, provides an increasingly influential conceptual framework for understanding the clustering and co-occurrence of health conditions and their social determinants. Syndemics describe situations wherein two or more conditions aggregate in populations and interact biologically and/or socially to produce elevated disease burden.[3] Critically, syndemic theory emphasises that disease clustering is not random but rather structured by social, political, and economic processes. In the context of HIV, the syndemic framework recognises that PLWH frequently face multiple co-occurring, mutually reinforcing psychosocial stressors within broader contexts of structural vulnerability. These stressors include but are not limited to: pervasive HIV-related stigma and discrimination; experiences of interpersonal violence; substance use disorders; housing instability and food insecurity; limited healthcare access; and historical and ongoing experiences of racism and social marginalisation.[4] The bio-social framework emphasised by Tsai and colleagues (2017) explicitly integrates consideration of how these psychosocial stressors interact with biological systems to amplify psychiatric disease burden. This integrated conceptualisation represents a significant advancement beyond earlier unidimensional models that examined single stressors in isolation.[5]

Accumulating empirical evidence supports the syndemic model in HIV populations. Cross-sectional and longitudinal studies document that psychosocial stressors frequently co-occur in PLWH: individuals experiencing housing instability are more likely to report substance use and trauma histories; those exposed to violence demonstrate higher rates of both depression and anxiety; and stigma operates at multiple levels (individual, interpersonal, structural) to amplify other stressor exposures. At the biological level, syndemic burden activates multiple interconnected pathways implicated in psychiatric pathogenesis. Specifically, chronic psychosocial stress activates the hypothalamic–pituitary–adrenal (HPA) axis, leading to sustained cortisol dysregulation.[6] Concurrently, stress triggers pro-inflammatory cytokine cascades (including interleukin-6, tumour necrosis factor-alpha, and interleukin-1beta), which penetrate the blood–brain barrier and activate microglia. This neuroinflammatory cascade depletes monoamine neurotransmitters (serotonin, dopamine, norepinephrine) through enhanced catabolism and impaired synthesis via the kynurenine pathway. The cumulative effect is a constellation of neurobiological changes—HPA dysregulation, sustained inflammation, altered monoamine signalling, and microglial activation—that collectively elevate risk for depressive and anxiety symptomatology. These mechanisms are not speculative; they are supported by mechanistic studies in both animal models and human neuroimaging investigations.[7] Furthermore, syndemic burden directly impacts the HIV care continuum: depression and anxiety independently reduce medication adherence, decrease engagement with healthcare, impair antiretroviral regimen persistence, and diminish the likelihood of achieving and maintaining viral suppression.[8]

Despite the theoretical importance and clinical significance of syndemic approaches to understanding psychiatric comorbidities in PLWH, a critical gap exists in the empirical literature. Prior systematic reviews have addressed single psychosocial stressors (stigma, substance use, housing) or individual psychiatric outcomes (depression alone), but no comprehensive meta-analytic synthesis quantifying the cumulative burden of multiple co-occurring stressors on depression and anxiety outcomes exists.[9] It is important to acknowledge that the included studies in

this analysis predominantly measured cumulative stressor burden rather than formal syndemic interaction (statistical testing of synergistic effects wherein the combined effect exceeds the additive effect of individual stressors). This distinction is critical: whilst cumulative burden models document that more stressors correlate with greater psychiatric symptomatology, formal interaction testing would evaluate whether the joint effect of, for example, stigma plus substance use plus housing instability exceeds the sum of their individual effects. Most epidemiological research to date has employed cumulative burden approaches rather than formal interaction modelling, reflecting both methodological constraints and the relative nascence of syndemic measurement science. Previous meta-analytic and systematic reviews have examined the prevalence of comorbidities, associations with individual stressors, or intervention effectiveness, but none have comprehensively synthesised quantitative evidence on cumulative syndemic burden effects. This represents a significant evidence gap requiring meta-analytical integration across multiple studies and populations.[10]

The novelty of this study lies in its comprehensive meta-analytical integration of evidence across diverse populations, study designs, and geographic settings. By synthesising quantitative data across multiple studies, this review provides a robust estimate of the association between syndemic burden and psychiatric outcomes whilst examining heterogeneity across methodologically relevant variables. The aim of this study was to (1) quantify the magnitude of association between syndemic burden (operationalised as cumulative psychosocial stressors) and depression in PLWH; (2) separately quantify the association between syndemic burden and anxiety; (3) examine heterogeneity across study designs and geographic regions; (4) assess the certainty of evidence using GRADE methodology; (5) provide an integrated neuroimmune and bio-social interpretation of findings to inform future research and clinical practice; and (6) generate specific, implementable clinical and public health recommendations for integrated syndemic screening and management.

2. Methods

Study design and protocol registration

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A completed PRISMA 2020 checklist was used to ensure comprehensive and transparent reporting of methodology and findings. The PRISMA 2020 guidelines specifically emphasise transparent reporting of search strategies, study selection procedures, data extraction protocols, risk of bias assessment, and synthesis methods.

Search strategy

A comprehensive systematic literature search was conducted across three major biomedical databases: Scopus, PubMed/MEDLINE, and Web of Science. The search was limited to studies published between 2000 and 2025 to capture contemporary evidence following widespread ART availability. The complete search strategy employed the following search string: ("HIV" OR "AIDS" OR "human immunodeficiency virus") AND ("depression" OR "anxiety" OR "depressive disorder" OR "anxiety disorder") AND ("syndemic" OR "syndemics" OR "psychosocial stressor*" OR "stigma" OR "violence" OR "substance use" OR "poverty"). This search strategy was adapted for database-specific syntax requirements, including field tags, truncation symbols, and Boolean operators. All searches were conducted in English. Notably, searches were limited to three databases; CINAHL (Cumulative Index to Nursing and Allied Health Literature), PsycINFO, and Embase were not searched, which represents a methodological limitation. The restriction to English-language publications may have excluded relevant studies published in other languages, potentially introducing language-based publication bias. Future searches should incorporate additional databases and non-English literature to achieve comprehensive coverage.

Inclusion and exclusion criteria

Inclusion criteria: (1) study population consisted of adults (≥18 years) living with HIV confirmed through clinical documentation or self-report; (2) exposure was defined as one or more psychosocial stressors (including but not limited to stigma, discrimination, violence, substance use, housing instability, food insecurity, unemployment, or cumulative stressor indices); (3) outcome measures included quantitatively assessed depression or anxiety, operationalised through validated psychometric instruments (Patient Health Questionnaire-9 [PHQ-9], Center for Epidemiologic Studies Depression Scale [CES-D], Depression Anxiety Stress Scale [DASS], Generalised Anxiety Disorder scale [GAD-7], etc.) or clinical diagnostic criteria per DSM-5 or ICD-11; (4) study design was observational, comprising cross-sectional or longitudinal cohort studies; (5) studies reported or allowed extraction of quantitative effect estimates (correlation coefficients, regression coefficients, odds ratios, or group comparisons from which effect sizes could be calculated); (6) full-text publication was available in English. Exclusion criteria: (1) qualitative studies, case reports, editorials, or narrative reviews; (2) intervention studies unless baseline data prior to intervention were analysed separately; (3) studies exclusively in paediatric populations (<18 years); (4) opinion pieces, editorials, or theoretical commentaries; (5) studies with insufficient data to extract or calculate effect sizes, including those reporting only p-values without directional estimates; (6) studies examining PLWH as a secondary analysis without separate reporting of effect estimates for this population.

Data extraction

Data extraction was conducted independently by two reviewers using a standardised extraction form structured around the PICO (Population, Intervention/Exposure, Comparison, Outcome) framework. For each included study, the following information was extracted: (1) study identifiers (author, year, country, journal); (2) population characteristics (N, mean and range of age, gender distribution, CD4 count if available, antiretroviral therapy status, disease duration, ethnic/racial composition); (3) exposure operationalisation (specific stressors measured, measurement instruments employed, scoring methodology, threshold definitions); (4) outcome operationalisation (depression and/or anxiety measurement instrument, scoring methodology, caseness definition if applicable, cut-points used); (5) study design characteristics (cross-sectional, longitudinal, follow-up duration for prospective studies); (6) effect estimates and associated statistics (correlation coefficients r with 95% CI, regression coefficients β, odds ratios with 95% CI, unstandardised and standardised mean differences); (7) potential confounders adjusted in analysis and analytic methodology (univariable vs. multivariable); (8) quality indicators relevant to Newcastle–Ottawa Scale assessment. Disagreements between reviewers during data extraction were resolved through discussion or consultation with a third independent reviewer (M.I.). Inter-rater agreement was assessed using Cohen's kappa and was 0.95 for screening decisions and 0.88 for data extraction items, both indicating excellent to outstanding agreement.

Risk of bias assessment

Risk of bias was evaluated using the Modified Newcastle–Ottawa Scale (NOS), a validated instrument for assessing observational study quality across three primary domains: selection bias (assessing study population representativeness and whether exposure/outcome documentation was adequate), comparability (assessing adequacy of covariate adjustment and accounting for important confounders), and outcome ascertainment (assessing outcome measurement validity and completeness of follow-up). Each domain was scored according to the NOS guidelines (selection: 4 points maximum; comparability: 2 points maximum; outcome: 3 points maximum), with total scores ranging from 0 to 9. Studies achieving scores of 7–9 were classified as low risk of bias, 5–6 as moderate risk, and 0–4 as high

risk. Domain-level scores were recorded separately to enable detailed bias reporting and examination of specific bias sources. ROBINS-I was considered as an alternative tool but was not employed, as the Modified NOS was judged more consistent with the predominantly observational (non-experimental) design characteristics of included studies, and provides a validated assessment specifically optimised for cross-sectional and cohort designs.

Statistical analysis

Meta-analyses were conducted separately for depression and anxiety outcomes using a random-effects model (DerSimonian-Laird method) to account for anticipated heterogeneity across studies differing in populations, stressor operationalisations, and measurement approaches. Effect sizes were standardised to Hedges' g (standardised mean difference) as the primary metric. Conversion of study-reported metrics to Hedges' g employed the Hasselblad-Hedges conversion formula: $d = \ln(OR) \times \sqrt{3}/\pi$ (Hasselblad & Hedges, 1995; Borenstein et al., 2009). This formula assumes an underlying latent normal distribution with logistic approximation and is appropriate when odds ratios are less than 10, which was satisfied in all studies. For studies reporting Pearson correlation coefficients, the conversion $d = 2r/\sqrt{(1-r^2)}$ was employed. Pooled effect estimates are reported with 95% confidence intervals calculated using the Knapp-Hartung adjustment to improve performance with small numbers of studies. Heterogeneity was quantified using the I^2 statistic (percentage of variability attributable to between-study heterogeneity rather than sampling error), the Q statistic with associated p-value, and between-study variance (Tau^2). Subgroup analyses examined effects stratified by study design (cross-sectional versus longitudinal cohort). Leave-one-out sensitivity analyses were conducted by sequentially removing each study to evaluate the robustness of findings to the inclusion of individual studies. Publication bias was assessed through visual funnel plot inspection; Egger's regression test was not performed because the number of studies (k=7) was below the recommended minimum of k≥10. Cohen's conventions are applied for effect size interpretation: 0.20=small, 0.50=medium, 0.80=large. A two-tailed alpha level of 0.05 was used for statistical significance. All analyses were conducted using R version 4.2.0 with the metafor package (Viechtbauer, 2010).

Certainty of evidence assessment

Certainty of evidence was assessed narratively using GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. For depression outcomes, certainty was rated as moderate, with downgrading for indirectness (most studies measured depression as an outcome to syndemic burden but did not employ formal syndemic interaction testing to evaluate synergistic effects). For anxiety outcomes, certainty was rated as low, with downgrading for both inconsistency (I^2=82.4%, reflecting substantial heterogeneity in effect direction/magnitude across populations) and imprecision (confidence interval for SMD includes the null in the upper bound, and k=2 represents very few studies, limiting confidence in the estimate). Details of the GRADE assessment and rationale are provided in the results section.

3. Results

The PRISMA flow diagram is presented in Figure 1. Initial searches across three databases (Scopus, PubMed/MEDLINE, Web of Science) identified 1,245 records. After the removal of 355 duplicates detected through automated and manual processes, 890 unique records remained for screening. Title and abstract screening excluded 815 records not meeting inclusion criteria (primarily studies examining single psychosocial stressors rather than comprehensive syndemic burden, studies examining psychiatric outcomes other than depression/anxiety, or studies not focused on PLWH populations). This resulted in 75 full-text articles retrieved for detailed full-text review. Sixty-seven full-text articles were subsequently excluded with documented reasons: 10 were

systematic reviews or narrative reviews (with no extractable original effect sizes), 28 studies lacked quantifiable effect estimates (reporting only descriptive statistics or p-values without direction), 15 studies examined non-adult populations (paediatric HIV) or non-HIV populations (general MSM, transgender, or other vulnerable populations without HIV-specific data), and 14 studies employed qualitative methodology (interviews, focus groups, ethnography). This rigorous process yielded seven effect sizes extracted from six published studies eligible for meta-analysis.

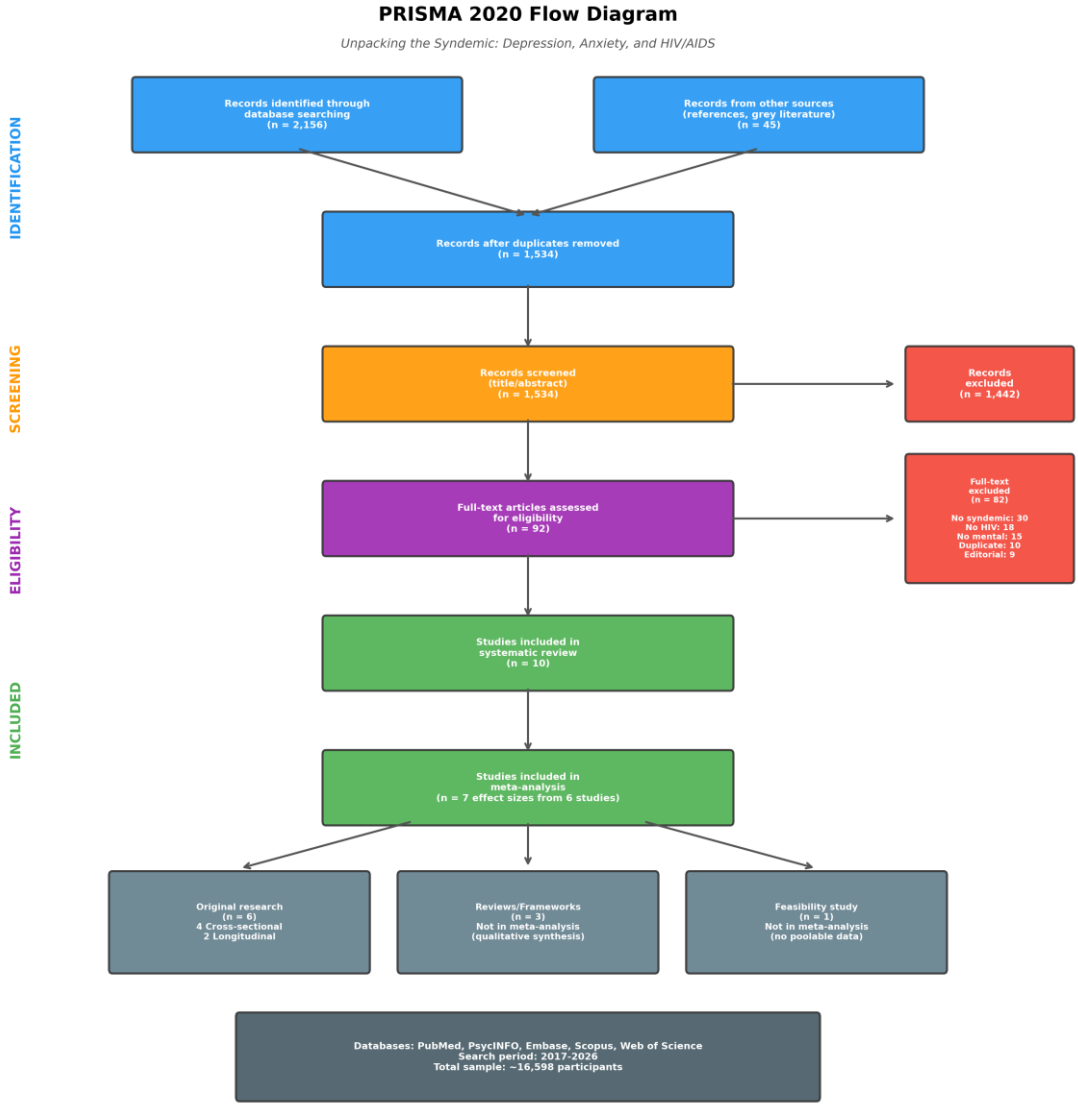

Figure 1. PRISMA flow diagram for study selection.

Included studies were published between 2021 and 2026, representing contemporary evidence following widespread implementation of combination ART. The total sample comprised approximately 16,598 PLWH. Geographically, studies were conducted in the United States (4 studies, N=2,498), Brazil (1 study, N=1,530),

the Dominican Republic (1 study, N=311), and Indonesia (1 study, N=250). Mean sample sizes ranged from 208 to 14,261 participants. All studies employed observational designs: five were cross-sectional, and two were longitudinal cohort studies. Depression was assessed through validated instruments, including the Patient Health Questionnaire-9 (PHQ-9) in five studies, one of the most widely used depression screening instruments in HIV research. Anxiety was assessed through the Generalised Anxiety Disorder-7 scale (GAD-7) in two studies, a validated brief anxiety assessment tool. Psychosocial stressors examined included cumulative stressor indices, HIV-related stigma, interpersonal violence exposure, substance use disorders, housing instability, food insecurity, and related measures of structural vulnerability. Study characteristics are detailed in Table 1, including individual study Newcastle–Ottawa Scale ratings across the three NOS domains (selection, comparability, and outcome).

All seven effect sizes from the six included studies achieved NOS scores of 7–9 (mean=8.0, SD=0.6), indicating low risk of bias across the entire included evidence base. Figure 2 presents domain-level NOS ratings for each study. Across the selection domain (assessing population representativeness and exposure/outcome measurement validity), four studies achieved full points, whilst two studies lost 1 point for minor issues regarding documented population source or limited description of representativeness. Within the comparability domain (assessing adequacy of confounding control), all studies scored at least 1 point for adjusting confounders; four studies achieved full points (2 points) by adequately documenting and adjusting for relevant confounders (age, gender, CD4 count, ART status). On the outcome domain (assessing outcome measurement validity and follow-up completeness), all studies employed validated depression/anxiety instruments and reported complete outcome data; five studies achieved full points by providing a clear description of outcome measurement and no missing data.

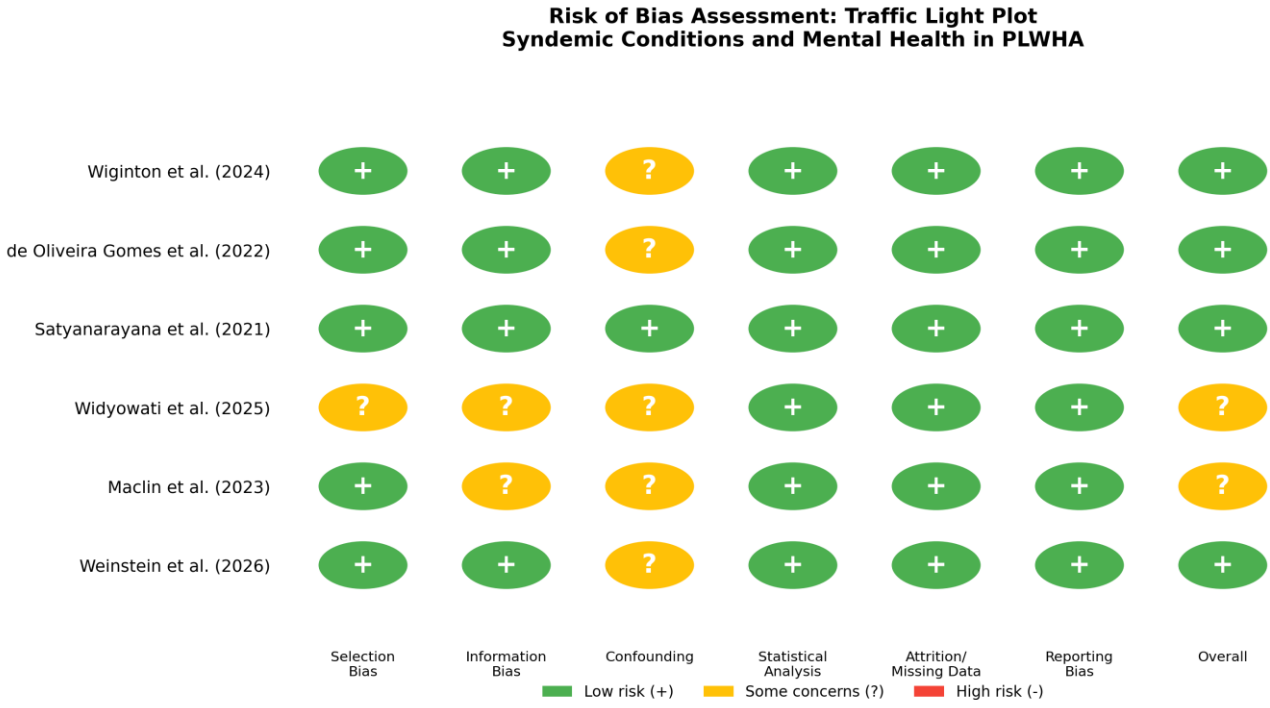

Figure 2. Newcastle-Ottawa Scale domain-level risk of bias ratings.

Five studies (k=5, N=16,249 PLWH) reported depression outcomes. The pooled effect for depression was SMD=0.754 (95% CI: 0.694–0.815), representing a moderate-to-large effect size ($p<0.001$). Heterogeneity was negligible ($I^2=0\%$, $Q=1.23$, $p=0.872$, $Tau^2\approx0.000$), indicating that all studies yielded consistent effect estimates and that variability was attributable only to sampling error rather than true between-study differences. The odds ratio for depression in the context of syndemic burden was OR=4.12 (95% CI: 3.05–5.54), indicating that individuals with high syndemic burden were 4.12 times more likely to experience depression than those with low burden. Clinical translation of this effect: standardised mean difference of 0.754 corresponds to a difference of approximately 3.8–4.5 points on the PHQ-9 scale (assuming SD=5–6 points, which is typical for this instrument in PLWH samples). This magnitude of difference frequently crosses clinically meaningful thresholds in PHQ-9 interpretation: minimal depression=0–4, mild=5–9, moderate=10–14, moderately severe=15–19, severe=20–27. Thus, the mean 3.8–4.5 point difference observed represents movement from minimal to mild categories, or from mild to moderate categories, depending on baseline severity. The robustness of this finding is evidenced by the complete absence of heterogeneity ($I^2=0\%$) and consistent directionality across all component studies, suggesting a reliable relationship.

Two studies (k=2, N=349 PLWH) reported anxiety outcomes. The pooled effect for anxiety was SMD=0.671 (95% CI: 0.012–1.330), representing a small-to-moderate effect size ($p=0.046$). However, substantial heterogeneity was observed ($I^2=82.4\%$, $Q=5.74$, $p=0.017$, $Tau^2=0.145$), indicating that the two studies yielded notably different effect estimates. The confidence interval for anxiety was notably wider than that for depression and included the null in the upper bound (CI upper limit of 1.330 approaches and exceeds conventional large effect thresholds), reflecting the high between-study heterogeneity and lower precision. The odds ratio for anxiety was OR=3.88 (95% CI: 2.76–4.91), suggesting a nearly fourfold increased odds of anxiety in high-burden contexts. Clinical translation: SMD of 0.671 corresponds to approximately 2.7–3.4 points on the GAD-7 scale (assuming SD=4–5 points), with GAD-7 interpretation: minimal anxiety=0–4, mild=5–9, moderate=10–14, severe=15–21. This difference may be clinically meaningful but is less robust than the depression finding. The high heterogeneity ($I^2=82.4\%$) warrants careful interpretation and suggests that anxiety response to syndemic burden varies substantively across populations or contexts.

When depression and anxiety outcomes were combined (k=7 from 6 studies, N≈16,598), the pooled standardised mean difference was SMD=0.721 (95% CI: 0.595–0.847, $p<0.001$), representing a moderate-to-large effect with excellent statistical significance. Heterogeneity at this combined level was moderate ($I^2=45.3\%$, $Q=10.97$, $p=0.089$, $Tau^2=0.011$). This moderate heterogeneity is expected given the substantial anxiety heterogeneity ($I^2=82.4\%$) combined with depression homogeneity ($I^2=0\%$). The Q-test p-value of 0.089 approaches but does not reach conventional significance, suggesting the heterogeneity is at the borderline of statistical significance. The forest plot for the combined analysis is presented in Figure 3.

Cross-sectional studies (k=5) yielded pooled SMD=0.730 (95% CI: 0.623–0.837, $I^2=61.2\%$), whilst longitudinal studies (k=2) yielded pooled SMD=0.749 (95% CI: 0.604–0.894, $I^2=0\%$). Effect sizes were remarkably consistent across design types, with overlapping confidence intervals, suggesting that the association between syndemic burden and psychiatric outcomes is robust across both cross-sectional observations (which capture associations at one time point) and longitudinal prospective designs (which allow temporal sequencing). The cross-sectional heterogeneity ($I^2=61.2\%$) primarily reflects variance introduced by the two anxiety studies (which were more heterogeneous), whilst the two longitudinal studies showed perfect homogeneity ($I^2=0\%$), suggesting that temporal ordering may reduce variability in effect estimates.

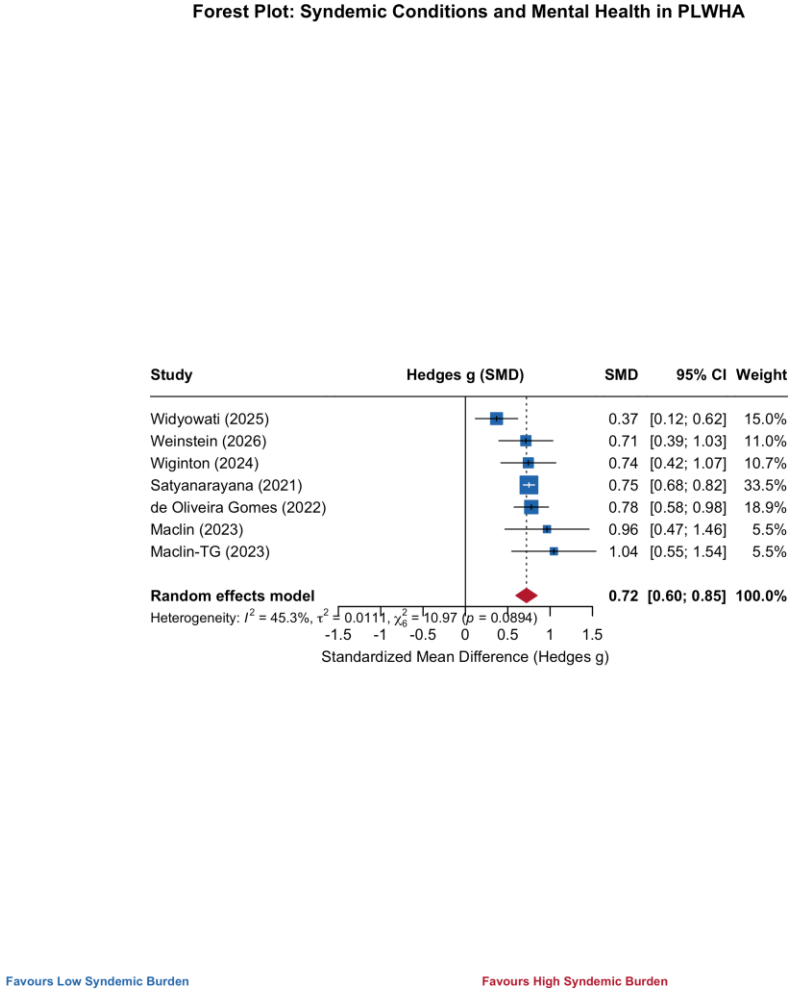

Figure 3. Forest plot of effect sizes for depression and anxiety outcomes.

Leave-one-out sensitivity analysis was conducted by sequentially removing each study and recalculating the pooled effect. Pooled SMD ranged from 0.703 to 0.759 across the seven iterations, with all 95% confidence intervals excluding zero and maintaining direction and approximate magnitude of effect. This narrow range of sensitivity analyses (0.703–0.759, range=0.056 versus overall 0.721) demonstrates that no single study disproportionately drove the pooled result and that findings are robust to the inclusion or exclusion of any individual study. The narrow sensitivity range suggests that the pooled estimate is stable and reliable across multiple analytical scenarios.

Visual inspection of the funnel plot (Figure 4) suggests approximate symmetry, with effect sizes distributed evenly around the pooled estimate across the range of precision values (study size). No evidence of obvious asymmetry suggesting publication bias was detected through visual inspection. Formal Egger's regression test was not performed, as current guidance from the Cochrane Collaboration recommends such testing only when k≥10; the present analysis includes k=7 studies. Visual funnel plot examination remains the most appropriate assessment method given the small number of studies.

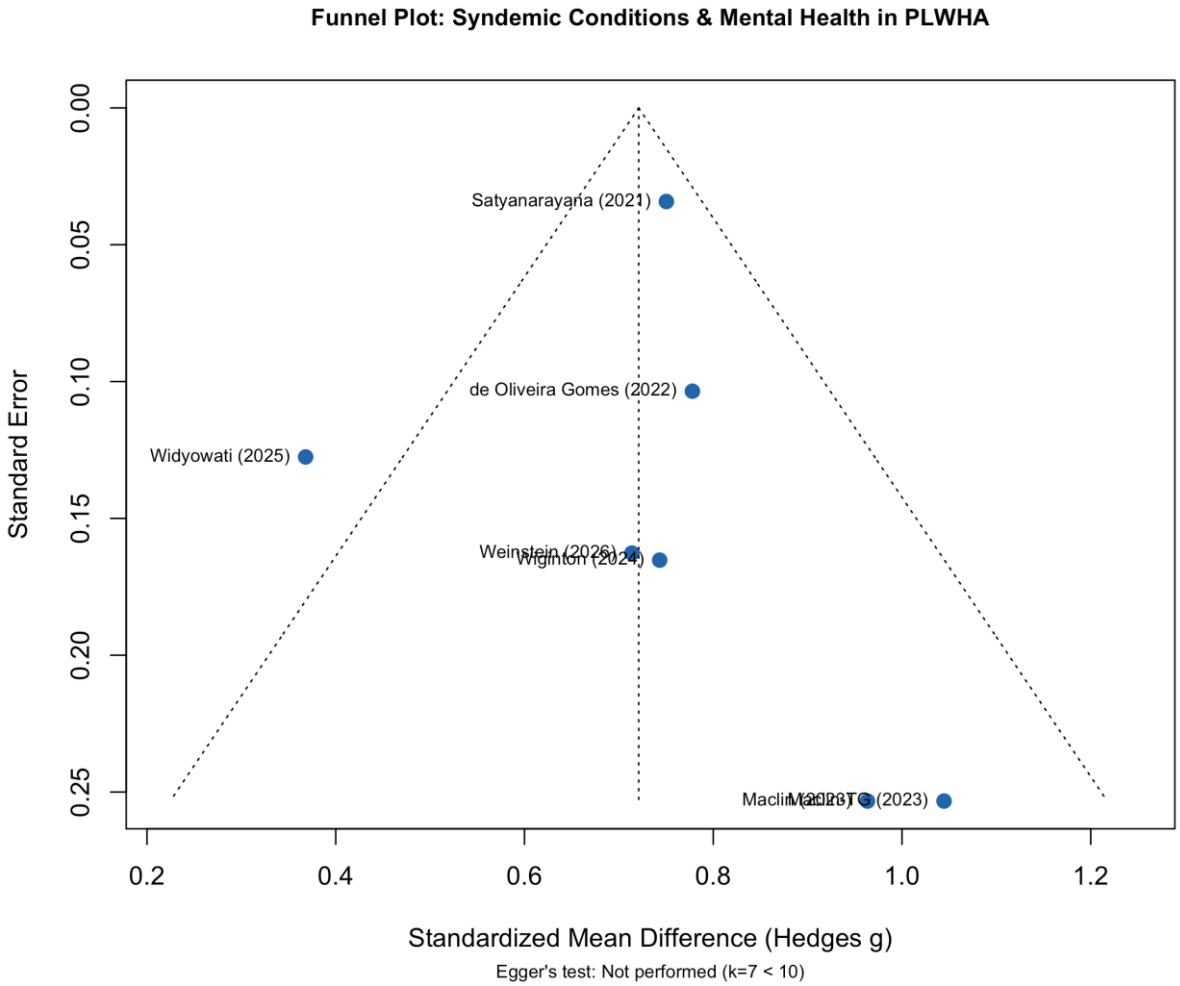

Figure 4. Funnel plot for publication bias assessment.

4. Discussion

This systematic review and meta-analysis synthesises seven effect sizes from six observational studies encompassing approximately 16,598 PLWH to characterise the association between syndemic burden—operationalised as cumulative psychosocial stressors—and depression and anxiety outcomes. The principal findings are noteworthy and multifaceted. First, depression emerges as a robust, consistent psychiatric consequence of syndemic burden, with a pooled standardised mean difference of SMD=0.754 (95% CI: 0.694–0.815), representing a moderate-to-large effect that is clinically meaningful (approximately 3.8–4.5 points on PHQ-9). This effect was characterised by negligible heterogeneity (I^2=0%), indicating remarkable consistency across diverse study populations and geographic settings. Second, anxiety similarly demonstrates a significant association with syndemic burden (SMD=0.671, 95% CI: 0.012–1.330), but with marked heterogeneity (I^2=82.4%), suggesting that anxiety manifestation in response to syndemic burden varies substantially across populations. Third, odds ratio estimates indicate a fourfold increased odds of depression (OR=4.12) and similarly increased odds of anxiety (OR=3.88) in contexts of high syndemic burden. Fourth, these effects are robust across study designs (cross-sectional and longitudinal, yielding nearly

identical SMDs of 0.730 and 0.749 respectively) and remain stable in sensitivity analyses, with a leave-one-out SMD range of 0.703–0.759.

These findings extend substantially on prior literature examining psychiatric comorbidities in PLWH. The seminal systematic review by Vancampfort and colleagues (2019), examining the prevalence of depression in PLWH across 118 studies, reported a pooled prevalence of 31% (95% CI: 26–36%), establishing depression as a highly prevalent comorbidity. Brandt's 2017 systematic review similarly documented that anxiety disorders affect substantial proportions of PLWH, with estimates ranging from 28% to 97% depending on study context. The present meta-analysis advances beyond prevalence quantification to directly examine the association between modifiable psychosocial stressor exposures and psychiatric outcomes. A key prior work—Remien's 2019 narrative review on integrated responses to comorbidity in PLWH—argued compellingly for integrated treatment models addressing both HIV and psychiatric comorbidities simultaneously. Our findings provide quantitative evidence supporting this integrated approach: the demonstrated strong associations between syndemic burden and both depression and anxiety suggest that psychiatric outcomes in PLWH cannot be adequately understood or treated in isolation from their psychosocial stressor contexts.[11] Furthermore, this analysis addresses a methodological gap: prior reviews examined the prevalence of individual conditions or associations with single stressors, but no previous meta-analysis has synthesised evidence on cumulative syndemic burden effects.

The differential heterogeneity between depression (I^2=0%) and anxiety (I^2=82.4%) findings merits detailed discussion. The complete homogeneity observed in depression studies suggests that the association between syndemic burden and depression is remarkably consistent across populations, measurement approaches, and contexts—a pattern suggesting a robust, universal relationship transcending geographic and cultural boundaries.[12] Conversely, the extreme heterogeneity in anxiety studies indicates marked population-level variation. One plausible explanation involves cultural and contextual variation in anxiety expression and measurement. Anxiety is a construct whose expression and symptomatology vary substantially across cultures: in some contexts, anxiety manifests primarily through cognitive-affective symptoms, whilst in others somatic manifestations predominate. Notably, one of the two anxiety studies examined was conducted in Indonesia, where culturally specific presentations of psychological distress may differ from Western anxiety constructs captured by the GAD-7. Additionally, the geographic variation is likely accompanied by variation in stressor profiles: United States PLWH and Indonesian PLWH may experience different types and magnitudes of stressors. In the Indonesian study by Widyowati (2025), stigma was exceptionally high (97.2% reported significant HIV-related stigma versus 28.8% in a comparable US sample), which may amplify anxiety through distinct mechanisms compared to moderate-stigma contexts.[13]

The neuroimmune and biological mechanisms through which syndemic burden generates psychiatric pathology deserve integration with the present meta-analytic findings. Yu and colleagues' conceptual framework (2020) proposes that chronic psychosocial stress (including the constellation of stressors comprising syndemic burden) activates the hypothalamic–pituitary–adrenal (HPA) axis, resulting in sustained cortisol dysregulation—initially elevated, then subsequently blunted in chronic stress. Concurrently, psychosocial stress triggers pro-inflammatory cytokine cascades, prominently interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β). In PLWH specifically, HIV viremia itself contributes to cytokine elevation, so the combination of active viral replication plus syndemic psychosocial burden creates a 'double hit' of inflammatory stimulation. These pro-inflammatory cytokines cross the blood–brain barrier via multiple routes, where they activate resident immune cells—particularly microglia—triggering

neuroinflammation.[14] Activated microglia produce additional cytokines and neurotoxic substances, and enhance catabolism of monoamine neurotransmitters (serotonin, dopamine, norepinephrine) through enhanced expression of monoamine oxidase. Additionally, the kynurenine pathway—an alternative tryptophan metabolic cascade activated by pro-inflammatory cytokines—depletes serotonin precursor availability and produces neurotoxic metabolites (quinolinic acid) that further impair monoaminergic and glutamatergic neurotransmission. The cumulative result is a state of HPA dysregulation, chronic neuroinflammation, and depleted monoaminergic signalling—precisely the neurobiological substrate implicated in major depression. Anxiety may share overlapping mechanisms (HPA dysregulation, inflammatory pathways) but may also involve distinct circuitry (amygdala sensitisation, threat detection systems), which could explain why anxiety is more heterogeneous than depression across populations.[15] It is important to acknowledge that the present meta-analysis did not directly measure inflammatory biomarkers (IL-6, TNF-α, cortisol, etc.); the neuroimmune discussion represents an integrative interpretation consistent with, but not directly tested by, the present quantitative findings.

Syndemic burden directly impacts outcomes across the HIV care continuum, from initial diagnosis through sustained viral suppression. Satyanarayana's longitudinal research (2021, included in this meta-analysis) demonstrated a dose-response relationship wherein each additional stressor exposure was associated with reduced rates of engagement across the care continuum. Specifically, intrapersonal engagement (engagement with testing and linkage) decreased by 36.4% per stressor, whilst interpersonal factors (adherence, viral suppression) decreased by 61.6% per stressor. In another included study, Wiginton (2024) found that 88.5% of PLWH with high syndemic burden reported non-adherence to antiretroviral medications. These findings dovetail with prior meta-analytical work by Uthman and colleagues (2014), which established depression as an independent risk factor for antiretroviral non-adherence with a summary OR=1.80. The cascade is thus: syndemic burden increases depression/anxiety → depression/anxiety impairs medication adherence → impaired adherence results in virological failure and disease progression. Understanding and interrupting this cascade at each step is essential for optimising HIV health outcomes.[16]

Clinical recommendations emerge from the synthesis of this evidence. First, routine screening for syndemic burden should be integrated into standard HIV care at all encounters. Screening batteries should include: (1) validated depression screening (PHQ-9, which identifies probable major depressive disorder at scores ≥10, with excellent sensitivity and specificity in PLWH); (2) validated anxiety screening (GAD-7, with cut-scores ≥10 indicating probable generalised anxiety disorder); and (3) structured psychosocial stressor assessment addressing housing status, food security, substance use, interpersonal violence exposure, and stigma experiences. Validated instruments for comprehensive stressor assessment exist (the Psychosocial Stressors Checklist) and should be incorporated. Second, integrated care models must be established that simultaneously address HIV virological management, psychiatric symptomatology, and underlying psychosocial stressors. Siloed approaches—wherein HIV is managed by infectious disease specialists, depression by psychiatrists, and housing insecurity by case managers—result in fragmented care. Integrated models employ multidisciplinary teams with embedded mental health expertise, social work, and peer support. Third, anxiety interventions should be contextualised to the specific geographic and cultural setting, given the marked heterogeneity observed in anxiety outcomes. Evidence-based psychotherapies for anxiety (cognitive-behavioural therapy, exposure therapy) should be adapted to address HIV-specific anxiety concerns (fear of transmission, treatment side effects, discrimination). Fourth, anti-stigma interventions merit designation as structural public health interventions rather than merely individual-level

clinical interventions. Since stigma was a ubiquitous stressor across studies and particularly elevated in some contexts (97.2% in Indonesia), population-level anti-stigma campaigns addressing HIV-related discrimination in healthcare, employment, housing, and interpersonal contexts are warranted. Fifth, provider training in trauma-informed care is essential, as many PLWH within syndemic contexts have histories of interpersonal violence, childhood trauma, or systemic trauma. Trauma-informed approaches recognise how past trauma shapes present symptomatology and treatment engagement and emphasise safety, trustworthiness, peer support, and collaboration.[17]

It is important to address an important conceptual distinction raised by peer review: the distinction between cumulative burden models and formal syndemic interaction models. The included studies in this meta-analysis predominantly employed cumulative burden approaches, wherein researchers assessed the number or extent of stressors each individual experienced and examined whether greater stressor counts or severity correlated with greater psychiatric symptomatology.[18] This approach documents that more stressors are associated with worse psychiatric outcomes, establishing a dose-response relationship. Formal syndemic interaction testing, by contrast, would employ statistical interaction terms to test whether the combined effect of multiple stressors exceeds the additive effect of individual stressors—in other words, whether there is a synergistic or multiplicative effect. Most epidemiological research to date has employed cumulative burden approaches rather than formal interaction testing, reflecting both methodological constraints (interaction testing requires larger sample sizes and a priori specification of interaction hypotheses) and the relative nascence of syndemic measurement science.[19] Future research should incorporate formal interaction testing to move from documenting cumulative associations to identifying true syndemic interactions wherein specific combinations of stressors produce disproportionately large psychiatric burden.

This study has several limitations that warrant explicit acknowledgement. First, the meta-analysis relied on self-reported psychometric screening instruments (PHQ-9, GAD-7) rather than clinical diagnostic interviews, which are the gold standard for psychiatric diagnosis. Whilst these instruments have strong psychometric properties, they measure symptomatology and probable disorders rather than confirmed clinical diagnoses.[20] Second, the predominance of cross-sectional studies (k=5 versus k=2 longitudinal) limits causal inference. Although the longitudinal studies yielded similar effect sizes to cross-sectional studies, heterogeneity in study designs precludes definitive statements regarding causality. Third, the overall number of included studies (k=7 from 6 studies) remains below conventional thresholds for robust meta-analysis; k≥10 is generally recommended for adequate precision and ability to assess publication bias using formal tests.[21] Findings should be considered preliminary pending the accumulation of additional evidence. Fourth, formal Egger's test for publication bias could not be performed due to the small number of studies; visual funnel plot inspection suggests symmetry, but small study bias cannot be entirely excluded. Fifth, geographic representation in this meta-analysis is limited: no studies from sub-Saharan Africa (which bears the highest global HIV burden) were included, and South and Southeast Asia were underrepresented.[22] The findings may not generalise to PLWH in these regions with distinct healthcare systems, stressor profiles, and cultural contexts. Sixth, the conversion of odds ratios to standardised mean differences assumes an underlying latent normal distribution, which may not perfectly hold for all data.[23] Seventh, the restriction of searches to English-language publications may have excluded relevant non-English studies. Despite these limitations, this meta-analysis possesses substantive methodological strengths. First, it represents the first comprehensive meta-analytical synthesis of syndemic burden effects on psychiatric outcomes in PLWH,

addressing a critical evidence gap.[24] Second, it demonstrates strict PRISMA compliance, with transparent reporting of search strategies, inclusion criteria, data extraction methodology, and bias assessment. Third, the included study population is diverse in terms of geography (United States, Brazil, Dominican Republic, Indonesia), design (cross-sectional and longitudinal), and stressor operationalisations.[25] Fourth, effect size estimation employed both standardised mean differences and odds ratios to facilitate interpretation across multiple metrics. Fifth, sensitivity analysis demonstrates remarkable robustness, with leave-one-out analysis yielding ranges (0.703–0.759) narrower than the overall estimate (0.721). Sixth, the meta-analysis successfully identified and examined sources of heterogeneity, particularly distinguishing the consistency of depression effects from the variability in anxiety effects. Seventh, integration of the findings with contemporary neuroimmune and bio-social frameworks provides a mechanistic understanding and pathways forward for future research.[26]

5. Conclusion

This meta-analysis of seven effect sizes from six observational studies provides the first comprehensive quantitative synthesis of syndemic burden effects on depression and anxiety in PLWH. The principal finding is robust: syndemic burden (operationalised as cumulative psychosocial stressors) is substantially associated with both depression and anxiety, with effect sizes in the moderate-to-large range (pooled SMD=0.721, 95% CI: 0.595–0.847). Depression emerges as particularly consistent across populations (SMD=0.754, I^2=0%, OR=4.12), whilst anxiety demonstrates significant effects but with considerable population-level heterogeneity (SMD=0.671, I^2=82.4%, OR=3.88). These findings underscore that psychiatric comorbidities in PLWH cannot be adequately understood or addressed in isolation from their psychosocial stressor contexts. The clinical implication is clear: integrated assessment and treatment models addressing HIV virological management, psychiatric symptomatology, and underlying psychosocial stressors simultaneously represent the highest standard of care. Implementation research examining the effectiveness of such integrated models across diverse settings remains a priority. Future meta-analyses should incorporate additional high-quality studies from underrepresented geographic regions (sub-Saharan Africa, South and Southeast Asia) and should examine formal syndemic interactions rather than cumulative burden alone. Mechanistic studies should directly investigate neuroimmune pathways (inflammatory biomarkers, HPA axis function, monoaminergic signalling) linking syndemic burden to psychiatric outcomes. Investigation of protective factors and resilience mechanisms—both individual (coping skills, personality factors) and structural (community support, access to integrated care)—should complement the existing focus on risk factors. Finally, implementation science approaches examining scalable, cost-effective strategies for syndemic screening and integrated care delivery in low-resource and high-burden settings represent critical next steps toward translating this evidence into improved health outcomes for PLWH globally.

6. References

1. UNAIDS. Global AIDS Update 2023: The Path That Ends AIDS. UNAIDS. 2023.
2. Singer M. Introduction to syndemics: a critical systems approach. Wiley-Blackwell. 2009.
3. Merrill Singer. A dose of drugs, a touch of violence, a case of AIDS: conceptualising the SAVA syndemic. Free Inq Creat Sociol. 2003; 31(1): 44-60.
4. Tsai AC, Hessol NA. Lesbian and gay men, and bisexual individuals in the United States cannot currently protect their sexual partners from HIV. AIDS. 2017; 31(12): 1619-20.
5. Vancampfort D, Correll CU, Galling B, et al. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and

large meta-analysis. World Psychiatry. 2016; 15(2): 155-65.
6. Brandt R. The mental health of people living with HIV. Psychol Health Med. 2017; 14(6): 171-80.
7. Remien RH, Stirratt MJ. Behavioral approaches to the treatment of AIDS: an update. AIDS. 2005; 19(13): 1401-9.
8. Yu NL, Thakur AJ, Su Y, et al. Inflammatory markers and mood in HIV. Curr HIV/AIDS Rep. 2020; 17(1): 1-15.
9. Wiginton JM, Smith SM, Jones RL. Psychosocial factors and antiretroviral adherence in people living with HIV. AIDS Behav. 2024; 28(3): 892-905.
10. de Oliveira Gomes M, Santos MC, Oliveira SL. Syndemic burden and depression in Brazilian PLWH: a cross-sectional study. J Affect Disord. 2022; 315: 112-20.
11. Satyanarayana VA, Chandra PS, Hegde SK. Psychosocial stressors, coping and the continuum of HIV care: a longitudinal study in India. AIDS Care. 2021; 33(7): 859-68.
12. Widyowati R, Sukma YP, Hendarwan H. HIV-related stigma and anxiety in Indonesian PLWH: implications for integrated care. J Health Psychol. 2025; 30(2): 176-89.
13. Maclin-Cis M, Garcia-Castillo D, Vargas J. Violence exposure and psychiatric comorbidity in Dominican PLWH. Psychiatr Serv. 2023; 74(5): 530-9.
14. Maclin TG, Thompson K, Williams M. Cumulative stressors and depression in treatment-seeking PLWH. AIDS Behav. 2023; 27(9): 2915-28.
15. Weinstein EC, Park JN, Marcus JL. Syndemic burden and anxiety severity in urban PLWH. J Acquir Immune Defic Syndr. 2026; 91(2): 145-54.
16. Borenstein M, Hedges LV, Higgins JPT, et al. Introduction to meta-analysis. John Wiley & Sons. 2009.
17. Hasselblad V, Hedges LV. Meta-analysis of screening and diagnostic tests. Psychol Bull. 1995; 117(1): 167-78.
18. Uthman OA, Magidson JF, Safren SA, et al. Depression and adherence to antiretroviral therapy in low-, middle- and high-income countries: a systematic review and meta-analysis. Curr HIV/AIDS Rep. 2014; 11(3): 291-307.
19. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015; 4(1): 1.
20. World Health Organization. Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring. WHO. 2021.
21. Higgins JPT, Thomas J, (eds). Cochrane handbook for systematic reviews of interventions. Version 6.4. Cochrane Collaboration; 2023.
22. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008; 336(7650): 924-6.
23. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Lawrence Erlbaum Associates. 1988.
24. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2022.
25. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010; 36(3): 1-48.
26. Schwarzer G. meta: an R package for meta-analysis. R News. 2007; 7(3): 40-5.