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Global Mental Health and HIV Prevention and Care

Guest Editors: Robert H Remien, Melanie Amna Abas, Vikram Patel, Dixon Chibanda
Supplement Editor: Marlène Bras

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EDITORIAL

Integrating mental health into HIV prevention and care: a call to action

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Mental health is a universal human asset, indivisible from other public health priorities, and especially important to people living with and at risk for HIV [1,2]. Much has been written about mental health and HIV in high-resource settings, especially in the United States. However, 90% of all those living with HIV globally, and 83% of the world's total population, live in low-income and middle-income countries (LMIC). Knowledge generated in high-income countries may not translate to the very diverse contexts encountered in LMIC where factors such as poverty, patterns of the burden of disease, gender norms, discrimination against specific groups, and mental health resources vary greatly. Given this context, this Special Issue of the *Journal of the International AIDS Society* focuses on mental health and HIV, predominantly in LMIC settings with a high HIV burden, and among key populations at greatest risk of HIV, to highlight: (1) the linkage between mental health problems, and other psychosocial factors, which increase HIV risk; (2) the interventions and strategies to prevent HIV among people with mental health problems; (3) factors associated with common mental disorders among young people and adults living with HIV and (4) interventions to improve mental health among persons with HIV (PWH).

Papers in this Supplement related to HIV prevention focused on vulnerable groups at elevated risk for HIV acquisition. Collins *et al*., synthesized the literature on HIV prevention and mental health among key populations, including gay men and other men who have sex with men, female sex workers, transgender women, people who inject drugs and incarcerated people. This review highlights the relationship between mental health problems and HIV prevention outcomes, showing that symptoms of mental disorders and distress are associated with increased sexual risk behaviours and poor engagement with HIV prevention. The authors found that integrating a mental health component into a behavioural change intervention, or linking mental health services to combination prevention activities, significantly reduced risk behaviour and mental distress, and improved access to mental healthcare [3]. Velloza *et al*., studied mental health and use of pre-exposure prophylaxis (PrEP) in adolescent girls and young women in Zimbabwe and South Africa, a population at high risk of HIV acquisition. They found that depressive symptoms were common and persistent, particularly in the context of engagement in transactional sex, inter-personal violence and traumatic stress symptoms [4]. Notably, all these factors were associated with worse adherence to PrEP. Among female sex workers in Kenya, Leis *et al*., observed elevated levels of depression and anxiety, and the strong association between these symptoms and reported interpersonal violence. They also found that recent client-perpetrated emotional violence and increased years in sex work were associated with decreased PrEP use [5].

Two papers in this Supplement examined the burden and impact of mental health problems among PWH. Too *et al*., conducted a systematic review on the prevalence and correlates of common mental disorders among young people living with HIV in sub-Saharan Africa. They report that there was an increased risk of common mental disorders, especially depression, in youth living with HIV, compared to their peers who were not living with HIV. They also highlight how bullying, HIV-related stigma, lack of social support and poor adherence to antiretroviral therapy (ART) were associated with depressive symptoms [6]. Nguyen *et al*., found that depression and anxiety symptoms were associated with sub-optimal adherence to ART among PWH in Vietnam and that hazardous alcohol use and alcohol dependence interacted with anxiety symptoms to exacerbate poor adherence to ART [7].

This Supplement includes two reviews on the effectiveness of mental health interventions in PWH. Bhana *et al*., carried out a narrative review of mental health interventions for young adults living with and affected by HIV [8]. They identified some promising approaches while concluding that there is a paucity of evidence on effective approaches and on understanding the corresponding mechanisms of change for this population. The diversity of existing interventions – many of which are not specific – make it difficult to discern best practice. They suggest a need to test simple, brief transdiagnostic interventions which are likely to be feasible in low resource settings by utilizing, for example lay counsellors who are supported by digital technology. Nakimuli-Mpungu *et al*.,

conducted a systematic review on mental health interventions for PWH [9]. They found that psychological interventions with three or more "active ingredients" (e.g. positive coping skills, social support, sharing personal problems, behaviour activation and cognitive re-structuring) are likely to be more effective than interventions with fewer ingredients; and that people are also more likely to adhere to interventions tailored to the cultural context. They found that studies testing the implementation of pharmacological treatments for mental disorders in PWH had been compromised by poor adherence (e.g. to antidepressant medication), and by "stock-outs" of basic psychotropic drugs. These authors call for large-scale definitive trials providing long-term follow-up data, including among PWH with severe mental disorders.

Also in this Supplement, Senn *et al*., provide us with a Viewpoint perspective highlighting three research gaps in the study of mental health among PWH: (a) understanding the complex interactions between biological, psychological, social and structural factors that influence mental disorders in PWH; (b) developing and testing interventions to address mental health, as well as co-occurring psychological, social and structural factors, to improve HIV outcomes and (c) implementation science to understand how to best implement and scale-up efficacious interventions to improve mental health and HIV outcomes [10]. Among the gaps in knowledge is how to improve both mental health and HIV outcomes in low-resource settings [11]. In the United States, combined interventions which address health behaviours (e.g. addressing barriers to medication adherence) and also mental health serve to enhance physical health, mental health and overall well-being [12,13]. In this issue, Magidson *et al*., report on a pilot trial of "*Khanya*," a task-shared, peer-delivered behavioural intervention in South Africa [14]. *Khanya* blends ingredients to improve ART adherence with those to address alcohol and substance use. They studied implementation outcomes and found that *Khanya* was feasible, acceptable, appropriate and delivered with fidelity by peers, suggesting that peers may be a potential strategy to extend task-sharing models for behavioural health.

The research described in the series of papers in this Special Issue emphasizes the importance of integrating mental health care within the full range of HIV programmes, from those which seek to reduce risks for acquiring HIV in vulnerable populations to those which seek to improve mental health outcomes and HIV outcomes in persons who are receiving ART. Drawing on this evidence, and the evidence synthesized in a series of recent global mental health and reports from the World Health Organization (WHO) [15-17], we recommend a number of key strategies.

First, interventions to promote mental health literacy should be made available for everyone involved in HIV prevention and care in low-resource settings. This should include those directly affected and their families, as well as informal and formal service providers, so that all key stakeholders are aware of the importance of mental health for HIV risk, and treatment and care. Second, we endorse WHO advice to integrate screening and treatment of depression into the HIV care cascade in prevention and healthcare settings, including community-based practices [18]. For those with depression and also poor adherence to HIV medication, we endorse the integration of evidence-based treatment for depression with evidence-based adherence counselling [19,20]. We recommend that mental health interventions be provided for those with a range of vulnerabilities and distress experiences, and not be restricted only to those with narrowly defined and diagnosed mental illness. Third, prevention must target social determinants across the life course, particularly in adolescence where risk factors can be similar to those in adults, but even more pronounced in terms of their negative consequences. These include experiences of trauma and violence and poor educational attainment, which are associated with both poor mental health and HIV health outcomes. Fourth, interventions should follow the principles of stepped care, with access to self-help and simple, brief, transdiagnostic evidence-based interventions for all, with a pathway in place to offer more intensive care for those with severe mental illness [21]. Fifth, programmes must leverage the resources available in the community, including deploying the strategy of peer support and existing HIV health workers, which have clearly defined roles in the HIV sector. In addition, because of the exponential rise in the use of mobile devices in LMIC there is a need to leverage digital technology particularly mobile phone-based apps to improve reach, fidelity and efficient data collection. Sixth, there needs to be a focus not just on access to care but also its quality, in particular for psychosocial interventions which are proven to be highly effective when delivered by non-specialists such as lay counsellors and community-based outreach workers. Finally, we need to emphasize social justice and equity to reduce disparities and inequities, for example as experienced by sexual, gender, racial and ethnic minorities. Fairness must also be applied to the principles of building research capacity in LMIC [22,23]. We hope for, and look forward to seeing more research on mental health and HIV led by researchers based in LMIC [24].

In our collective goal of taking interventions to scale, it is critical that models are developed from the outset with a focus on feasibility and long-term sustainability. A key guiding principle is to combine mental health into HIV programmes, rather than siloing into specialist mental health services, which, apart from being scarce in most countries, are also associated with stigma and low levels of acceptability. A way to do this would be to utilize key points of the routine HIV care cascade for mental health integration, such as HIV testing, PrEP and ART initiation, and viral load testing, rather than requiring separate appointments and/or at different locations. Research is needed to learn about barriers and enablers of such integration, and about cost-effectiveness of interventions which can be delivered by trained and supervised non-specialists.

Unfortunately, recent progress in achieving global HIV targets has fallen behind, as a result of the COVID-19 pandemic [25]. Furthermore, the health and psychosocial burden and inequities have not been shared equally within and between countries. Stigma and discrimination, along with other widespread inequalities, continue to serve as major barriers to ending AIDS, as well as addressing the COVID-19 pandemic and mental health. As we strive to get back on track in combatting HIV and AIDS, we call upon HIV programmes to recognize that the aspiration of a world without HIV cannot be realized without integrating mental health across all HIV programmes and prevention and care settings. Investing in mental health pays dividends – for example every US$ 1 invested in expanding treatment for depression and anxiety leads to a

return of US$ 4 in better health and capacity to work [26]. As decisions are made about spending money on HIV services, in the face of the COVID-19 pandemic, we need to spend available funds wisely, guided by the best science and human rights. This calls for evidence-informed mental healthcare to be at the core of the HIV response, and to embrace the diversity of experiences and strategies which work to improve the lives and well-being of all citizens of the world.

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COMPETING INTERESTS

The authors have declared no conflict of interest.

AUTHORS' CONTRIBUTIONS

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REVIEW

Intervening for HIV prevention and mental health: a review of global literature

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Abstract

Introduction: Numerous effective HIV prevention options exist, including behaviour change interventions, condom promotion and biomedical interventions, like voluntary medical male circumcision and pre-exposure prophylaxis. However, populations at risk of HIV also face overlapping vulnerabilities to common mental disorders and severe mental illness. Mental health status can affect engagement in HIV risk behaviours and HIV prevention programmes. We conducted a narrative review of the literature on HIV prevention among key populations and other groups vulnerable to HIV infection to understand the relationship between mental health conditions and HIV prevention outcomes and summarize existing evidence on integrated approaches to HIV prevention and mental healthcare.

Methods: We searched five databases for studies published from January 2015 to August 2020, focused on HIV prevention and mental health conditions among key populations and individuals with serious mental illness. Studies were included if they evaluated an HIV prevention intervention or assessed correlates of HIV risk reduction and included assessment of mental health conditions or a mental health intervention.

Results and discussion: We identified 50 studies meeting our inclusion criteria, of which 26 were randomized controlled trials or other experimental designs of an HIV prevention intervention with or without a mental health component. Behaviour change interventions were the most common HIV prevention approach. A majority of studies recruited men who have sex with men and adolescents. Two studies provided distinct approaches to integrated HIV prevention and mental health service delivery. Overall, a majority of included studies showed that symptoms of mental disorder or distress are associated with HIV prevention outcomes (e.g. increased risky sexual behaviour, poor engagement in HIV prevention behaviours). In addition, several studies conducted among groups at high risk of poor mental health found that integrating a mental health component into a behaviour change intervention or linking mental health services to combination prevention activities significantly reduced risk behaviour and mental distress and improved access to mental healthcare.

Conclusions: Evidence suggests that mental health conditions are associated with poorer HIV prevention outcomes, and tailored integrated approaches are urgently needed to address overlapping vulnerabilities among key populations and other individuals at risk.

Keywords: HIV prevention; mental health; prevention & control; severe mental illness

Additional Supporting information may be found online in the Supporting Information tab for this article.

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1 | INTRODUCTION

Despite an estimated 23% reduction in the global rate of human immunodeficiency virus (HIV) infection since 2010, dramatic disparities in the risk of HIV infection persist along the lines of entrenched social inequities. Over 60% of new HIV infections occur among key populations and their sexual partners, including gay men and other men who have sex with men (MSM), female sex workers (FSW), transgender women (TGW) (primarily), people who inject drugs (PWID), and prisoners and other incarcerated people [1]. In sub-Saharan Africa, adolescent girls and young women (aged 15 to 24 years) account for 24% of new HIV infections despite representing only 10% of the population [1]. People with severe mental illnesses (SMI) are also over-represented among new HIV infections [2,3]. A diverse range of HIV prevention practices and technologies are effective, acceptable and increasingly available in many settings, including condom distribution and voluntary testing and counselling [4], universal test-and-treat [5], voluntary medical male circumcision (VMMC) [6],

oral pre-exposure prophylaxis (PrEP) [7], the dapivirine ring and other new, longer-acting PrEP modalities [8] and combination prevention packages incorporating behavioural, biological and structural interventions [9,10]. However, the over-representation of key populations and other vulnerable groups among new HIV infections suggests that it is critical to improve their engagement with these effective HIV prevention strategies.

Among key populations and other vulnerable groups, the same inequities that drive HIV infection also increase the risk for mental health conditions [11]. Social exclusion and marginalization, poverty, violence and discrimination create cycles of vulnerability to both HIV and worsening mental health status [12]. A review of the mental health of sexual minorities reported elevated rates of depression, bipolar disorder, suicide attempts and drug use disorders across sexual orientation and genders [13]. Mental health conditions are disproportionately prevalent among incarcerated people; people in prisons are at increased risk of all-cause mortality, suicide, self-harm, violence and victimization [14].

Vulnerability to HIV and mental health conditions also intersect in adolescence, a sensitive period of neuropsychological and social development during which adolescents seek greater autonomy, takes risks and initiate sexual activity, with gender-specific consequences [15,16]. Globally, 1.7 million adolescents (ages 10 to 19) live with HIV, and nearly 60% of adolescents living with HIV are girls [17]. Most mental disorders that persist in adulthood begin in adolescence [18]. Young key populations have elevated rates of depression, suicidal ideation and intent and traumatic stress [19,20]; meanwhile, adolescents with mental health conditions may be vulnerable to deficits in emotion regulation when making decisions about sex [21].

Lastly, people with SMI experience specific challenges related to living with symptoms that can be disabling, in addition to social, economic and gender-specific vulnerabilities [22-27]. These increase their risk of coercive sexual encounters, transactional sex, and sex with partners at high risk of HIV and unsafe drug use [28-30]. Notably, these groups are not mutually exclusive: individuals often have multiple marginalized identities leading to overlapping and intersecting vulnerability to both HIV and mental health conditions.

Few studies have examined HIV prevention and mental health among HIV-negative key populations and vulnerable groups eligible for combination prevention, condom promotion, PrEP and other HIV prevention services. HIV prevention programmes providing behavioural counselling and PrEP interventions have found that young key populations have a high prevalence of depressive, anxiety and traumatic stress symptoms [19,20,31,32]. Consequently, expert commentaries have called for integrated, culturally appropriate mental health and HIV prevention interventions to address the needs of people living with mental health conditions; these include social interventions, like cash transfer programmes, economic empowerment strategies and gender-based violence services, alongside HIV prevention counselling, or PrEP delivery with psychotherapy and social support interventions to address mental health conditions [19,20,33,34].

From 2014 to 2016, several reviews reported the evidence on the need for and results of HIV prevention interventions focusing on people with SMI [2,35-37]. These reviews found that there was considerable heterogeneity in the outcomes of HIV prevention interventions in this population. Behavioural skills training and HIV risk reduction counselling were effective in reducing the number of sexual partners and condomless sex in some trials, but few studies demonstrated lasting effects post-intervention [36].

A synthesis of more recent literature on the range of mental health conditions (from stress to SMI) is needed to understand the latest evidence on HIV prevention interventions and their outcomes for people managing or at risk for mental health conditions. We conducted a narrative review of global research on mental health and HIV prevention among adolescents and young women, key populations and people with SMI. Our primary aim was to understand how symptoms of mental health conditions influence HIV prevention intervention engagement and outcomes among these groups. We also reviewed evidence of integrated approaches to HIV prevention and the management of mental health conditions. We organize our findings around two questions: 1) what do we know about the relationship between mental health and HIV prevention or risk behaviours? 2) what do we know about interventions that address mental health in the context of HIV prevention?

2 | METHODS

We conducted a structured narrative review of the literature in peer-reviewed journals to examine the relationships between HIV prevention, risk reduction and mental health conditions.

2.1 | Search strategy

Two authors worked with a university informationist to select search terms and determine filters for five databases. We searched PubMed, Web of Science, CINAHL, PsychINFO and EMBASE for English-language studies published between 1 January 2010 and 25 August 2020. We constructed search terms on HIV prevention; interventions, services or programmes; and mental disorders. We ran these base search terms with search terms for each of the three populations of interest: (1) adolescents (boys and girls) and young women, (2) people with SMI and (3) UNAIDS-defined key populations (i.e. MSM, sex workers, transgender persons, PWID and prisoners and other incarcerated people as key population groups [38]). (See Additional File S1: Search Strategy.)

2.2 | Inclusion and exclusion criteria

Studies were eligible if they met the following criteria: (1) assessed correlates of HIV risk reduction activities or evaluated an HIV prevention intervention; (2) included assessment of mental health conditions, cognitive processes or tailored an intervention for people with mental disorders. We included studies related to the use of structural and behavioural HIV risk reduction approaches as well as biomedical prevention interventions. We excluded qualitative studies. Given the scope of the literature on drug use and HIV prevention, which merits its own review, we eliminated studies focused on harm reduction and prevention or treatment of substance use disorders if there was no mental disorder data. We also eliminated studies exclusively focused on HIV treatment as prevention

for this review. Although treatment as prevention studies have the ultimate goal of preventing HIV transmission, they tend to focus on populations living with HIV who may have distinct HIV care and mental health needs compared with at-risk, HIV-negative populations. Eligible studies reported the outcomes of HIV prevention trials, cross-sectional and longitudinal analyses or quasi-experimental studies.

2.3 | Study selection and data extraction

We restricted our review of papers to January 2015 to August 2020. There were overlapping topical reviews of the literature prior to 2015 (e.g. for people with SMI). Given the scope of prevention research publications and the rapid evolution of HIV prevention science, the criterion of a 5-year period of review targets current research most relevant to practitioners and researchers. However, if studies from this time period were sub-studies, secondary analyses or otherwise related to a primary trial that met our inclusion criteria, we also added the primary trial to the dataset. We identified five such studies, three of which were published between 2010 and 2014. We included six studies published from 2015 to 2020 identified in the PrEP literature (e.g. references of other publications or adjacent studies in a search database) that met our criteria for inclusion. All studies were imported into Endnote (X9) to remove duplicates, book chapters, conference abstracts and theses. The resulting set was imported into Abstrackr (Tufts Evidence-based Practice Center, beta version) for title and abstract review [39].

Authors (TC, JV, LO) conducted an initial screening of 20 abstracts to arrive at consensus on studies for inclusion and exclusion, followed by screening of all abstracts using Abstrackr Beta [39]. Full-text manuscripts were assessed independently by authors (PC, TC, JV, LO, LC, JS). PC resolved disagreement in the process of study selection.

Authors used spreadsheet software to extract the following information: lead author, year of publication, country of study, sample size, study population, study design, study objective, HIV prevention approach, approach category, mental health component in intervention, HIV prevention outcome, mental health assessment used, and key HIV prevention/mental health finding. PC and JV conducted a second-level review of all eligible manuscripts. Due to the heterogeneity of our sample in terms of intervention type, outcome and populations, we conducted a qualitative synthesis of study findings.

3 | RESULTS AND DISCUSSION

3.1 | Study characteristics

A total of 3340 articles were identified through search criteria. After removing duplicates, book chapters, conference abstracts and theses, and restricting to 2015 to 2020 publication years, 1023 articles were eligible for the title/abstract screen. A total of 148 articles were full-text reviewed and 46 were eligible to be included in this review. We added 11 articles after full-text review, yielding a total of 57 articles in this review (Figure 1). We counted the full texts of multiple articles as one study if the same interventions were administered to the same study population or to a subset of the study population, reducing our total number of studies to 50.

Of the 50 studies we identified, 26 were randomized controlled trials or other experimental designs (e.g. quasi-experimental designs with a pre- and post-intervention period evaluation) testing the efficacy of an HIV prevention intervention with or without a mental health component, two were secondary analyses of randomized controlled trials, five were longitudinal studies examining risk reduction behaviour and 17 were cross-sectional studies assessing the relationship of mental health status and HIV risk or prevention. The studies represent samples from 26 countries: United States (n = 23), Kenya (n = 5), South Africa (n = 4), Brazil (n = 5), Ecuador (n = 1), Peru (n = 3), Thailand (n = 3), Burkina Faso (n = 2), Belgium (n = 1), Canada (n = 2), China (n = 1), Colombia (n = 1), Côte d'Ivoire (n = 1), England (n = 2), Ethiopia (n = 1), India (n = 1), Jamaica (n = 1), Malaysia (n = 1), Mali (n = 1), Mexico (n = 1), Nepal (n = 1), Togo (n = 1), Uganda (n = 1), Vietnam (n = 1), Zambia (n = 1) and Zimbabwe (n = 1). The majority of studies recruited MSM (n = 19) and adolescents (n = 19). The remainder were transgender (n = 9), young women (n = 6), people with SMI (n = 3), FSW (n = 3), PWID (n = 3), mental health facilities (n = 1) and incarcerated persons (n = 1). The studies examined a range of HIV prevention approaches: 22 focused on HIV risk behaviour interventions, 12 on oral PrEP, 10 on condom use, 10 on voluntary counselling and testing, 6 on HIV knowledge/education, and 2 considered structural HIV prevention approaches such as free schooling and conditional cash transfers. Fewer studies examined biomedical interventions like treatment of sexually transmitted infections (STI) (n = 4), systems interventions (n = 1) and VMMC (n = 1). The studies measured mental health outcomes using screening assessments (n = 30), structured clinical interviews (diagnostic assessments) (n = 10) and other self-report items (n = 32). We present study findings according to three population groups (adolescents and young women, key populations and people with SMI) and service integration, first describing trials and quasi-experimental studies followed by non-experimental designs for each group.

3.2 | Adolescents and young women

Nineteen studies enrolled adolescents or young women and reported HIV prevention and mental health-related factors as explanatory or outcome variables (Table 1). Depressive and anxiety symptoms were not associated with retention in a combined HIV risk reduction and alcohol and drug use reduction programme for homeless young adults [40].

3.2.1 | Behavioural intervention trials and quasi experiments with a mental health component

Thirteen studies tested the efficacy of an HIV prevention intervention utilizing theory-based skills building and reported both HIV and mental health outcomes among adolescents and young adults (Table 1). All studies demonstrated statistically significant effects on HIV prevention outcomes through follow-up periods ranging from immediately post-intervention to 12 months [41-52].

Several studies clearly articulated behavioural or mental health symptom targets and integrated dialectical behaviour therapy techniques [41,42], emotion regulation [44,49], cognitive behavioural skills training and psychoeducation for self-

Table 1. Adolescents (boys and girls) and young women – HIV prevention interventions with a mental health component or outcome (N = 19 unique studies)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Behavioural interventions							
Brown 2013 [41][a]	United States	RCT	377 youth (13 to 19 years)	3 arms with HIV prevention intervention focused on affect management, standard HIV knowledge and skills intervention, and general health promotion intervention control **Target**: HIV risk behaviour, affect dysregulation **Delivery**: Group / Schools **Facilitator**: Psychology postdoctoral fellows and bachelor-level research assistants	Yes: affect management, informed by dialectic behaviour therapy techniques	Affect Dysregulation Scale, CIS, and C-DISC-IV	**MH-related prevalence**: Affect dysregulation (14%) **MH outcome**: No effect on Affect Dysregulation Scale (ADS) score **HIV outcome**: Increased condom use affect management group after one month ($F(2, 95) = 3.22$, $p = 0.04$); HIV knowledge increased in both intervention groups ($F(2, 314) = 7.89$, $p < 0.001$)
Brown 2017 [42]							**MH-related prevalence**: Affect dysregulation (14%) **MH outcome**: No effect on ADS or CIS scores **HIV outcome**: Increased condom use (aOR = 3.42, 95% CI: 1.10 to 10.63) and decreased sexual activity (aOR = 0.28, 95% CI: 0.08 to 0.96) in affect management intervention group at six months; HIV knowledge ($F = 4.44$, $p = 0.04$) and condom use attitudes ($F = 3.86$, $p = 0.05$) improved in both intervention groups.

(*Continued*)

Table 1. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Brown 2014 [48][a]	United States	RCT	721 youth (13 to 18 years) and caregivers	3 arms with family-based HIV prevention, adolescent-only HIV prevention, or adolescent-only health promotion **Target:** HIV risk behaviour, parental communication **Delivery:** Individual & Group / Inpatient and outpatient mental health settings **Facilitator:** One master or doctoral-level clinician and one research assistant	Yes: skills training; framework that HIV behaviours are a function of psycho-pathology and parenting	DISC, CIS-13 item	**MH-related prevalence**: Mental disorder (42%) **MH outcome**: Not reported (NR) **HIV outcome**: Increase in percentage of protected sex acts (RR = 59.04; 95% CI:16.50 to 82.23; p = 0.01) and decrease in unprotected sex acts (RR = 0.49; 95% CI: 0.28 to 0.86; p = 0.01) at three months
Barker 2019 [56]							**HIV outcome**: No difference in sexual behaviour 12 months; improved sex communication/parent monitoring at 12 months (d = .28 /d = .24)
Hadley 2015 [55]						SCL-90R, GSI	**MH-related prevalence**: Parental psychiatric impairment (32%) **HIV outcome**: Parents with elevated psychiatric symptoms had greater improvements on sexual communication at three months (t(211) = 2.09; p = 0.04; d = 0.17) and six months (t(315) = 2.23; p = 0.03; d = 0.18) and improved parental monitoring at three months (t(475) = 2.05; p = 0.04; d = 0.16).

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Table 1. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Donenberg 2015 [49]	United States	Pre- and post-test comparison design	54 juvenile offenders (13 to 17 years)	Social learning theory-based comprehensive sex education programme **Target**: HIV risk behaviour; HIV knowledge, attitudes, beliefs; peer influence, partner relationships **Delivery**: Group / Community-based Probation Service **Facilitator**: Trained study staff	Yes: emotion regulation	TAS and YSR – affect regulation	**MH**: NR **MH outcome**: No change in affect regulation **HIV outcome**: greater likelihood HIV counselling at three months (OR: 3.67, 95% CI: 1.66 to 8.11); improved HIV attitudes among girls (B = 2.25, p = .04); increased HIV knowledge (B = 1.74, p = 0.004)
Esposito-Smythers 2017 [43]	United States	RCT	81 adolescents (13 to 17 years) and parents	Adjunctive cognitive-behavioural family-based alcohol, self-harm, HIV prevention programme vs Assessment-only control **Target**: HIV risk behaviour, suicidal self-harm, substance use **Delivery**: Individual & Group / NR **Facilitator:** Master's level interventionist	Yes: psycho-education, cognitive behavioural skills training	CASA, DIS-C, SITBI 2.0-SF	**MH-related prevalence**: Self-harm (30.9%); risk of self-harm (33.3%) **MH outcome**: Fewer self-harm acts at 12 months (OR = 0.16, 95% CI: 0.03, 0.94) **HIV outcome**: greater refusal of sex to avoid an STI (OR = 4.87, 95% CI: 1.14, 20.9)
Houck 2016 [44]	United States	RCT	420 adolescents (12 to 14 years)	Emotion regulation intervention versus health promotion control **Target**: HIV risk behaviour, emotion regulation **Delivery**: Group / Schools **Facilitator**: Mental health clinician or trainee & research assistant	Yes: emotion regulation education and skills	DANVA-2; DERS; ER Behaviours Scale	**MH-related prevalence**: NR **MH outcome**: Significant difference on DANVA at six months, favouring ER condition (unstandardized estimate [b] = 2.91, 95% CI = 0.29 to 5.52) **HIV outcome**: Decreased likelihood of initiating vaginal sexual activity at 1 year (aHR = 0.58, 95% CI: 0.36 to 0.94, p = 0.01)

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Table 1. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Jani 2016 [45]	Ethiopia	Pre- and Post-comparison design	576 female and 154 male adolescents (15 to 18 years)	Psychosocial counselling with individuals, groups, and creative therapies **Target**: HIV testing, HIV knowledge **Delivery**: Individual & Group / Service delivery organizations **Facilitator:** Study counsellors	Yes: problem-solving therapy, group art therapy for emotional issues	YSR	**MH-related prevalence**: Aggressive behaviour (23.0% females, 43.2% males); anxiety/depression (21.5% females, 47% males); any mental health problem (37.3% females, 80.8% males) **MH outcomes**: Decreased aggressive behaviour among females (aOR: 0.4, 95% CI: 0.25 to 0.65); decrease in reporting a mental health problem at three months (aOR: 0.5, 95% CI: 0.36 to 0.81) **HIV outcome**: Increased HIV knowledge (aOR: 1.6, 95% CI: 1.08 to 2.47) and HIV testing (aOR: 1.8, 95% CI: 1.13 to 2.97) for females; Increased HIV knowledge (aOR: 2.1, 95% CI: 1.10 to 3.94) and HIV testing (aOR: 7.3, 95% CI: 2.6 to 20.7) for males
Kendall 2020 [46]	United States	RCT	199 African American young females (14 to 18 years) and their mothers	Informed Motivated, Aware & Responsible about AIDS (IMARA) mother-daughter dyad counselling intervention versus health promotion control **Target**: STI risk reduction **Delivery:** Group / Research site **Facilitator:** African American women with Bachelor's or Master's degree	Yes: exercises on externalizing and internalizing symptoms	YSR	**MH-related prevalence**: NR **MH outcome**: No effect on internalizing or externalizing symptoms **HIV outcome**: Decreased incident STI infections through 12 months (Estimate = −.090, SE = 0.43, df = 195, t = −2.12, p = 0.035)

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Table 1. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Logie 2015 [53]	Canada	Quasi-experimental study	44 LBQ women (18+ years)	Group intervention targeting intrapersonal, community, and structural factors related to HIV **Target**: depression, STI knowledge, sexual stigma, HIV risk behaviour **Delivery:** Group / Weekend retreats **Facilitator:** Research coordinator and community facilitators	Yes: skills training, coping techniques	PHQ-2	**MH-related prevalence**: NR **MH outcome**: No effect on depression at six-week follow-up. **HIV outcomes**: Changes in sexual risk practices (β2 = −2.96, 95% CI - 4.43, - 1.50), barrier use self-efficacy (β2 = 1.52, 95% CI 0.51, 2.53), STI knowledge (β2 = 4.41, 95% CI 3.52, 5.30), and sexual stigma (β2 = −2.62, 95% CI - 3.48, - 1.75) at six-week post-intervention.
Nall 2019 [58]	Kenya	Cross-sectional	651 adolescents (13 to 24 years)	No intervention group **Outcome**: depressive symptoms, HTC	No	DASS-21	**MH-related prevalence**: NR **HIV outcome**: Depressive symptoms associated with lower intent to seek HIV testing (β = 0.019, χ^2 = 3.72, p = 0.054)
Pearson 2019 [47]	United States	RCT	73 AI/AN women (18+ years)	Cognitive processing therapy intervention versus six-week waitlist control **Target**: HIV risk behaviours, PTSD symptom severity, alcohol use **Delivery:** Individual / Behavioural health clinic **Facilitator:** Trained counsellors	Yes: cognitive-processing therapy without a trauma narrative component	DSM-IV symptom criteria, PTSD Symptom Scale Self-report	**MH-related prevalence**: PTSD diagnosis (65.8%) **MH outcome**: Reduction in PTSD through six weeks (d = 1.03, p < 0.001) **HIV outcome**: Reduction in HIV risk behaviours through six weeks (d = 1.02, p = 0.004)

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Table 1. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Pedersen 2018 [40]	United States	RCT (group)	200 homeless young adults (18 to 25 years)	AWARE: Four-session AOD and risky sex reduction programme **Target**: reducing AOD use behaviour, reducing risky sexual behaviours **Delivery**: Group / Drop-in centres **Facilitator**: NR	No (Motivational interviewing for substance use and sexual risk reduction)	PHQ-2 and GAD-7	**MH-related prevalence**: None reported **MH outcome**: No differences in HIV intervention retention by MH status (PHQ-2, $p = 0.654$; GAD-7, $p = 0.573$); retention significantly associated with homelessness severity (e.g. slept outside; estimate = −1.31, SE = 0.54, $p = 0.015$) HIV outcome : programme retention not related to sexual risk behaviour or severity of drug use
Puffer 2016 [50]	Kenya	Stepped wedge cluster RCT	237 adolescents (10 to 16 years) and 203 caregivers	*READY* family-based intervention on economic empowerment, emotional support, and HIV education and prevention **Target**: family communication, HIV risk knowledge, self-efficacy, and beliefs, HIV risk behaviour **Delivery:** Group / Churches **Facilitator:** Lay providers	Yes: cognitive behavioural approaches, mental health promotion	Subset of items from MASC-10, CDI, and SDQ	**MH-related prevalence**: None reported **MH outcome**: No effect on MH outcomes **HIV outcome**: Improved HIV risk knowledge ($\beta = 0.03$, 95% CI: 0.01, 0.31, $p = 0.01$), sex self-efficacy ($\beta = 0.41$, 95% CI: 0.18, 0.64, $p = 0.12$), and high-risk sex ($\beta = -0.25$, 95% CI: −1.31, −0.02, $p = 0.12$) at one month

(*Continued*)

Table 1. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Thurman 2018 [51]	South Africa	Quasi-experimental pilot study	105 adolescents (13 to 17 years) and 95 female caregivers	*Let's Talk* support group interventions with adolescents and their caregivers **Target**: HIV knowledge, behavioural skills, caregiver and adolescent mental health, parenting practices, HIV risk behaviour **Delivery:** Group / Community-based organizations **Facilitator:** Trained facilitator	Yes: cognitive behavioural approaches, problem solving	DASS 21	**MH-related prevalence**: NR **MH outcome**: improved adolescent (Coeff. = −0.169, p = 0.004, Δ = −26.440%) and caregiver mental health (Coeff. = −0.223; p = 0.007; Δ = −22.468%) **HIV outcome**: improved adolescent HIV knowledge (Coeff. = 0.417, p = 0.008, Δ = 7.313%) and condom negotiation self-efficacy (Coeff. = 0.501, p = 0.005, Δ = 11.710%),
Thurman 2020 [54]			64 female adolescents 13 to 17 years) and caregivers				**HIV outcome**: Caregivers' MH affected relationship quality, which affected parental sexual communication (R^2 = 0.161 – indirect effects)
Zellner 2016 [52]	United States	Quasi-experimental study	192 African American youth (18 to 24 years)	Colour It Real Programme, a culturally tailored HIV and substance use intervention **Target**: perceived stress, alcohol and drug use, HIV risk behaviour **Delivery:** Group / Colleges **Facilitator:** Trained staff	Yes: problem-solving, skills training	Perceived Stress Scale	**MH-related prevalence**: NR **MH outcome**: Decreased stress (t(70) = 2.38, p = 0.020) **HIV outcome**: Increased condom use (F = 4.43, p = 0.0360)
Biomedical intervention							
Luseno 2019 [61]	Kenya	Cross-sectional	1939 young men (15 to 19 years)	No intervention group **Outcome**: depressive symptoms, VMMC	No	CES-D-R	**MH-related prevalence**: Depressive symptoms (35%) **MH outcome**: Circumcised men had lower depressive symptoms (40.8% vs. 34.5%, χ^2 = 4.40, p = 0.036)

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Table 1. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Velloza 2020 [59][a]	South Africa	Prospective cohort	174 women	**Exposure**: Depressive symptoms **Outcome**: PrEP adherence	No	CES-D	**MH-related prevalence**: Depressive symptoms (45.4%) **HIV outcome**: Depressive symptoms associated with PrEP adherence (aRR: 0.79, 95% CI: 0.63 to 0.99, $p = 0.05$)
Social/structural intervention							
Handa 2017 [57]	Kenya	Cluster RCT	1429 OVC (15 to 25 years)	Kenya Cash Transfer-Orphans and Vulnerable Children (CT-OVC) intervention providing household cash transfers to encourage fostering and retaining children **Target**: Depressive symptoms, sexual debut, schooling, socio-economic status **Delivery**: Post offices	Yes	CESD-10 and six-item Hope Scale	**MH-related prevalence**: Depressive symptoms (72.6%) **MH outcome**: Intervention improved mental health for males only ($p = -0.031$). No direct programme effects on mental health of girls. **HIV outcome**: Intervention reduced likelihood of sex by 9.4%. Schooling had a strong protective effect for girls (31% reduction in sexual debut probability). Psychosocial factors did not mediate relationship between intervention and sexual debut for girls. Among girls, fewer depressive symptoms and elevated hope reduced likelihood of sex debut by 10% ($p < 0.10$) and 8.6% ($p < 0.05$) respectively. No effect in boys.

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Table 1. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Meinck 2019 [62]	South Africa	Prospective cohort	1498 adolescent girls (12 to 17 years)	**Exposure**: Access to free school **Outcome**: ACEs, depression, anxiety, HIV risk behaviour	No	UNICEF Scales for National-Level Monitoring of Orphans and Other Vulnerable Children, CDI, RCMAS, MINI-Kid	**MH-related prevalence**: NR **MH outcome**: ACEs associated with internalizing behaviour (Effect: 0.808, $p < 0.001$) **HIV outcome**: ACEs associated with HIV risk behaviour (Effect: 0.145, $p < 0.005$). Free schooling weakened associations (Effect: 0.099, $p < 0.05$).
Combination prevention							
Sila 2020 [60]	Kenya	Cross-sectional	470 AGYW	No intervention group **Outcome**: PrEP initiation, depressive symptoms, access to sexual and reproductive health services	No	CESD-10	**MH-related prevalence**: Depressive symptoms (13%) **HIV outcome**: Depressive symptoms associated with increased PrEP initiation (PR: 5.36, 95% CI: 2.62 to 10.95, $p < 0.001$)

ACEs, adverse childhood experiences; ADS, affect dysregulation scale; AGYW, adolescent girls and young women; AI/AN, American Indian/Alaska Native; CASA, the child and adolescent services assessment; CDI, children's depression inventory; C-DISC-IV, computerized diagnostic interview schedule for children; CES-D, center for epidemiological studies depression scale; CES-D-R, center for epidemiological studies depression scale revised; CIS, Columbia Impairment Scale; DANVA, diagnostic analysis of nonverbal accuracy; DASS, depression, anxiety, and stress scale; DISC, diagnostic interview schedule for children 4.0; DSM-IV, diagnostic and statistical manual of mental disorders, fourth edition; ER, emotion regulation; GAD, generalized anxiety disorder; GSI, global severity index; HIV, human immunodeficiency virus; LBQ, Lesbian Bisexual Queer; MASC, multi-dimensional anxiety scale for children; MINI-Kid, mini International psychiatric interview for children and adolescents; MH, mental health; NR, not reported; OVC, orphans and vulnerable children; PHQ, patient health questionnaire; PrEP, pre-exposure prophylaxis; PTSD, post-traumatic stress disorder; RCMAS, revised children's manifest anxiety scale; RCT, randomized controlled trial; SCL-90R, the symptom checklist-90 revised; SDQ, strengths and difficulties questionnaire; SITBI 2.0-SF, self-injurious thoughts and behaviour interview 2.0 - Short Form; STI, sexually transmitted infections; TAS, toronto alexithymia scale; UNICEF, United Nations Children's Fund; YSR, youth self report.

[a]Paper added after original search.

harm prevention [43] cognitive processing therapy [47], problem-solving for stress reduction [52] and problem-solving therapy and creative therapies for anxiety and aggressive behaviour [45]. Others identified externalizing/internalizing symptoms [46], emotional and mental health [53] as intervention components, but did not specify the interventional approach. Two studies integrated mental health promotion activities, including psychoeducation and cognitive-behavioural skills-building for parent-youth communication, while introducing behavioural strategies for reducing sexual risk [50,51]. The efficacy of the mental health components was mixed: six studies reported no effect of the mental health intervention on adolescents or young women [41,42,46,48-50,53].

Parental mental health outcomes were indirectly related to adolescent HIV risk behaviours in two behavioural intervention studies [48,54,55]. One showed that building a closer relationship to support improved communication about sexual health is partially contingent on supporting the mental health of the adolescent and the caregiver [54]. Another produced greater improvements in sexual communication and parental monitoring among parents with more psychiatric symptoms at the three-month follow-up [55]; adolescents reported significant reductions in sexual risk behaviours at three months [48], but not after 12 months [56].

3.2.2 | *Structural intervention trials*

One randomized controlled trial tested a cash transfer intervention, which significantly reduced depressive symptoms among young men only and delayed sexual debut among young men and women [57].

3.2.3 | *The relationship of mental health to HIV prevention behaviours*

Five studies assessed mental health as an explanatory variable for HIV risk or preventive behaviours (Table 1). Depressive symptoms were associated with a slightly lower intent to undergo HIV testing and counselling among Kenyan youth [58] and with lower PrEP adherence among South African young women, even after accounting for stigma and for PrEP optimism, i.e. belief in the protective effects of PrEP [59]. Depressive symptoms were associated with a greater likelihood to initiate PrEP, as were low social support and high perceived self-efficacy to take medication daily, among Kenyan adolescent girls and young women [60].

Depressive symptoms were also measured in the context of VMMC service uptake and parental consent among circumcised and uncircumcised adolescents [61]. Circumcision without parental consent was associated with being an orphan, out of school, probable clinical depression (CES-D score >16), and poorer quality of life. In addition, higher proportions of uncircumcised youth were depressed compared to the circumcised, possibly due to social pressure associated with VMMC campaigns or shaming of uncircumcised boys in high uptake communities.

A South African study of HIV risk, adverse childhood experiences (ACEs), adolescent mental health, and free schooling for adolescent girls, found that relationships between ACEs and HIV risk behaviour were mediated by internalizing and externalizing symptoms [62]. Free schooling was associated with fewer externalizing symptoms, suggesting that the mental health-promoting effects of free education confer some protection against HIV risk.

3.3 | Key populations

Twenty-six studies enrolled members of key populations and reported HIV prevention outcomes and mental health-related factors as explanatory or outcome variables (Table 2).

3.3.1 | *Behavioural intervention trials and quasi-experiments*

Eight studies reported the efficacy of a theory-based intervention for HIV risk reduction [63-70]. Most reported favourable changes in risk reduction. One pilot intervention's results did not achieve significance [69], and a community-level intervention yielded positive and negative outcomes [63] (Table 2). Of these studies, six integrated mental health components including psychoeducation for depression and post-traumatic stress disorder (PTSD) and affect management to reduce dissociation [64], behavioural activation for methamphetamine-related anhedonia [65,66], psychoeducation and cognitive-behavioural and acceptance-based coping with stressors [67], cognitive behavioural therapy (CBT) for trauma [68], and CBT for depression [70]. With the exception of one study that did not describe the mental health component [63], interventions with significant reductions in mental disorder symptoms (depression, anhedonia, PTSD) utilized CBT, behavioural activation and affect management with psychoeducation. All interventions were delivered in group formats.

3.3.2 | *Biomedical intervention trials*

Analysis of a PrEP safety trial among MSM and TGW revealed a high prevalence of moderate depression across participants in both study arms, but no difference in depression-related adverse events or reports of suicide attempts and self-harm between participants in the PrEP and placebo arms [71]. A sub-group analysis showed possible severe depression for MSM and possible moderate depression for TGW were associated with reduced PrEP adherence, but were infrequent [72]. The authors emphasized the importance of ensuring access to PrEP for people with depressive symptoms [71-73].

3.3.3 | *The relationship of mental health to HIV prevention behaviours*

Eighteen studies examined mental health as a correlate of HIV risk reduction in studies of HIV or STI testing and counselling, condom use, and awareness of, adherence to or engagement with PrEP (Table 2).

Of these, seven examined the relationship of mental health variables to HIV or STI testing in cohorts and community samples (Table 2). In four studies, *fewer symptoms* of a mental disorder were associated with HIV or STI testing, and greater severity of symptoms was associated with less testing [74-76]. HIV testing among TGW in Malaysia was associated with higher current scores of mental health functioning as well as having a *previous* diagnosis of depression [77]. In contrast, ever having a depressed mood for more than two weeks was independently associated with having an STI test in the past

Table 2. Key populations— HIV prevention interventions with a mental health component or outcome (N = 26 unique studies)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Behavioural Intervention							
Bao 2016 [74]	Vietnam	Cross-sectional	204 TGW	No intervention group **Outcome**: HTC	No	Four-item PTSD primary care screening tool.	**MH-related prevalence**: None reported **HIV outcome**: PTSD associated with lower odds of HIV testing (aOR: 0.79, 95% CI: 0.64 to 0.96, $p = 0.018$)
Eke 2019 [63]	United States	Quasi-experimental study	666 young black MSM	Mpowerment-based community-level intervention on psychosocial determinants of HIV risk behaviour **Target**: HIV risk behaviour, HTC, social diffusion **Delivery**: Group / Community **Facilitators**: Core groups and volunteers	Not specified	CES-D-9	**MH-related prevalence**: None reported **MH outcome**: Significant favourable participation effect on reduction of depressive symptoms (3.9 vs. 4.7, $F(1, 947) = 4.54$, $p = 0.03$). **HIV outcome**: Community effects: favourable changes in social diffusion of safer sex messages ($z\ (2477) = 2.92$, $p = 0.004$) and comfort with being gay ($z(2477) = 2.45$, $p = 0.01$); Individual level: more social diffusion of safer sex messages ($F(1926) = 6.58$, $p = 0.01$); participants responded less favourably ($p < 0.01$) on sex in difficult situations and attitudes towards condom use
Hsu 2015 [82]	United States	Cross-sectional	182 homeless MSM	No intervention group **Outcome**: Condom use	No	3-item depression screen, PTSD Screen	**MH-related prevalence**: Depression (52.2%); **HIV outcome**: Condom efficacy is an intervening variable ($\chi^2 = 5.78$, $p < 0.001$) on consistent condom use directly affected by depression ($T = -3.53$, $p < 0.001$)

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Table 2. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Johnson 2015 [64]	United States	Pilot feasibility study	14 incarcerated women (18+ years)	Women's Prison CoOp **Target**: unprotected vaginal or anal sex occasions, interpersonal violence, PTSD and depressive symptoms, alcohol and drug use, HIV risk behaviour, condom use **Delivery**: Small group & individual / Prison **Facilitators**: social worker, prison discharge planner, public health student	Yes: affect management psycho-social education	THQ-24, DTS-17, and QIDS,	**MH-related prevalence**: None reported **MH outcome**: PTSD symptoms ($t = -2.27$, $df = 12$, $p = 0.04$) and depressive symptoms ($t = -2.87$, $df = 12$, $p = 0.01$) decreased from baseline to 2 months post-release follow-up **HIV outcome**: Unprotected sex ($t = -2.45$, $df = 12$, $p = 0.03$) decreased from baseline to two months post-release follow-up
Logie 2018 [83]	Jamaica	Cross-sectional	556 MSM	No intervention group **Outcome**: Condom use	No	PHQ-2	**MH-related prevalence**: None reported **HIV outcome**: Depression (ß = −0.035, $p < 0.01$) mediated relationship between stigma and condom use (ß = −0.169, $P < 0.001$)
Mimiaga 2012 [65][a]	United States	Open phase pilot of intervention	19 MSM, PWID (18+ years)	Behavioural activation therapy and risk reduction counselling (BA-RR) versus IMB skills change approach to sexual risk reduction control **Target**: HIV risk behaviour, drug use, anhedonia **Delivery**: Individual / Research centre **Facilitators**: Therapist	Yes: BA therapy	MADRS, Behavioural Activation Scale	**MH-related prevalence**: None reported **MH outcome**: Statistically significant reductions in depressive symptoms were maintained (ß = −7.44, 95% CI: −13.04, −1.84, $p = 0.013$) **HIV outcome**: Intervention was associated with decreased unprotected anal intercourse at 3 (ß = −4.86; 95% CI: −7.48, - 2.24; $p = 0.0015$) and six months (ß = −5.07; 95% CI: −7.85, - 2.29; $p = 0.0017$)

(*Continued*)

Table 2. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Mimiaga 2019 [66]	United States	RCT	41 MSM, PWID (18+ years)		Yes: BA therapy	MADRS, Behavioural Activation Scale	**MH-related prevalence**: None reported **MH outcome**: Intervention did not reduce depression (β = 2.47; 95% CI: −4.51, 9.45; p = 0.489) **HIV outcome**: Intervention reduced condomless anal sex at six months post intervention (β = −0.95; 95% CI: −1.44, −0.46; p < 0.0001
Newcomb 2017 [67]	United States	Pre-test post-test design	57 partners MSM	2GETHER couples-based HIV prevention and relationship education consisted of four weekly, face-to-face sessions **Target**: HIV knowledge, relationship functioning, stress reduction **Delivery**: Group & individual couples / NR **Facilitators**: Bachelor's and Master's level clinical trainees, clinical psychologists; advanced clinical training not required	Yes: 2-session psycho-educational groups	PROMIS	**MH-related prevalence**: None reported **MH outcome**: Intervention did not influence depression (t = 0.47, p = 0.641, d = 0.04) **HIV outcome**: Intervention showed decreases in HIV risk behaviour (t = −2.18, p = 0.032, d = 0.15)
O'Cleirigh 2019 [68]	United States	RCT	43 MSM (18+ years)	CBT for trauma and self-care with HTC versus HTC alone control **Target**: HIV risk behaviour, condom use, and PTSD **Delivery**: Individual / Community health centre **Facilitators**: Clinical psychologists & pre- and post-doctoral fellows in clinical psychology	Yes: CBT for trauma and self-care	MINI-6, DTS	**MH-related prevalence**: None reported **MH outcome**: Intervention associated with reductions PTSD symptoms (γ_{slope} = −1.63, t(41) = −1.61, p = 0.11) through nine months **HIV outcome**: Intervention associated with reductions in condomless sex (γ_{slope} = −0.11, t (41) = 2.07, p = 0.04) through nine months

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Table 2. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Ortblad 2020 [79][a]	Uganda, Zambia	Secondary analysis from RCT	1925 FSW	3 study arms: (1) direct provision of an HIV self-test from a peer educator; (2) facility collection of an HIV self-test, or (3) referral to standard-of-care HIV testing services by a peer educator. **Target**: HTC, HIV knowledge **Delivery**: Group / Community **Facilitators**: Peer educators	No	PHQ-9	**MH-related prevalence**: Depressive symptoms: Uganda: 42.3%; Zambia 45.7%; Suicidal ideation: Uganda, 31.5%; Zambia, 56.7% **MH outcome**: Knowledge of any HIV status associate with reductions in severity of depressive symptoms in both sites. Knowledge of HIV-positive status associated with a 1.01-point decrease in depressive symptoms in Uganda (95% CI: −1.82, −0.20, $P = 0.02$) and 1.98-point decrease in depressive symptoms in Zambia (95% CI: −3.09, −0.88, $P = 0.001$). Knowledge of any HIV status associated with reduced prevalence of likely depression in Zambia
Reisner 2016 [69]	United States	Open phase pilot of intervention	17 young transgender MSM (18 to 29 years)	LifeSkills for Men (LS4 M) uses modified social ecological model of HIV risk to conceptualize the multiple contexts and dimensions of sexual risk behaviours for young transgender MSM. **Target**: HIV risk behaviour **Delivery**: Small group / NR **Facilitators**: Study team and transgender MSM community member	No	BSI	**MH-related prevalence**: None reported **MH outcome**: Trends suggest that intervention may reduce psychological distress: BSI 19.4 baseline to 17.5 at four months ($t = -1.66$, df = 16, $p = 0.28$), not significant. **HIV outcome**: increase in condom self-efficacy (t = 2.11, df = 16, $p = 0.05$) at four months; other changes not significant.

(*Continued*)

Table 2. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Rutledge 2018 [77]	Malaysia	Cross-sectional	199 TGW	No intervention group **Outcome**: HTC	No	HRQoL SF-12; self-report	**MH-related prevalence**: High MH functioning (49.2%) and previous depression diagnosis (7.0%) **HIV outcome**: High MH functioning associated with HIV testing (aOR: 2.27, 95% CI: 1.04 to 4.96, $p = 0.041$), previous depression diagnosis associated with HIV testing (aOR: 6.16, 95% CI: 1.56 to 24.24, $p = 0.010$).
Shrestha 2017 [75]	Nepal	Cross-sectional survey	1010 FSW, MSM, TG	No intervention group **Outcome**: HTC	No	CES-D and SI	**MH-related prevalence**: None reported **HIV outcome**: Depression associated with not using HTC for FSW (aPR 1.4, 95% CI 1.1 to 1.6).
Tobin 2017 [70]	United States	RCT	315 PWID (18+ years)	Fiveweeks, 10 session CBT and HIV integrated intervention **Target**: CBT skills, HIV risk behaviour, condom use **Delivery**: Group / NR **Facilitators**: Lay facilitators w/ high school education/ equivalent & 10 years group facilitation experience	Yes: Integrated CBT and HIV prevention intervention	CES-D	**MH-related prevalence**: Depressive symptoms (100%) **MH outcome**: Intervention reduced depressive symptoms at 12 months (OR: −2.83, 95% CI: −5.28, −0.38, $p < 0.05$); significant reductions in CES-D over baseline at 6 months and 12 months, though no difference from control group at six months. **HIV outcome**: Intervention increased condom use with non-main partner at six months (OR: 1.99, 95% CI: 1.03, 3.83, $p < 0.05$)

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Table 2. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Wei 2016 [76]	China	Cross-sectional survey	523 MSM	No intervention group **Outcome**: HTC	No	CES-D-10	**MH-related prevalence**: None reported **HIV outcome**: Depression/ stigma associated with lower odds of HIV testing (aOR: 0.96, 95% CI: 0.92 to 0.99; and aOR: 0.91, 95% CI: 0.84 to 0.99 respectively). Relationship between homophobia and testing mediated 35.0% through depression (OR_{NIE}: 0.96, 95% CI: 0.93 to 0.98).
Biomedical							
Edeza (2019)[116][a]	Mexico, Brazil, Colombia	Online survey	22,698 MSM	No intervention group **Outcome**: PrEP awareness, PrEP use and interest in PrEP trial participation	No	CES-D-10	**MH-related prevalence**: Depressive symptoms (72.7%) **HIV outcome**: 10.4% were aware of PrEP; Transactional sex and CAS were associated with increased PrEP awareness (aOR: 1.29, 95% CI: 1.05–1.59, $p < .001$ and aOR: 1.22, 95% CI: 1.11–1.34, $p < 0.001$ respectively) and PrEP trial interest (aOR: 1.45, 95% CI: 1.25–1.71, $p < 0.001$ and aOR: 1.74, 95% CI: 1.57–1.95, $p < 0.001$ respectively)
Goodman 2016 [78]	Burkina Faso	Cross-sectional	672 MSM	No intervention group **Outcome**: STI testing	No	Questions on depressive symptoms and SI	**MH-related prevalence**: Depressive symptoms (36%) **HIV outcome**: Ever having depression was associated with STI testing (aOR: 1.49, 95% CI: 1.01 to 2.20, $p < 0.05$)

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Table 2. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Grant 2010 [73][a]	United States, South Africa, Thailand, Peru, Ecuador, Brazil	RCT	2499 MSM, TGW	Pre-exposure Prophylaxis Initiative (iPrEx) trial **Target**: Safety and efficacy of PrEP **Delivery**: Individual / Clinic **Provider**: Study investigators	No	Depression-related AEs, suicide attempts	**MH-related prevalence**: Depression-related AEs (69%), suicide attempts (5%) **MH outcome**: No difference in depression-related AEs by PrEP (3% of patients) versus placebo arms (4% of patients)
Defechereux 2016 [71]						CES-D and 4-item suicidal ideation screen	**MH-related prevalence**: Suicidal ideation: 8%, n = 36 suicide attempts **MH outcome**: Predictors of depression: forced anal sex debut (Coeff: 3.23, 95% CI: 1.24 to 5.23), TGW (Coeff: 1.22, 95% CI: 0.51 to 2.40), younger age (Coeff: 1.25, 9% CI: −0.07 to 2.57). Predictors of SI: African American (OR: 2.15, 95% CI: 1.09–4.26); participants reporting forced anal sex debut (OR: 2.2, 95% CI: 1.31 to 5.53). **HIV outcome**: Non-condom receptive anal intercourse associated with higher CES-D (OR: 1.46, 95% CI: 1.09 to 1.94, Wald test for linearity: $p = 0.012$)
Mehrotra 2016 [72][a]		Nested case-control	334 MSM and TGW			CES-D	**MH-related prevalence**: Depressive symptoms (28%) **HIV outcome**: Depressive symptoms were moderately associated with PrEP nonadherence (OR: 0.41, 95% CI: 0.22, 0.77), results differed between MSM and TGW.

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Table 2. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Miltz 2019a [86][a]	England	Open label PrEP RCT	554 GBMSM	The PROUD clinical trial evaluated the efficacy of PrEP against HIV acquisition among GBMSM in England **Target**: PrEP benefit **Delivery:** Individual / Clinic **Facilitators:** NR	No	PHQ-9	**MH-related prevalence:** Depression (9.1%) **MH outcome:** Depression increased significantly from baseline (9.1%) to the 12-month (14.4%) and 24-month (14.4%) follow-up. IPV (aPR 2.57, 95% CI: 1.71 to 3.86), internalized homophobia (aPR 1.91, 95% CI: 1.29 to 2.83) and concealment of sexual identity (aPR 1.75, 95% CI: 1.16 to 2.65) were strongly associated with depression
Miltz 2019b [85][a]			436 GBMSM				**MH outcome:** Depressive symptom prevalence was higher in men who reported combined lifetime IPV victimization/ perpetration (aPR: 3.87, 95% CI: 2.43 to 6.16, $p < 0.001$) **HIV outcome:** Depressive symptoms were not associated with sexual risk behaviours in unadjusted or adjusted analysis; lifetime and past IPV were not associated with sexual risk behaviours
Nostlinger 2020 [84]	Belgium	Prospective cohort	200 MSM	**Exposure**: PrEP **Outcome**: Depressive symptoms **Delivery**: Individual / Clinic **Facilitator:** NR	No	PHQ-9	**MH-related prevalence**: Depressive symptoms (12%) **HIV outcome**: Interaction of drug use and depression on sexual risk at baseline (Estimate: 0.097, $p = 0.039$); after PrEP introduced, no interaction seen at month 9 and 18

(*Continued*)

Table 2. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Pagkas-Bather 2020 [89]	United States	Cross-sectional survey	95 MSM	No intervention group **Outcome**: Peer navigator acceptability and PrEP uptake	No	PHQ-9	**MH-related prevalence**: None reported **HIV outcome**: High PHQ-9 associated with higher peer navigator acceptability (ß = 0.04, 95% CI: 0.01 to 0.07, p = 0.01), but the association was not significant in adjusted models
Pasipanodya 2018 [88]	United States	Secondary analysis from RCT	181 MSM	Text-messaging versus standard of care **Target**: PrEP adherence **Delivery**: Individual / Clinic **Facilitators**: NR	No	PHQ-9	**MH-related prevalence**: Depressive symptoms (48.6%) **HIV outcome**: Depression symptoms associated with lower PrEP adherence (OR:1.111, 95% CI: 1.005 to 1.227, $p < 0.05$)
Shuper 2020 [90][a]	Canada	Cross-sectional	141 GBMSM	No intervention group **Outcome**: PrEP non-adherence	No	CES-D	**MH-related prevalence**: Depressive symptoms (23.7%); Harmful/hazardous drinking (31.9%); moderate/high risk substance use (43.3%) **HIV outcome**: Depression was not associated with nonadherence
Young 2020 [87]	United States	Cross-sectional	31 young MSM/ TGW of colour	No intervention group **Outcome**: PrEP adherence	No	PHQ-9, GAD-7, and ACEs	**MH-related prevalence**: None reported **HIV outcome**: Anxiety (80.7% vs. 92.7%, p = 0.04) and trauma experiences (84.5% vs. 95.7%, p = 0.05) associated with PrEP non-adherence; depression not associated (p = 0.28)

(*Continued*)

Table 2. (*Continued*)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Combination prevention							
Chabata 2020 [81]	Zimbabwe	Cohort study	2431 young women who sell sex (18 to 24 years)	DREAMS programme: biomedical, social and economic interventions **Target**: PrEP, HIV risk behaviour, condom use **Delivery**: Community / NR **Facilitators**: Community, faith-based and non-governmental organizations	No	SSQ-14	**MH-related prevalence**: CMD (33.6%) **HIV outcome**: Lower odds of condom use for those at risk of CMD in past week (aOR = 0.76; 95% CI: 0.60 to 0.97; p = 0.029)
Coulaud 2019 [80]	Mali, Cote d'Ivoire, Burkina Faso and Togo	Longitudinal study	621 MSM	Community-based cohort providing quarterly HIV testing and counselling **Target**: HIV risk behaviour, HTC, STI treatment, PrEP, condom use **Delivery**: Individual / Clinic **Facilitators**: Physicians & peer educators	No	PHQ-9	**MH-related prevalence**: None reported **HIV outcome**: High level of depressive symptoms was associated with inconsistent condom use during receptive anal sex with male partners of unknown HIV status (OR: 1.06, 95% CI: 1.00 to 1.13, p = 0.049)

ACEs, adverse childhood experiences; AE's, adverse events; BA, Behavioural Activation; BSI, brief symptom inventory; CBT, cognitive-based therapy; CES-D, center for epidemiological studies depression scale; CMD, common mental disorders; DTS, davidson trauma scale; FSW, female sex worker; GAD, Generalized Anxiety Disorder; GBMSM, gay and bisexual men who have sex with men; HIV, Human Immunodeficiency Virus; HRQoL SF-12, Health-Related Quality of Life SF-12; HTC, hiv testing and counselling; IMB, Information-motivation-behavioural; IPV, intimate partner violence; MADRS, montgomery-asberg depression rating scale; MH, mental health; MINI, mini international neuropsychiatric interview; MSM, men who have sex with men; PHQ, Patient Health Questionnaire; PrEP, Pre-Exposure Prophylaxis; PROMIS, patient-reported outcomes measurement information system depression—short form 8b; PTSD, post-traumatic stress disorder; PWID, Persons Who Inject Drugs; Qids, Quick Inventory Of Depressive Symptomatology; RCT, randomized control trial; SI, suicidal intent; SSQ, shona symptom questionnaire; STI, sexually transmitted infections; TG, transgender person; TGW, transgender women; THQ, trauma history questionnaire.
[a]Paper added after original search.

Table 3. People with a serious mental illness—HIV prevention interventions with a mental health component or outcome (N = 3)

Author year	Country	Study design	Study population	Intervention description	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Behavioural intervention							
Hughes 2019 [91]	England	RCT	72 adults (18+ years) with SMI	Sexual health promotion intervention (RESPECT) versus usual care alone **Target**: HIV risk behaviour and condom use **Delivery**: Individual / Community mental health services **Facilitator**: Mental health worker	No	Diagnosis through EMR and self-referral	**MH-related prevalence**: None reported **HIV outcome**: Intervention was associated with decrease in the number of unprotected sex acts through three months (4% reduction vs. 9.7% increase in control).
Pinho 2020 [92]	Brazil	Cross-sectional	467 adults with SMI	No intervention group **Outcome**: Condom use	No	BPRS	**MH-related prevalence**: None reported **HIV outcome**: Greater negative symptom severity was related to worse condom-self efficacy ($F(1, 452) = 3.75$, $p < 0.01$) ($\beta = -0.05$, $t = -2.69$, $p < 0.01$), while greater activation symptom severity (e.g. elated mood) was related to better condom self-efficacy ($\beta = 0.04$, $t = 2.13$, $p = 0.03$)
Wainberg 2018 [93]	Brazil	Cross-sectional	641 adults with SMI	No intervention group **Outcome**: Participation in HIV risk reduction programme.	No	MINI PLUS	**MH-related prevalence**: None reported **HIV outcome**: Only 9% of adults with SMI participated in a HIV risk reduction programme

BPRS, the expanded brief psychiatric rating scale; EMR, electronic medical record; HIV, human immunodeficiency virus; MINI PLUS, mini international neuropsychiatric interview – PLUS; MH, mental health; RCT, randomized control trial; SCID, structured clinical interview for DSM-IV diagnosis; SMI, serious mental illness.

Table 4. Integrated services (N = 2)

Author year	Country	Study design	Study population	Intervention focus	MH component	MH assessment	MH baseline prevalence and HIV/MH key findings
Combination prevention							
Shaikh 2016 [94]	India	Pre-post non-randomized design	268 TG	Pehchan programme supports CBOs in technical capacity, linkage to care and prevention interventions, and packages of care for supportive environments for transgender communities through legal, social, mental health, and psychosocial services **Target**: HIV, health, legal and social protection services **Delivery**: CBO / Community **Implementor**: India HIV/AIDS Alliance	No	Questions on access to psychological services	**MH-related prevalence**: None reported **MH outcome**: Access to psychological services increased (+33.0%, $p < 0.001$) **HIV outcome**: Increase in access to HIV education (+20%, $p < 0.001$), referral for HIV testing (+33.7%, $p < 0.001$), access to condoms (+12.5%, $p < 0.001$) and condom use with regular (+18.1%, $p < 0.001$) and casual (+8.1%, $p < 0.001$) partners
McKinnon 2020 [95]	United States	Survey	132 outpatient mental healthcare agencies	No intervention group **Outcome**: Condom use, HTC	No	Licensed outpatient mental healthcare programmes	**MH-related prevalence**: None reported **HIV outcome**: MH providers report decreases in condom distribution ($p < 0.001$) and increases in on-site HIV testing ($p < 0.001$).

CBO, community-based organization; HIV, human immunodeficiency virus; HTC, HIV testing and counselling; MH, mental health; STI, sexually transmitted infections; TG, transgender person.

Table 5. RCTs and comparison design studies that include both MH and HIV components (n = 21 unique study samples; n = 25 unique analyses)

	MH intervention components (by unique study samples)				Outcomes (by unique analysis)	
	Behavioural interventions incorporating parental communication skills	**Non-specific management of psychological processes or distress[a]**	**Disorder-specific management[b]**	**Other interventions**	**Any favourable MH outcome**	**Any favourable HIV prevention outcome**
AYW (n = 13 unique study samples; n = 17 unique analyses)	1 Brown 2014 [48]/ Barker 2019 [56]/ Hadley 2015 [55] 2 Esposito-Smythers 2017 [43] 3 Kendall 2020 [46] 4 Puffer 2016 [50] 5 Thurman 2018 [51]/ Thurman 2020 [54]	1 Brown 2013 [41]/ Brown 2017 [42] 2 Donenberg 2015 [49] 3 Houck 2016 [44] 4 Kendall 2020 [46] 5 Zellner 2016 [52]	1 Esposito-Smythers 2017 [43] 2 Jani 2016 [45] 3 Logie 2015 [53] 4 Pearson 2019 [47]	Social/Structural 1 Handa 2017 [57]	1 Esposito-Smythers 2017 [43] 2 Houck 2016 [44] 3 Jani 2016 [45] 4 Pearson 2019 [47] 5 Thurman 2018 [51] 6 Zellner 2016 [52] 7 Handa [57]	1 Brown 2013 [41] 2 Brown 2017 [42] 3 Brown 2014 [48] 4 Barker 2017 [56] 5 Hadley 2015 [55] 6 Esposito-Smythers 2017 [43] 7 Houck 2016 [44] 8 Jani 2016 [45] 9 Kendall 2020 [46] 10 Logie 2015 [53] 11 Pearson 2019 [47] 12 Puffer 2016 [50] 13 Thurman 2018 [51] 14 Zellner 2016 [52] 15 Handa [57] 16 Donenberg 2015 [49]
Key Populations (n = 7 unique study samples; n = 7 unique analyses)		1 Johnson 2015 [64] 2 Newcomb 2017 [67]	1 Eke 2019 [63] 2 Johnson 2015 [64] 3 Mimiaga 2012 [65] 4 Mimiaga 2019 [66] 5 O'Cleirigh 2019 [68] 6 Tobin 2017 [70]		1 Eke 2019 [63] 2 Johnson 2015 [64] 3 Mimiaga 2012 [65] 4 O'Cleirigh 2019 [68] 5 Tobin 2017 [70]	1 Eke 2019 [63] 2 Johnson 2015 [64] 3 Mimiaga 2012 [65] 4 Mimiaga 2019 [66] 5 Newcomb 2017 [67] 6 O'Cleirigh 2019 [68] 7 Tobin 2017 [70]
Integrated Services (n = 1 unique study samples; n = 1 unique analyses)				Systems integration 1 Shaikh 2016 [94]	1 Shaikh 2016 [94]	1 Shaikh 2016 [94]

AYW, adolescents and young women; MH, mental health; RCT, randomized controlled trial.
[a]i.e. emotion regulation, affect management, stress reduction, externalizing, internalizing behaviours. [b]i.e. depressive symptoms, anxiety, aggressive behaviour, posttraumatic stress symptoms, self-harm acts, anhedonia.

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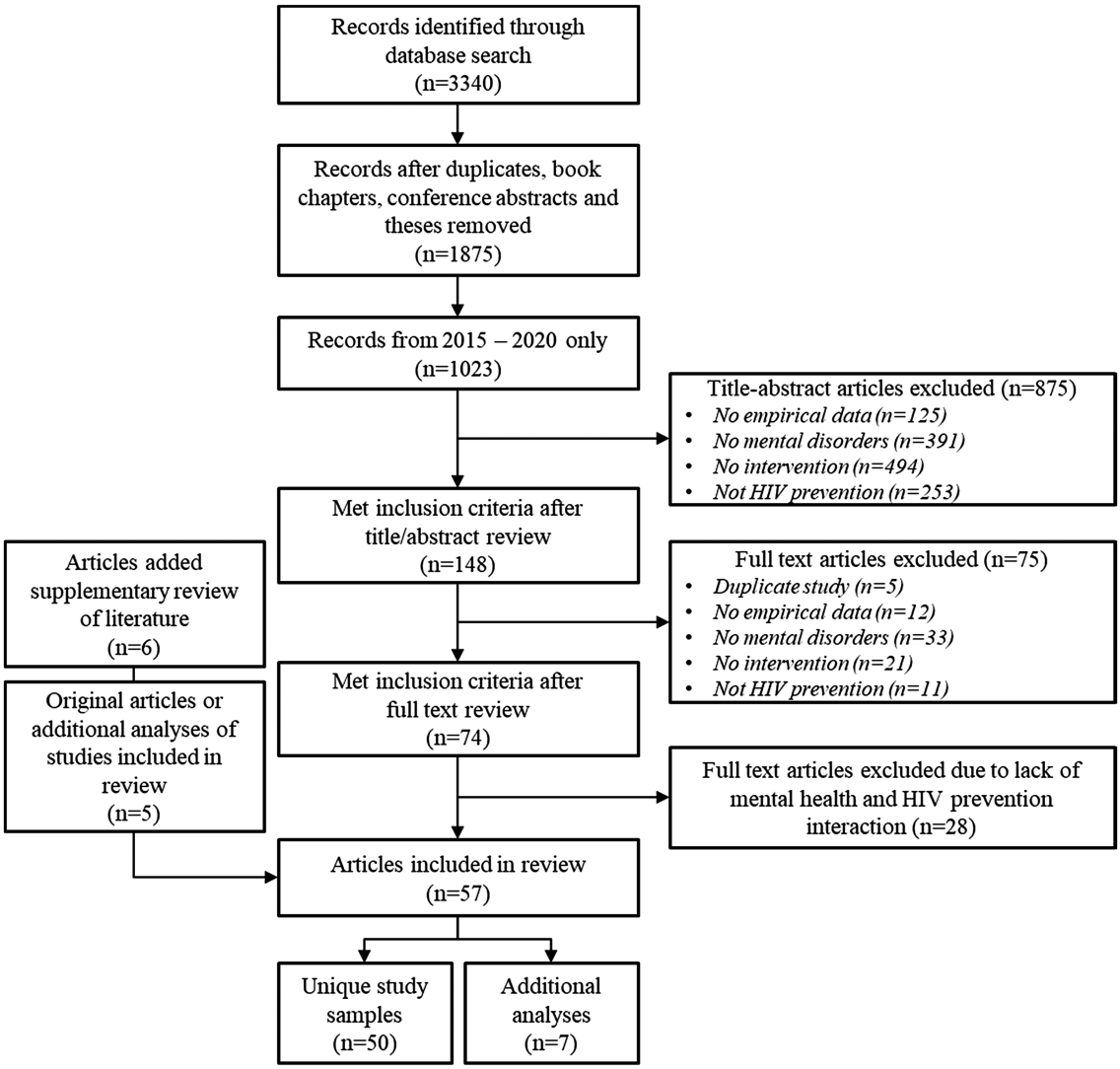

Figure 1. Flow diagram of search strategy.

month among MSM in Burkina Faso [78]. Notably, learning one's HIV status, whether positive or negative, was associated with significant reductions in the severity of depressive symptoms among Ugandan and Zambian FSW populations and was not associated with suicidal ideation [79].

Several studies demonstrated that poorer mental health (especially severe depression, depression and PTSD, or anxiety) was associated with less consistent condom use or less perceived condom self-efficacy among MSM [80], young women who sold sex [81], and homeless men who also used drugs and traded sex [82]. Condom use self-efficacy and depression were partial mediators of the relationship between sexual stigma and inconsistent condom use among MSM [83]. MSM on PrEP who reported poly-drug use and depression were significantly more likely to report receptive condomless anal intercourse than those who only reported poly-drug use or only reported depression at baseline assessment [84]. Conversely, among gay and bisexual MSM receiving PrEP in the United Kingdom, despite increased depressive symptoms over time, neither depressive symptoms nor interpersonal violence were associated with sexual risk behaviours [85,86].

Two studies showed that distinct categories of mental disorder symptoms were associated with lower adherence to PrEP: anxiety symptoms and a history of childhood trauma [87], baseline depression and substance use among MSM in a PrEP adherence trial [88]. A third study reported higher depression scores were significantly related to greater acceptability of peer navigation to assist with PrEP engagement among Black and Latinx MSM [89]. A fourth study found no relationship of depressive symptoms to PrEP adherence, but harmful alcohol use and moderate/high-risk cocaine use predicted nonadherence [90].

3.4 | People with severe mental illness

Three studies enrolled people with SMI in a clinical trial or cross-sectional surveys.

3.4.1 | HIV prevention interventions tailored for adults with severe mental disorders

A randomized controlled trial tested a sexual health promotion intervention among adults with SMI [91] (Table 3).

Participants attending a three-session theory-based group intervention reported fewer episodes of unprotected sex acts through six months [91]. This study examined sexual health, broadly, as an area of attention for people with SMI.

3.4.2 | *The relationship of mental health to HIV prevention behaviours*

Two Brazilian studies examined people with SMI and HIV risk correlates (Table 3). One study showed that psychiatric symptom clusters had differential effects on condom self-efficacy: people with more severe negative symptoms (e.g. blunted affect, emotional withdrawal) were less likely to perceive themselves as capable of using condoms, condom negotiation, and/or condom acquisition [92]. In a second study, three-fourths of patients in eight public psychiatry clinics reported unprotected sex, but only 9% had participated in the clinics' risk-reduction programmes [93]. Participation was significantly associated with ethnicity, higher HIV knowledge, and receiving HIV testing in the past three months.

3.5 | HIV prevention and mental health service integration

Two studies in our sample described distinct approaches to HIV prevention and mental health service integration (Table 4). One assessed the outcomes of the Pehchan programme, a community-level intervention, which linked transgender persons to comprehensive community-based services providing combination prevention to transgender persons in India [94]. The programme yielded significant increases in testing referrals, HIV education reach, and access to mental health support through referrals to psychological services.

A survey of mental health programme directors in New York State showed that a majority of programmes treated people known to have HIV, assessed HIV risk, and provided HIV educational materials, and just over half referred people for HIV testing [95]. Between 20% and 32% of programmes offered services related to *End the Epidemic* activities in the state (e.g. HIV testing, PrEP education and PrEP prescriptions). Compared to past surveys, fewer mental health programme directors reported integration of HIV services and psychiatric services, and fewer identified themselves as fully integrated in 2017 compared to 2004, despite more programmes reporting larger caseloads of people with HIV or AIDS.

3.6 | Summary: Interventions that address mental health in the context of HIV prevention

Thirteen studies in our sample describe HIV prevention interventions (11 at the individual level, one social intervention, and one community systems intervention) with an embedded or linked mental health component(s) that reduced HIV risk behaviours and produced a more favourable mental health outcome (Table 5). The majority of these interventions or services occurred in the community, and one occurred in a prison.

To our knowledge, this is the first review of global research on mental health and HIV prevention among adolescents and young women, key populations and people with SMI that includes multiple prevention modalities. We aimed to understand how mental disorder symptoms influence risk for HIV and preventive intervention outcomes among three populations vulnerable to HIV infection. Overall, this selection of studies, dominated by behavioural interventions to reduce sexual risk, suggests that poorer mental health is associated with HIV risk behaviour. Study findings help to answer two questions: 1) What do we know about the relationship between mental health and HIV prevention behaviours and 2) What do we know about the interventions that address mental health in the context of HIV prevention?

3.7 | The relationship between mental health and HIV prevention behaviours

Having symptoms of a mental health condition was more often associated with fewer HIV prevention behaviours. In all but one study, depression impaired PrEP adherence. In the majority of HIV testing and counselling studies, having fewer symptoms of a mental disorder increased HIV testing. Depressive, anxiety and trauma symptoms usually reduced the likelihood of condom use or condom self-efficacy.

In a subset of studies, depressive symptoms (current or past) were associated with a greater likelihood of getting an HIV test, and with PrEP initiation [60]. In these cases, the negative effect of poor mental health may be mitigated by other factors that facilitate taking action (e.g. high perceived self-efficacy [60]), or poor mental health may enhance recognition of vulnerability and a need for support [77,89]. Evidence also showed that learning one's HIV status, whether negative or positive, did not worsen depressive symptoms or increase suicidality [79].

The relationship between HIV risk and mental health is sometimes indirect. For adolescents, parent–child communication skills, parenting styles and parental mental health status influenced successful sexual communication, which in turn reduced HIV risk [55]. Consistent with this finding, a recent review highlighted the benefits of family strengthening interventions for the mental health of youth affected by or living with HIV [96]. Gender and social adversity add to the complexity of understanding these associations. Cash transfers led to better HIV risk outcomes for boys and girls, but better mental health outcomes for boys [57]. Nevertheless, for vulnerable girls, access to social resources such as free school or cash transfers reduced behaviours directly and indirectly related HIV risk [57,62]. HIV programme implementers must also consider how the social vulnerabilities of adolescents may increase the risk of coercive participation in HIV prevention or may indirectly create barriers to interventions (e.g. VMMC), and consequently, greater emotional stressors for young people [61].

3.8 | What do we know about interventions that address mental health in the context of HIV prevention?

Prevention scientists emphasize the importance of combination prevention and comprehensive, layered approaches that address contextual and individual risk factors for HIV prevention [34,97,98]. Relatively few examples of such comprehensive approaches emerged in our search. Although some interventions integrated elements to address intrapersonal, community and structural stressors (e.g. self-esteem,

discrimination, minority stress, negative sexual identity, community connectedness, access to care) with HIV prevention [53,63], these may not be sufficient to reduce symptoms of depression, trauma or severe anxiety. When they yield positive effects on mental health, more research is needed to understand which components and delivery modes facilitate these outcomes. Assessment also influences outcomes: most studies in the sample utilized screening tools to assess mental health status, but did not always distinguish between diagnoses and symptoms. Some studies assessed mental health even if the HIV preventive intervention had no mental health component.

The thirteen studies in Table 5 that reported HIV risk reduction and improved mental health outcomes used three broad intervention approaches. At the systems level, effective linkage of key populations to HIV testing and mental health services occurred through robust referrals within a community setting managed by a trusted community organization and peer network [94]. The individual-level behavioural interventions, conducted in North America and Africa, applied elements of evidence-based psychological therapies or psychoeducation within a structured HIV risk reduction intervention for adolescents and young women and for key populations. Across these studies, the sample size, duration and strength of effects, and specification of the mental health component varied considerably. However, several interventions integrating CBT approaches for the treatment of trauma, depression, or self-harm reduction showed enduring mental health effects nine months to one-year post-intervention [43,68,70]. Though this latter group of interventions were often delivered by trained mental health specialists in our study sample, current global mental health literature demonstrates that less specialized providers can be trained and supervised to deliver effective, evidence-based psychological interventions like CBT in community settings [99-101].

Notably, few new intervention studies for people with SMI have been published since 2012, and studies from Africa, Asia, or Latin America are scarce [2]. The absence in the literature is mirrored by diminishing attention to HIV prevention, access to HIV services in public mental health settings in the United States [95]. Although social functioning—including establishing intimacy and expressing sexuality—is an essential part of the recovery process for people living with SMI, sexual health is largely unaddressed in typical mental health services [24,102].

3.9 | Implications for integrating HIV prevention and mental health and achieving global HIV targets

The Global AIDS Targets for 2025 call for «people-centred and context-specific integrated approaches» so that 90% of people at high risk of HIV are linked to services for mental health, sexual and gender-based violence and other relevant care [103]. The results of our review suggest that mental health and HIV prevention could be integrated by (1) identifying community partners and leaders for co-design, delivery and linkage of HIV and mental health resources and services; (2) using task shifting to train adherence counsellors, peers and nurses to administer evidence-based psychological therapies (e.g. problem-solving therapy, CBT, cognitive processing therapy) embedded in theory-based risk reduction for populations experiencing trauma and depression [104]; (3) making use of available mental health capacity-building resources from the World Health Organization and other sources [105-107]; (4) supporting gender-sensitive structural interventions for young people, like access to free schooling for girls and vulnerable youth; (5) expanding access to family-based interventions that enhance parenting and communication skills and (6) introducing a mental health component to adherence support for PrEP. True integration requires shared human resources, budgeting, and planning across HIV and mental health services in partnership with diverse community stakeholders [106,108-110]. Prevention service providers can learn from task-sharing interventions that integrate mental health and HIV care [111-113].

3.10 | Limitations

Our study has several limitations. The included studies were heterogeneous and precluded the use of a meta-analysis of the results and effect sizes. Our review was systematized, though not systematic, and we may not have captured all representative studies. We did not rate the quality of the studies or conduct a bias assessment, but reported findings qualitatively. Although we captured studies from a diverse set of countries, the majority of studies are from the United States and interventions reflect the contextual specificities of the study populations and settings. Self-report of HIV risk behaviours, non-randomized study designs and small sample sizes may bias some study findings. Despite these weaknesses, the included study results reflect a broad range of countries and support the assertion that poorer mental health is linked to fewer HIV prevention behaviours and activities globally and that integrated interventions can reduce risk.

4 | CONCLUSIONS

Consistent with previous studies, current evidence suggests that mental health conditions are more often associated with poor HIV prevention outcomes, and integrated approaches are urgently needed to address overlapping vulnerabilities among key populations, vulnerable groups and individuals with SMI. Our review contributes a new synthesis of global literature on mental health and HIV prevention, spanning a broad range of prevention modalities; studies from high-, middle- and low-income countries; and diverse samples of key populations, high-risk groups, and people with SMI. We highlight the components of interventions that address symptoms of mental illness or psychological processes that influence mental health status. Importantly, these findings, in concert with the broader global mental health literature [11,114,115], suggest that integrating structural, social and individual-level HIV prevention and mental health interventions is feasible in diverse community settings. A renewed focus on implementing these integrated interventions and services could contribute to ending the AIDS epidemic, and specifically, to achieving the 2025 Global AIDS targets.

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COMPETING INTERESTS

The authors have declared no conflict of interest.

AUTHORS' CONTRIBUTIONS

PC, TC and JV developed search criteria. TC, JV and LO completed the primary title/abstract review of studies. PC, TC, JV, LO, LC and JS completed the secondary full-text review of studies. PC, TC, JV, LO, LC, BW and JS assisted with data coding and analysis. PC, TC, JV, LO, LC, JS and CK contributed to development, writing and editing of this manuscript.

ABBREVIATIONS

ACEs, Adverse childhood experiences; ADS, Affect Dysregulation Scale; AE's, Adverse events; AGYW, Adolescent girls and young women; AI/AN, American Indian/Alaska Native; BPRS, The Expanded Brief Psychiatric Rating Scale; BSI, Brief Symptom Inventory; CASA, The Child and Adolescent Services Assessment; CDI, Children's Depression Inventory; C-DISC-IV, Computerized Diagnostic Interview Schedule for Children; CES-D, Center for Epidemiological Studies Depression Scale; CES-D-R, Center for Epidemiological Studies Depression Scale Revised; CMD, Common mental disorders; DANVA, Diagnostic Analysis of Nonverbal Accuracy; DASS, Depression, Anxiety, and Stress scale; DERS, Difficulties in Emotion Regulation Scale; DISC, Diagnostic Interview Schedule for Children 4.0; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DTS, Davidson Trauma Scale; EMR, Electronic medical record; EPDS, The Edinburgh Postnatal Depression Scale; ER, Emotion regulation; FSW, Female sex worker; GAD, Generalized Anxiety Disorder; GHQ12, General Health Questionnaire; GSI, Global Severity Index; HADS, Hospital Anxiety and Depression Scale; HIV, Human Immunodeficiency Virus; HRQoL SF-12, Health-Related Quality of Life SF-12; HSCL, Hopkins Symptom Checklist; HSCL-D, Hopkins Symptoms Checklist for Depression; HTC, HIV Testing and Counselling; LBQ, Lesbian Bisexual Queer; MADRS, Montgomery-Asberg Depression Rating Scale; MASC, Multi-Dimensional Anxiety Scale for Children; MH, Mental health; MINI PLUS, Mini International Neuropsychiatric Interview – PLUS; MINI, Mini International Neuropsychiatric Interview; MINI-Kid, Mini International Psychiatric Interview for Children and Adolescents; MSM, Men who have sex with men; NR, Not reported; OVC, Orphans and vulnerable children; PHQ, Patient Health Questionnaire; PrEP, Pre-Exposure Prophylaxis; PROMIS, Patient-Reported Outcomes Measurement Information System Depression—Short Form 8b; PTSD, Post-Traumatic Stress Disorder; PWID, Persons who inject drugs; QIDS, Quick Inventory of Depressive Symptomatology; RCMAS, Revised Children's Manifest Anxiety Scale; RCT, Randomized control trial; SCID, Structured Clinical Interview for DSM-IV Diagnosis; SCL-90R, The Symptom Checklist-90 Revised; SDQ, Strengths and Difficulties Questionnaire; SI, Suicidal intent; SITBI 2.0-SF, Self-Injurious Thoughts and Behaviour Interview 2.0 - Short Form; SMI, Serious Mental Illness; SSQ, Shona Symptom Questionnaire; STI, Sexually transmitted infections; SW, Sex worker; TAS, Toronto Alexithymia Scale; TasP, Treatment as prevention; TG, Transgender person; TGW, Transgender women; THQ, Trauma History Questionnaire; UNICEF, United Nations Children's Fund; VMMC, Voluntary medical male circumcision; YSR, Youth Self Report.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:
Additional file S1. Search strategy.

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RESEARCH ARTICLE

Assessing longitudinal patterns of depressive symptoms and the influence of symptom trajectories on HIV pre-exposure prophylaxis adherence among adolescent girls in the HPTN 082 randomized controlled trial

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Abstract

Introduction: African adolescent girls and young women (AGYW) eligible for HIV pre-exposure prophylaxis (PrEP) experience high levels of depressive symptoms. Depression can reduce PrEP adherence among adults, although analyses have considered depression as a time-varying exposure rather than modelling distinct patterns of symptoms. The association between depressive symptoms and PrEP adherence has not been explored for AGYW. To address these gaps, we sought to understand depressive symptom trajectories among African AGYW initiating PrEP and the impact of time-varying depressive symptoms and symptom trajectories on PrEP adherence.

Methods: HPTN 082 was an open-label PrEP study among AGYW (ages 16 to 24) in Zimbabwe and South Africa from 2016 to 2018. Depressive symptoms were measured at enrolment and Weeks 13, 26 and 52, using the 10-item Center for Epidemiologic Studies scale; a score ≥10 is indicative of elevated depressive symptoms. PrEP adherence was defined as any detectable tenofovir diphosphate (TFV-DP) levels. Group-based trajectory modelling was used to model longitudinal patterns of depressive symptoms. We assessed psychosocial and behavioural predictors of depressive symptom trajectory membership (e.g. PrEP stigma, intimate partner violence [IPV], sexual behaviour). We modelled associations between (1) group trajectory membership and PrEP adherence at Week 52 and (2) time-varying depressive symptoms and PrEP adherence through follow-up.

Results: At enrolment, 179 (41.9%) participants had elevated depressive symptoms. Group-based trajectory models revealed persistent elevated depressive symptoms in 48.5%, declining symptoms in 9.4% and no consistent or mild depressive symptoms in 43.3%. AGYW who engaged in transactional sex, reported IPV, or had traumatic stress symptoms were more likely to be assigned to the persistent elevated symptom group compared with the consistent no/mild symptom group (Wald test *p*-value all <0.01). Participants assigned to the persistent elevated depressive symptom trajectory had a significantly lower risk of detectable TFV-DP at Week 52 than those in the no/mild symptom trajectory (adjusted prevalence ratio = 0.89; 95% CI: 0.80 to 0.98). Elevated depressive symptoms were significantly inversely associated with PrEP use throughout follow-up (adjusted relative risk = 0.73; 95% CI = 0.53 to 0.99).

Conclusions: Persistent depressive symptoms were common among African AGYW seeking PrEP. Integration of depressive symptom screening and treatment into PrEP programmes may improve PrEP effectiveness among African women.

Keywords: depression; psychosocial; HIV; pre-exposure prophylaxis; Africa; women

Additional Supporting information may be found online in the Supporting Information tab for this article.

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1 | INTRODUCTION

African adolescent girls and young women (AGYW) ages 15 to 24 face high rates of HIV. Recent trials among AGYW ages 18 to 25 years report HIV incidence rates as high as 7 per 100 person-years [1-3]. HIV pre-exposure prophylaxis (PrEP) is a highly efficacious HIV prevention strategy being scaled up for high-risk populations including AGYW in HIV endemic settings [4-9]. Demonstration projects with adolescents report high initial PrEP uptake but declines in adherence and continuation in real-world settings [10-12]. Lower PrEP adherence over time among AGYW is associated with complex psychosocial and behavioural factors such as lack of social support, intimate partner violence (IPV) and PrEP stigma [13-16].

AGYW at risk of HIV also face high levels of depression [15,16]. Studies in sub-Saharan African cohorts found that approximately 20% to 50% of young women initiating HIV prevention services have mild-to-moderate depressive symptoms [14,16,17]. Individual and interpersonal (e.g. IPV, stigma, low social support) and community-level and structural (e.g., food insecurity, gender inequality) factors, often acting together, can cause elevated risk of depression and HIV acquisition among women [17-19]. PrEP trials with South African, Kenyan and Ugandan women estimated that those with depressive symptoms had 25% to 27% lower PrEP adherence than those without symptoms and this relationship persists after adjusting for IPV, social support and stigma [14,16]. Negative relationships between depressive symptoms and PrEP adherence have also been reported among young men who have sex with men and transgender women, suggesting that these findings are generalizable across youth at risk for HIV [20,21]. The HIV treatment and contraceptive fields also consistently report negative associations between depressive symptoms and medication adherence among young women in the United States and Africa [22-27].

While prior research has explored associations between depressive symptoms and PrEP adherence in adult women, gaps remain in understanding distinct patterns of depressive symptoms over time and whether various trajectories of depressive symptom severity differentially impact PrEP use among AGYW. Depressive symptoms could change dynamically over time and recur, particularly among AGYW [17,28], and a nuanced view of depressive symptom patterns and how different patterns influence PrEP adherence is needed. Several studies have explored depressive symptom trajectories among adults in South Africa and the United States [29-31], but only one analysis to date modelled symptom trajectories in AGYW and was conducted in the United States [28]. These studies document differences between participants with distinct depressive symptom trajectories (e.g. declining, persistent, low or resurging symptoms) but did not explore associations between trajectory membership and HIV-related outcomes. To address these gaps, we analysed data on depressive symptoms and PrEP adherence from a clinical trial of AGYW initiating PrEP in South Africa and Zimbabwe. Our objectives were to (1) model depressive symptom trajectories among African AGYW; (2) assess baseline characteristics associated with trajectory membership and (3) estimate associations between time-varying depressive symptoms and depressive symptom trajectories on PrEP adherence. Our findings could guide future PrEP delivery efforts for African AGYW to improve both mental health and PrEP adherence outcomes in this population.

2 | METHODS

2.1 | Study design and participants

The HIV Prevention Trials Network (HPTN) 082 study was a randomized, open-label trial of adherence interventions among African AGYW initiating daily oral emtricitabine tenofovir (FTC/TDF)-based PrEP [32]. Eligible AGYW were HIV-negative, between 16 and 25 years old, sexually active and at high risk of HIV [33], literate in one or more study languages and residing in Johannesburg, Cape Town or Harare. Enrolment and follow-up occurred from 2016 to 2018.

Participants were offered daily oral PrEP at enrolment. Those who accepted PrEP were randomized in 1:1 ratio to either the control group with a standard PrEP adherence package (counselling sessions, weekly SMS reminders, monthly in-person adherence support clubs) or the intervention group (the standard package plus counselling based on PrEP drug levels, called "drug-level feedback counselling"). Follow-up visits took place at Weeks 4, 8, 13, 26, 39 and 52 post-enrolment. Participants received HIV testing, counselling and PrEP refills at all visits.

2.2 | Data collection

Sociodemographic data were collected at enrolment, including age, marital status and education. At enrolment and follow-up visits, participants completed computer-assisted self-interviewing (CASI) surveys to provide data on sexual behaviour (number of sex acts, condom use, number of partners, transactional sex), depressive symptoms, alcohol use, social support, stigma related to HIV and PrEP, IPV and post-traumatic stress.

Depressive symptoms were measured using the 10-item Center for Epidemiologic Studies (CES-D) scale at enrolment and Weeks 13, 26 and 52 [34]. Sum scores were calculated (range 0 to 30; Cronbach's alpha: 0.76), and a score ≥10 was indicative of elevated depressive symptoms [34]. This cut-off was previously used with African adolescents, enabling comparisons across studies, and has good sensitivity and sensitivity in several study languages (e.g. isiXhosa, isiZulu) [34-38]. Participants were provided with referrals for mental health care with a physician, psychologist or social worker based on participant request and/or clinician discretion.

Other psychosocial and behavioural variables were measured at enrolment and Weeks 13, 26 and 52. Alcohol use was measured using the three-item AUDIT-C scale with a score ≥3 indicative of alcohol misuse [39]. Social support was measured with two items assessing social support from adults, adapted from prior work with young African women (Table S1) [40,41]. Responses were scored from 0 to 2 and summed, with higher scores indicating higher support (range: 0 to 4). Internalized stigma related to HIV and PrEP use was assessed with six items (Table S2), adapted from PrEP stigma questions for adults and key findings on PrEP barriers among adolescents [42-44]. Items were scored from 0 to 4 and

summed, with a higher sum score indicating greater internalized stigma (range: 0 to 24; Cronbach's alpha: 0.89). IPV was assessed with four items (Table S3), developed from the World Health Organization's operational IPV definitions [45]. Participants were considered to have experienced IPV if they answered "yes" to at least one item. Traumatic stress was assessed with the four-item posttraumatic stress disorder (PTSD) Checklist for the DSM-5 (PCL-5) [46]. An answer of "yes" to any item was considered indicative of PTSD symptoms.

The primary outcome was PrEP adherence measured using intracellular tenofovir-diphosphate levels (TFV-DP) in dried blood spots (DBS) collected at Week 13, 26 and 52. TFV-DP provides an estimate of cumulative PrEP dosing and has been validated among women and men who have sex with men in directly observed therapy studies [47]. For our primary analyses, PrEP adherence was defined as detectable versus undetectable TFV-DP levels (≥16 fmol/punch as a limit of detection), which represents any PrEP use since the prior visit [47,48]. We also conducted descriptive analyses of high PrEP adherence, defined as TFV-DP levels ≥700 fmol/punch, which represents consistent dosing (≥4 PrEP doses per week) [47,48].

2.3 | Group-based trajectory modelling analysis

Group-based trajectory modelling was used to identify patterns of depressive symptoms during follow-up. Models estimate the proportion of a population belonging to different trajectories and calculate the posterior probability of an individual belonging to an assigned trajectory given observed data. Based on similar analyses conducted with populations in the United States, we hypothesized finding depressive symptom trajectories corresponding to low symptoms, recurring symptoms, declining symptoms, and/or persistent elevated symptoms. Depressive symptoms were modelled as a binary variable (CES-D score </≥10), using a binomial distribution.

The selection of the best-fitting trajectory model was a two-step process. First, we identified the optimal number of trajectory groups by fitting unconditional trajectory models for depressive symptoms with 2 to 6 trajectories. This range of trajectories was decided *a priori* to maximize interpretability and public health utility. All trajectory groups were modelled using cubic polynomial terms in this step [49]. We compared models using Bayesian Information Criterion (BIC) and average posterior probabilities, with average probabilities ≥0.70 indicating good fit [49]. Second, we identified the optimal function form for each trajectory. We compared linear, quadratic and cubic terms for each trajectory and selected the functional form based on BIC values, posterior probabilities and visual inspection. We also conducted an exploratory group-based trajectory model analysis using continuous CES-D score following the same two-step procedure with a censored normal distribution.

After determining optimal trajectory number and form, we subsequently assessed psychosocial and behavioural characteristics associated with depressive symptom trajectory membership. Individuals were assigned to trajectories with the highest posterior probability [50,51]. We added covariates for study arm, site, age, education, sexual behaviour, alcohol use, social support, stigma, any IPV and PTSD symptoms. We only included baseline values of these variables to ensure the temporality of our associations. We used Wald and Wilcoxon rank sum tests to compare baseline characteristics across trajectories.

Group-based trajectory models assume missing data are missing completely at random [49]. We compared participants with missing and complete depressive symptom data. In a sensitivity analysis, we used single mean imputation to fill in missing depressive symptom data and then repeated the two-step modelling procedure on the complete dataset.

2.4 | Analyses of associations between depressive symptoms and PrEP adherence

We conducted two analyses of depressive symptoms and PrEP adherence. First, we estimated the association between depressive symptom trajectory group membership and PrEP adherence at Week 52 to understand how distinct depressive symptom patterns may influence PrEP use. Second, we estimated longitudinal associations between depressive symptoms and PrEP adherence to explore the effect of time-varying symptoms on PrEP use through follow-up.

We conducted a regression analysis, with a Poisson distribution and a log link, to model prevalence ratios between assigned group trajectory membership and detectable TFV-DP at Week 52. We also explored associations between group membership and TFV-DP levels ≥700 fmol/punch. Any baseline factors associated with depressive symptom trajectory membership (with $p < 0.10$) were included in the multivariable models. We included arm as a covariate to average effects across the groups with different PrEP counselling. Site was also included *a priori* to adjust for differences in demographics and sexual behaviour between locations [32,52]. We focused only on baseline variables in this analysis for ease of interpretation and to ensure temporality.

We used generalized estimating equations to examine the association between longitudinal depressive symptoms and PrEP adherence. Models were fit with a log link, Poisson distribution and robust standard errors. Our primary model included elevated depressive symptoms as a categorical variable (CES-D </≥10). We assessed time-dependent covariates (e.g. sexual behaviour, IPV, stigma, social support). Any that resulted in a substantial change in the effect estimate (>10%) were included in the multivariable model. We lagged forward depressive symptom and covariate data by one visit (e.g. depressive symptoms at enrolment were used to predict PrEP adherence at Week 13) to reduce the concern of reverse temporality.

All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA) and group-based trajectory models were estimating using PROC TRAJ [51].

2.5 | Ethical statement

This protocol was approved by ethics review committees at each sites. All participants provided written informed consent (or assent with consent from a parent or guardian if <18 years old).

3 | RESULTS

3.1 | Participant characteristics

Of the 427 AGYW who initiated PrEP during the study, 33.3% were from Johannesburg, 32.8% from Cape Town and 34% from Harare (Table 1). The median age was 21 years (interquartile range [IQR]: 19 to 22; range: 16 to 25). Participants reported a median of 1 sexual partner in the three months prior to enrolment (IQR: 1 to 2), although 53 (12.4%) did not answer this question. Retention was high, with an overall retention rate of 85.4% at Week 52.

Overall, 41.9% of participants (N = 179) had CES-D scores ≥10 at enrolment, and this proportion was lower during follow-up with 33.0%, 36.7% and 36.9% reporting elevated depressive symptoms at Weeks 13, 26 and 52 respectively (*p*-value for trend: 0.04; intraclass correlation coefficient: 0.39). Complete CES-D data from all four visits were available for 320 participants. A total of 46 AGYW were missing CES-D data at only one visit, 27 were missing data from two visits, 30 were missing data from three visits and 4 were missing from all four visits. A total of 52 AGYW (12.2%) were lost to follow-up, defined as missing at least two CES-D measurements without attending a subsequent visit. Missing CES-D data were not associated with other observed data (Tables S4,S5).

3.2 | Group-based trajectory model

A group-based trajectory model with three groups and linear terms had the best fit while being meaningful (Table S6). The three groups could be described as persistent elevated depressive symptoms (47.8%), declining symptoms (8.7%) and consistent no/mild symptoms (44.4%) (Figure 1). Of the 202 participants assigned to the persistent elevated symptom trajectory, 84.7% had a ≥ 0.70 posterior probability of group membership (range: 0.54 to 0.98). Of 37 participants assigned to the declining symptom trajectory, 69.9% had a ≥ 0.70 posterior probability of membership (range: 0.49 to 0.91). Of the 188 participants assigned to the consistent no/mild symptom trajectory, 83.3% had a ≥ 0.70 posterior probability of membership (range: 0.54 to 0.91). Table S7 provides additional detail on the average predicted proportions for each trajectory. Similar results were found in an exploratory analysis with a continuous CES-D score (Figure S1) and a sensitivity analysis with imputed CES-D data.

Any transactional sex, IPV and PTSD symptoms at baseline were associated with the depressive symptom trajectory group (Table 2). Approximately 30.5% of participants in the persistent elevated depressive symptoms group reported any transactional sex, compared with 21.6% in the declining symptom group and 14.9% in the no/mild symptom group. In the persistent elevated depressive symptoms group, 62.3% reported IPV and 58.2% had PTSD symptoms. In the declining symptoms group, 54.1% reported IPV and 51.4% had PTSD symptoms and in the no/mild symptom group, 34.6% reported IPV and 33.0% reported PTSD symptoms.

Table 1. HPTN 082 participant characteristics at baseline (N = 427, unless otherwise indicated)

Baseline characteristics	Frequency[a]
Arm	
Standard package	212 (49.7)
Standard package plus drug-level feedback counselling	215 (50.4)
Study site	
Johannesburg, South Africa	142 (33.3)
Cape Town, South Africa	140 (32.8)
Harare, Zimbabwe	145 (34.0)
Age, y	21.0 (19.0 to 22.0)
Education	
Primary school	9 (2.1)
Secondary school	371 (86.9)
College or university	47 (11.0)
Number of sex partners in past three months (N = 372)	1.0 (1.0 to 2.0)
Primary sex partner in past three months (N = 425)	368 (86.6)
Number of vaginal sex acts (N = 338) [b]	4.0 (2.0 to 8.0)
Condom use with vaginal sex, past month (N = 329) [b]	
Always	68 (20.7)
Often	38 (11.6)
Sometimes	106 (32.2)
Rarely	52 (15.8)
Never	65 (19.8)
Any transactional sex in the past month (N = 425)	97 (22.8)
Elevated depressive symptoms (N = 418) [c]	179 (42.8)
Alcohol misuse (N = 419) [d]	160 (38.2)
Social support (N = 423) [e]	3.0 (2.0 to 4.0)
Support from adults in your life (N = 418)	
Almost never supported	23 (5.5)
Sometimes supported	150 (35.9)
Very well supported	245 (58.6)
Support from close friends (N = 416)	
Almost never supported	25 (6.0)
Sometimes supported	215 (51.7)
Very well supported	176 (42.3)
Stigma (N = 422) [f]	6.0 (1.0 to 7.0)
Any intimate partner violence (N = 424) [g]	209 (49.3)
Emotional intimate partner violence	157 (36.9)
Physical intimate partner violence	85 (20.0)
Sexual intimate partner violence	38 (8.9)
Ever felt afraid, unsafe, or in danger from a partner	79 (18.6)
Any posttraumatic stress disorder symptoms (N = 418) [h]	194 (46.4)

[a]Data are presented as median (interquartile range) for continuous variables given variability and skewness observed in several of the variables. Data are presented as frequency (percentage) for categorical variables.; [b]data on number of vaginal sex acts and condom use were only collected for participants who reported any vaginal sex in the past three months; [c]a sum CESD-10 score ≥10 was indicative of "elevated depressive symptoms"; [d]an AUDIT-C scale score ≥3 was indicative of alcohol misuse; [e]so-social support was measured as the sum score across two items assessing social support from adults and close friends (range: 0 to 4); [f]stigma was measured as the sum score across ten items assessing stigma related to HIV and PrEP use (range: 0 to 40); [g]participants were considered to have experienced any intimate partner violence if they answered "yes" that they had experienced at least one of four items asking about physical, emotional, sexual violence, or feeling unsafe or in danger from a sexual partner in the past month; [h]a response of "yes" to any of four items from the Posttraumatic Stress Disorder (PTSD) Checklist for the DSM-5 (PCL-5) was indicative of PTSD symptoms.

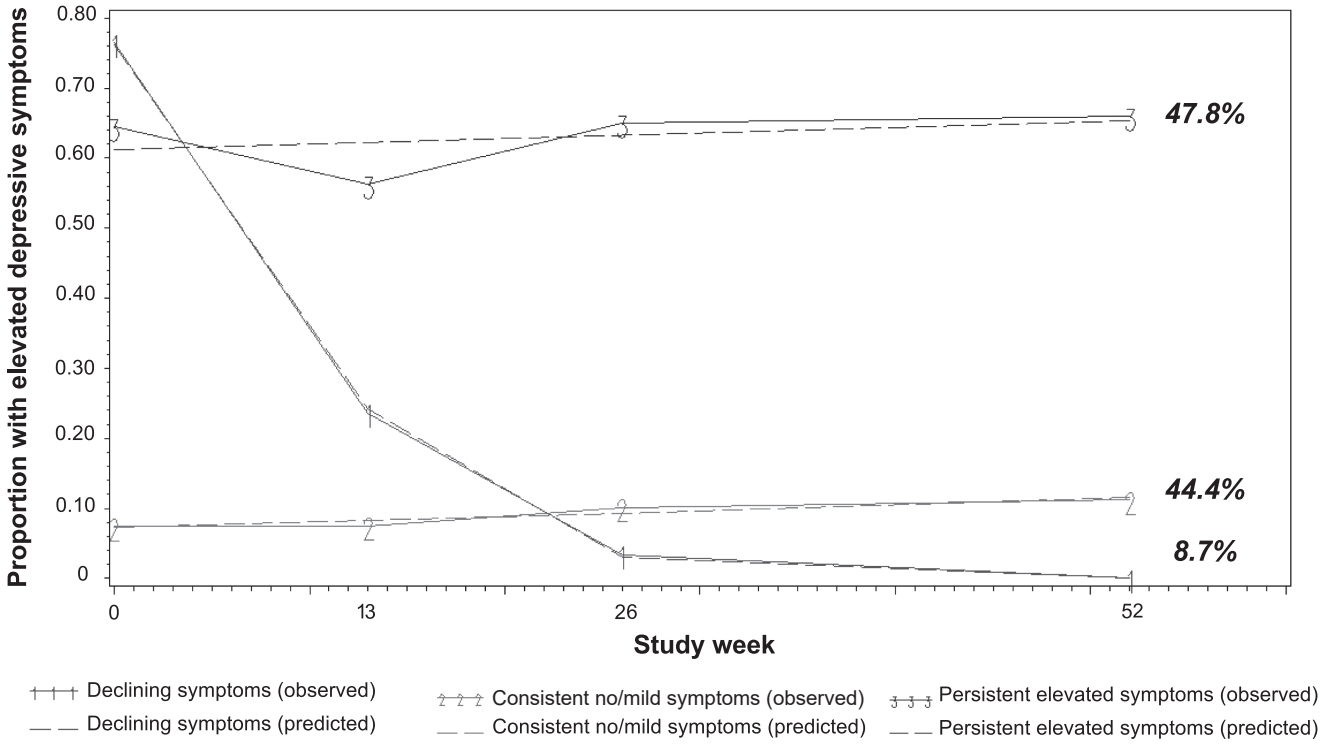

Figure 1. Depressive symptom trajectories for HPTN 082 participants through follow-up (N = 423).
*"Observed" data points show the average proportion of participants with elevated depressive symptoms at a given study visit; "Predicted" data points show the predicted proportion with elevated depressive symptoms in each trajectory group, as estimated from a group-based trajectory model with assigned trajectory group determined based on each participant's highest predicted posterior group-membership probability.

3.3 | Associations between group membership and PrEP adherence

DBS data were unavailable for 79 participants. At Week 52, 109 (31.3%) of 348 participants had detectable TFV-DP levels. Group membership was statistically significantly associated with detectable TFV-DP (Table 3). Participants in the persistent elevated depression symptom group were less likely to have detectable TFV-DP levels compared with those in the consistent no/mild symptom group (adjusted prevalence ratio [aPR]: 0.89; 95% CI: 0.80 to 0.98). We were not able to explore the association between group membership and high PrEP adherence at Week 52, as only 30 participants had TFV-DP levels ≥700 fmol/punch at the final study visit.

3.4 | Associations between longitudinal depressive symptoms and PrEP adherence

TFV-DP was detected at 607 (57.9%) follow-up visits (intraclass correlation coefficient: 0.46). In multivariable models adjusting for site, arm and time-varying transactional sex, IPV, PTSD symptoms, condom use, and number of sexual partners, depressive symptoms were significantly associated with detectable TFV-DP (adjusted relative risk [aRR]: 0.73; 95% CI: 0.53 to 0.99; Table 4). High PrEP adherence (TFV-DP levels ≥700 fmol/punch) was detected at 193 (18.4%) of follow-up visits. Depressive symptoms were not statistically significantly associated with high PrEP adherence (Table 4).

4 | DISCUSSION

In this population of AGYW in South Africa and Zimbabwe, we identified three depressive symptom trajectory groups: persistent elevated depressive symptoms, declining symptoms and no/mild symptoms. Approximately 42% of our sample experienced elevated depressive symptoms at enrolment. About 90% had unchanging depressive symptoms, either as no/mild or persistent elevated symptoms, based on group-based trajectory models fit with a linear functional form and CES-D data from four time points. A smaller proportion was assigned to a trajectory with depressive symptoms that declined within the three months indicating that the study interventions, time on PrEP or other factors may have reduced depressive symptoms only for 9% of the population. Persistent elevated depressive symptom group membership and time-varying depressive symptoms were significantly associated with detectable TFV-DP levels.

Ours is one of the first studies to focus on depressive symptom prevalence and patterns in a population of African AGYW seeking PrEP. Other studies with African AGYW engaged in HIV treatment, other types of prevention services, or those in nationally representative cohorts report

Table 2. Participant characteristics by depressive symptom trajectory group (N = 423)

	Frequency for each depressive symptom trajesctory[a]			
Baseline characteristics	**Consistent no/mild symptoms N = 188**	**Declining symptoms N = 37**	**Persistent elevated symptoms N = 202**	***p*-value[b]**
Standard package arm	91 (48.4)	18 (48.6)	103 (51.0)	0.87
Age, years	20.0 (19.0 to 22.0)	21.0 (20.0 to 23.0)	21.0 (19.0 to 22.0)	0.18
Education				
Primary school	4 (2.1)	0 (0.0)	5 (2.5)	0.12
Secondary school	158 (84.0)	37 (100.0)	176 (87.1)	
College or university	26 (13.8)	0 (0.0)	21 (10.4)	
Number of sex partners in past three months (N = 372)	1.0 (1.0 to 2.0)	1.0 (1.0 to 1.0)	1.0 (1.0 to 2.0)	0.06
Primary sex partner in past 3 months (N = 425)	163 (86.7)	32 (86.5)	173 (86.5)	0.99
Number of vaginal sex acts (N = 338) [c]	4.0 (2.0 to 8.0)	4.0 (3.0 to 12.0)	4.0 (2.0 to 8.0)	0.92
Condom use with vaginal sex, past month (N = 329) [c]				
Always	36 (24.3)	6 (20.7)	26 (17.1)	0.06
Often	15 (10.1)	1 (3.5)	22 (14.5)	
Sometimes	49 (33.1)	6 (20.7)	51 (33.6)	
Rarely	15 (10.1)	8 (27.6)	29 (19.1)	
Never	33 (22.3)	8 (27.6)	24 (15.8)	
Any transactional sex in the past month (N = 425)	28 (14.9)	8 (21.6)	61 (30.5)	<0.01
Likely depression (N = 418) [d]	0 (0.0)	37 (100.0)	142 (72.5)	<0.01
CES-D score [d]	5.0 (3.0 to 7.0)	12.0 (11.0 to 15.0)	11.0 (9.0 to 14.0)	<0.01
Alcohol misuse (N = 419) [e]	64 (34.2)	13 (35.1)	83 (42.6)	0.23
Social support (N = 423) [f]	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 3.0)	0.12
Support from adults in your life (N = 418)				
Almost never supported	12 (6.5)	1 (2.7)	10 (5.1)	0.29
Sometimes supported	56 (30.4)	14 (37.8)	80 (40.6)	
Very well supported	116 (63.0)	22 (59.5)	107 (54.3)	
Support from close friends (N = 416)				
Almost never supported	7 (3.9)	2 (5.6)	16 (8.1)	0.13
Sometimes supported	87 (47.8)	22 (61.1)	106 (53.4)	
Very well supported	88 (48.4)	12 (33.3)	76 (38.4)	
Stigma (N = 422) [g]	6.0 (1.0 to 7.0)	4.0 (0.0 to 8.0)	6.0 (1.0 to 8.0)	0.53
Any intimate partner violence (N = 424) [h]	65 (34.6)	20 (54.1)	124 (62.3)	<0.01
Any emotional violence (N = 424)	50 (26.6)	16 (43.2)	91 (45.5)	0.01
Any physical violence (N = 423)	26 (13.8)	6 (16.2)	53 (26.5)	0.02
Any sexual violence (N = 423)	8 (4.3)	6 (16.2)	24 (12.0)	0.04
Ever felt afraid, unsafe, or in danger (N = 424)	16 (8.5)	11 (29.7)	52 (26.0)	<0.01
Any posttraumatic stress disorder symptoms (N = 418) [i]	61 (33.0)	19 (51.4)	224 (58.2)	<0.01

CES-D=Center for Epidemiologic Studies – Depression Scale

[a]Data are presented as median (interquartile range) for continuous variables and frequency (percentage) for categorical variables; [b]*p*-values are based on the Wilcoxon rank sum test for continuous variables and Wald *p*-values from χ^2 test for categorical variables; [c]data on number of vaginal sex acts and condom use were only collected for participants who reported any vaginal sex in the past three months; [d]a sum CESD-10 score ≥10 was indicative of "likely depression". CES-D score is the sum value across ten CES-D items (range: 0 to 30); [e]an AUDIT-C scale score ≥3 was indicative of alcohol misuse; [f]social support was measured as the sum score across two items assessing social support from adults and close friends (range: 0 to 4); [g]stigma was measured as the sum score across ten items assessing stigma related to HIV and PrEP use (range: 0 to 40); [h]participants were considered to have experienced any intimate partner violence if they answered "yes" that they had experienced at least one of four items asking about physical, emotional, sexual violence, or feeling unsafe or in danger from a sexual partner in the past month; [i]a response of "yes" to any of four items from the Posttraumatic Stress Disorder (PTSD) Checklist for the DSM-5 (PCL-5) was indicative of PTSD symptoms.

Table 3. Associations between depressive symptom trajectory membership and PrEP adherence at Week 52, assessed via multivariable regression models

	Detectable DBS TFV-DP levels			
		Adjusted GEE analysis[a]		
Exposure group	Visits with detectable TFV-DP (N = 109/348)[b]	aPR (95% CI)	*p*-value	Global *p*-value
Consistent no/mild depressive symptoms	53 (35.6%)	REF	---	0.05
Declining depressive symptoms	12 (35.3%)	1.05 (0.46 to 2.21)	0.54	
Persistent elevated depressive symptoms	44 (26.7%)	0.89 (0.80 to 0.98)	0.04	

PrEP=pre-exposure prophylaxis; TFV-DP=tenofovir diphosphate; DBS=dried blood spots; aPR=adjusted prevalence ratio
[a]Multivariable models adjusted for study site, number of sexual partners, condom use during vaginal sex, any transactional sex, any intimate partner violence and posttraumatic stress disorder symptoms, all measured at baseline; [b]data are presented as median (interquartile range) for continuous variables and frequency (percentage) for categorical variables.

Table 4. Associations between time-varying depressive symptoms and PrEP adherence through follow-up, assessed via generalized estimating equations

	Detectable DBS TFV-DP Levels			DBS TFV-DP ≥700 fmol/punch		
		Adjusted GEE analysis[a]			Adjusted GEE analysis[a]	
Exposure group	Visits with detectable TFV-DP (N = 607/1048)[b]	aRR (95% CI)	*p*-value	Visits with TFV-DP ≥700 fmol/punch (N = 193/1048 visits)[b]	aRR (95% CI)	*p*-value
Elevated depressive symptoms (CES-D score ≥10)	206 (55.2%)	0.73 (0.53 to 0.99)	0.04	72 (19.3%)	1.10 (0.74 to 1.62)	0.65
No/mild depressive symptoms (CES-D score <10)	401 (59.4%)	REF	–	121 (17.9%)	REF	–

aRR, adjusted relative risk; CES-D, Center for Epidemiologic Studies – Depression Scale; DBS, dried blood spots; GEE, generalized estimating equations; PrEP, pre-exposure prophylaxis; TFV-DP, tenofovir diphosphate.
[a]Multivariable models adjusted for study site at baseline and time-varying data on number of sexual partners, condom use during vaginal sex, any transactional sex, any intimate partner violence and posttraumatic stress disorder symptoms; [b]data are presented as median (interquartile range) for continuous variables and frequency (percentage) for categorical variables.

depressive symptom prevalence estimates around 40% to 50% [17,53,54]. Consistent with our findings, analyses of depressive symptom patterns among populations living with or at-risk of HIV in the United States and South Africa also found distinct trajectories characterized by severe or persistent symptoms, declining symptoms and low or no symptoms [28-31]. Distinct from our results, several studies also found groups characterized by worsening and recurring depressive symptoms or consistent mild-to-moderate symptoms [28-31]. Importantly, these analyses were conducted with pregnant or recently postpartum South African adults and AGYW living with HIV in the United States. These populations likely have distinct mental health issues from African AGYW and our study adds insights on depressive symptom trajectories among African AGYW seeking PrEP. It is possible that HPTN 082 interventions may have been sufficient to prevent depressive symptoms from worsening and to address mild depressive symptoms [15,32]. Another HIV prevention trial with women in South Africa also found relatively stable depressive symptoms through follow-up, with about 45% of the sample reporting symptoms consistent with depression at each study visit during a six-month period, supporting our findings on the relative stability of more moderate-to-severe depressive symptoms in this population [16].

We observed significant differences in depressive symptom trajectory membership by site and baseline measures of transactional sex, IPV and symptoms of PTSD. Prior studies have also reported associations between depressive symptoms, transactional sex and other HIV risk behaviour, the combination of which may contribute to co-occurring mental health issues and HIV among AGYW [55-57]. For example recent work with 15- to 24-year-old AGYW in Kenya found that depressive symptoms were associated with transactional sex, intimate partner violence and HIV risk [58]. In HPTN 082, AGYW assigned to the persistent elevated depressive symptom trajectory group were significantly more likely to report IPV and PTSD symptoms. This may have been due to repeated experiences of IPV, difficulties accessing mental health and IPV services and unmeasured contextual factors such as lack of empowerment [59-62]. Prior studies in sub-Saharan Africa have found that IPV is associated both with a higher prevalence of depressive symptoms and PTSD symptoms, although this work has been primarily conducted with adult women [63,64]. We did not observe differences in depressive

symptom trajectory by intervention arm, possibly because participants in both arms received some PrEP adherence counselling, support groups, SMS and referrals. The drug-level feedback counselling intervention was not targeted at reducing depressive symptoms.

We observed high drop-offs in PrEP adherence by Week 52: only 348 (81.5%) participants had DBS samples and PrEP was detected in 31% samples at this visit. However, these results are consistent with other PrEP projects among AGYW that have reported declining PrEP adherence over time [12,65-67]. There are several potential mechanisms to explain our findings on the significant negative relationship between depressive symptoms and PrEP use. Depression could lead to lower self-efficacy, healthcare engagement, reduced motivation to engage in a protective health behaviour and poorer self-care behaviour [68-70]. Persistent elevated depressive symptoms could also lead to social isolation over a prolonged period of time and less support to assist with PrEP pill-taking [71-73]. Elevated depressive symptoms could also impact needs for PrEP, as depressive symptoms have been associated with reduced frequency of sex in some cohorts but increased condomless sex in other studies with sub-Saharan African women [74,75]. The impact of declining depressive symptoms on PrEP adherence is less clear. Participants in the declining depressive symptoms group had elevated depressive symptoms at enrolment which may have prevented PrEP pill-taking habit formation early. However, it is possible that participants with declining symptoms are able to improve their PrEP use over time as their mental health improves. Future analyses with larger cohorts may be better positioned to understand this relationship between declining symptoms and PrEP adherence.

Strengths of this study include a cohort with high retention and longitudinal depressive symptom measurement using a validated screening tool. We used biomarker data on PrEP adherence rather than relying on self-report or electronic monitoring tools. However, the small sample size, particularly among participants in the declining symptom trajectory, and drop-off in PrEP adherence could have led to imprecise estimates of group membership and associations between symptom trajectories and PrEP adherence. The sample size and length of follow-up may have also precluded us from identifying other trajectory groups. Approximately 12% of participants declined to answer sexual behaviour items. This may have resulted in unmeasured confounding of the relationship between depressive symptoms and PrEP adherence, although we did not detect significant associations between missing sexual behaviour data, depressive symptoms and PrEP adherence. We did not systematically collect clinical data on depression treatment and cannot make conclusions on participants' likelihood of improving with treatment. We also did not collect data on referrals given or referral visits attended. More data on depression presentation and access to counselling and pharmacotherapy would be needed to draw further conclusions. Our group trajectories are based on CES-D results alone and clinical evaluation was not conducted. We collected data on stigma, social support and IPV using items adapted for AGYW. However, these measures have not been widely used or validated which may have impacted the quality of construct measurement and limits comparability across populations. While we included these and other variables on sexual behaviour as covariates in our models, these factors may have a bidirectional relationship with depressive symptoms and PrEP adherence and additional research is needed to understand complex pathways between depressive symptoms, other psychosocial and behavioural factors, and PrEP use. Finally, results may not be generalizable to AGYW seeking PrEP as part of real-world service delivery.

5 | CONCLUSIONS

In conclusion, we found that about half of AGYW from South Africa and Zimbabwe initiating PrEP had elevated persistent depressive symptoms over one year, which was associated with lower likelihood of detectable PrEP use. Time-varying depressive symptoms were also associated with detectable PrEP use. These findings indicate that depression assessment at PrEP initiation among African AGYW may be useful to identify women who need more intensive PrEP adherence counselling and depression treatment. While the World Health Organization currently recommends that PrEP programmes screen for mental health issues that are common causes of poor PrEP adherence [9], our results indicate that PrEP programmes could additionally screen for factors associated with persistent elevated depressive symptoms, such as transactional sex, IPV and PTSD symptoms, to target delivery of enhanced adherence support and referrals. For example AGYW with characteristics associated with persistent elevated depressive symptoms and low PrEP adherence could be linked to evidence-based mental health and PrEP adherence interventions to increase PrEP use and reduce depressive symptoms. Evidence-based psychotherapy, delivered alone or alongside multi-level HIV, sexual and reproductive health, or gender-based violence services, can improve mental health, coping around gender-based violence and stigma and HIV-related outcomes among African women [76-82]. Given the high prevalence of depression in this population who are at high risk of HIV acquisition, additional research is needed to adapt and implement effective depression treatment approaches in PrEP delivery for African AGYW. Identifying women most at risk for persistent depressive symptoms and poor PrEP adherence and providing targeted, integrated mental health and PrEP services could improve cost-effective PrEP delivery for AGYW in HIV endemic settings.

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COMPETING INTERESTS

The authors report no conflicts of interest.

AUTHORS' CONTRIBUTIONS

CC, SDM, SH, LGB, DD, NM and MC designed the parent study. JV conducted all analyses, results interpretation and wrote the first draft of the manuscript. SH, MC, NM and LGB were involved in study design, results interpretation and

edited the manuscript. DD was involved in study design, statistical oversite, results interpretation and edited the manuscript. PLA was involved in study design, laboratory oversite, results interpretation and edited the manuscript. SDM and CC were involved in grant proposal development and securing funding, study design, results interpretation and edited the manuscript. All authors reviewed and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1. Social support measurement in HPTN 082

Table S2. Stigma measurement in HPTN 082

Table S3. Intimate partner violence measurement in HPTN 082

Table S4. Baseline characteristics for the full participant sample compared with those who had any missed CES-D data

Table S5. Baseline characteristics for the full participant sample compared with those who were lost to follow-up

Table S6. Group-based trajectory model fit statistics

Table S7. Group-based trajectory model output of predicted proportion with elevated depressive symptoms, by trajectory group and study visit

Figure S1. Depressive symptom trajectories for HPTN 082 participants through follow-up, using continuous CES-D score

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RESEARCH ARTICLE

Intimate partner and client-perpetrated violence are associated with reduced HIV pre-exposure prophylaxis (PrEP) uptake, depression and generalized anxiety in a cross-sectional study of female sex workers from Nairobi, Kenya

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Abstract

Introduction: UNAIDS has identified female sex workers (FSW) as a key HIV at-risk population. FSW disproportionately experience gender-based violence, which compounds their risk of HIV acquisition and may contribute to adverse mental health outcomes. Pre-exposure prophylaxis (PrEP) is a powerful but underused HIV prevention tool for these women. This study explored the associations between intimate partner violence (IPV) and client-perpetrated violence against FSW, mental health outcomes and PrEP use.

Methods: An anonymous questionnaire was administered to a convenience sample of 220 Nairobi FSW attending dedicated clinics from June to July 2019, where PrEP was available free of charge. A modified version of the WHO Violence Against Women Instrument assessed IPV and client-perpetrated violence, and the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7) assessed depressive and anxiety symptoms respectively. Multivariable logistic regressions evaluated predictors of depression, generalized anxiety and PrEP use.

Results: Of the total 220 women (median [IQR] age 32 [27-39]), 56.8% (125/220) reported depression (PHQ-9 $\geq$ 10) and 39.1% (86/220) reported anxiety (GAD-7 $\geq$ 10). Only 41.4% (91/220) reported optimal use of PrEP (taken correctly six to seven days/week) despite the cohort pursuing sex work for a median of 7 (4 to 12) years. Most women reported experiencing any violence in the past 12 months (90%, 198/220). Any recent IPV was frequent (78.7%, 129/164), particularly emotional IPV (66.5%, 109/164), as was any client-perpetrated violence in the past 12 months (80.9%, 178/220). Regression analyses found that violence was independently associated with depression (adjusted OR [aOR] 9.39, 95% CI 2.90 to 30.42, $p = 0.0002$) and generalized anxiety (aOR 3.47, 95% CI 1.10 to 10.88, $p = 0.03$), with the strongest associations between emotional IPV and both depression and anxiety. Recent client-perpetrated emotional violence (aOR 0.23, 95% CI 0.07 to 0.71, $p = 0.01$) was associated with decreased PrEP use, whereas client-perpetrated physical violence was associated with increased PrEP use (aOR 3.01, 95% CI 1.16 to 7.81, $p = 0.02$).

Conclusions: There was a high prevalence of recent violence by different perpetrators as well as depression and anxiety among FSW from Nairobi. PrEP use was relatively infrequent, and recent client-perpetrated emotional violence was associated with PrEP non-use. Interventions to reduce gender-based violence may independently enhance HIV prevention and reduce the mental health burden in this community.

Keywords: female sex workers; HIV; intimate partner violence; depression; anxiety; pre-exposure prophylaxis

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1 | INTRODUCTION

There have been substantial declines in global HIV/AIDS incidence since the peak of the epidemic in 1998, and UNAIDS estimates that new HIV infections have been reduced by 40% [1]. However, while these decreases constitute important advances in the HIV response, they may mask sustained or expanding spread among key populations who are disproportionately affected by HIV [2]. Two-thirds of the estimated 37 million people worldwide living with HIV/AIDS reside in sub-Saharan Africa, with Kenya currently experiencing the third largest HIV epidemic in the world [3]. Women and girls living in sub-Saharan Africa are more likely to be infected than men and boys [1,4]. In particular, female sex workers (FSW)

represent a key vulnerable population [1]. In Kenya, the overall prevalence of HIV in adults is 4.5 per 100 people; the prevalence of HIV in sex workers is 29.3 [3].

UNAIDS reports that more than one-third of women around the world have experienced physical and/or sexual violence at some time in their lives [1]. In some regions, women who experience violence are one and a half times more likely to become infected with HIV [1], particularly for women in sub-Saharan Africa [5]. Furthermore, violence is a common problem for women who sell sex [6]. A qualitative enquiry into experiences of violence for FSW in Kenya found that sexual and physical violence were pervasive, underscored by the extreme financial needs of FSW, gender-power differentials, illegality of trading in sex and cultural subscriptions to men's entitlement for sex without payment [7]. Further compounding HIV risk in this context is the fact that men who are violent towards women are more likely to have HIV [8]. Therefore, it is imperative to ensure access to effective HIV prevention methods as part of comprehensive violence prevention and response services for FSW populations.

Pre-exposure prophylaxis (PrEP) is a powerful method of HIV prevention [9,10]. Currently approved PrEP regimens consist of daily oral emtricitabine-tenofovir, which has been demonstrated to significantly reduce HIV acquisition among high-risk men who have sex with men, persons who use intravenous drugs and heterosexual men and women [11]. Among FSW, this may enable women to access an HIV prevention strategy that does not require disclosure to partners [12]. Additionally, women with a history of intimate partner violence (IPV) reported that they would be more willing to use PrEP compared to women without these experiences [13,14], further underscoring the importance of HIV prevention in at-risk populations. However, IPV is also associated with depression [15,16] and substance use among FSW [17]. As such, mental health symptomology may contribute to challenges with PrEP adherence, as has been shown with other antiretroviral medication adherence [18-20]. Furthermore, different patterns of violence have been shown to be differentially associated with sexual risk outcomes [21]; following, those who perceive themselves to be at higher risk of HIV acquisition (i.e. physical, sexual violence) may have increased PrEP adherence compared to those at lower perceived immediate risk (i.e. emotional violence) [22]. Research has demonstrated that violence and emotional manipulation from sexual partners specifically heightens FSW HIV risk through engagement in higher risk sexual behaviours (i.e. less condom use, more partners) [23]. Similarly, FSW often have lower perceived control in these emotional relationships, with abuse in these scenarios being linked to increased HIV risk behaviours, which may contribute to reduced PrEP uptake [23-25].

The Sex Worker Outreach Programme (SWOP) in Nairobi, Kenya has been operating for over 20 years to provide HIV prevention, care and treatment to key populations in Nairobi county, with over 42,000 FSW enrolled as of 2019. Seven clinics across the county provide free access to HIV testing and treatment at every visit (including PrEP to all HIV-negative FSW), reproductive healthcare services (including free condoms) and support for women who experience partner violence. Therefore, the SWOP provides the ideal opportunity to explore the associations between gender-based violence against FSW, mental health outcomes and the use of PrEP medication. We aimed to: (i) determine the differential associations of IPV and client-perpetrated violence with mental health outcomes; (ii) determine the potential effects of IPV and client-perpetrated violence on the uptake of PrEP and (iii) determine the potential role of mental health symptomatology in PrEP uptake. Specifically, we hypothesize: (i) greater IPV and client-perpetrated violence of any type will be associated with higher depressive and generalized anxiety symptoms, (ii) greater IPV and client-perpetrated physical and sexual violence will increase PrEP use, whereas greater emotional violence will decrease PrEP use and (iii) higher depressive and generalized anxiety symptoms will be associated with a reduction in PrEP use (Figure 1).

2 | METHODS

2.1 | Participant recruitment and survey administration

An anonymous questionnaire was administered to Nairobi FSW attending Kenya Aids Control Project (KACP) clinics during June-July 2019. All women who were currently exchanging sex for money or goods were considered FSW for the purposes of this study. Participants were eligible if they were HIV-negative and over the age of 18. Participants were recruited on a convenience basis across the seven clinics. Participation was voluntary, informed consent was provided and participants were compensated 300 KSH. The study was part of a quality improvement initiative approved by the Institutional Review Boards at Kenyatta National Hospital (Kenya) and the Universities of Toronto and Manitoba (Canada). Surveys were administered in a one-on-one interview in Kiswahili or English, and responses were recorded by staff administering the survey. HIV testing was performed according to Kenyan national guidelines, with initial screening by antibody-based rapid test Determine HIV 1/2 (Inverness Medical, Tokyo, Japan) and confirmation of positive tests using SD Bioline HIV 1/2 (Standard Diagnostics Inc., Kyonggi Do, South Korea).

2.2 | Measures of intimate partner, client-perpetrated and other violence

An intimate partner was defined as any non-paying partner, such as a husband or boyfriend. A client was defined as a paying partner (money, rent, school fees, etc.). IPV and client-perpetrated violence was defined as any violence perpetrated by intimate partners or clients against the women and manifested through acts of physical, sexual or emotional violence. Other perpetrators were defined as anyone other than an intimate partner or client (e.g. police, city askaris, family members) who also committed the aforementioned acts of violence. The items were structured using a modified version of the World Health Organization Violence Against Women Instrument (VAWI), which assessed experiences of 13 specific acts of physical (six items), sexual (three items) or emotional violence (four items) from regular partners such as husbands or boyfriends [26]. An extra item assessing forced sex without a condom was added to the sexual violence section, for a total of 14 items. A "yes" to at least one question in each category constituted an experience of violence, and women were dichotomized accordingly in each violence sub-group (physical,

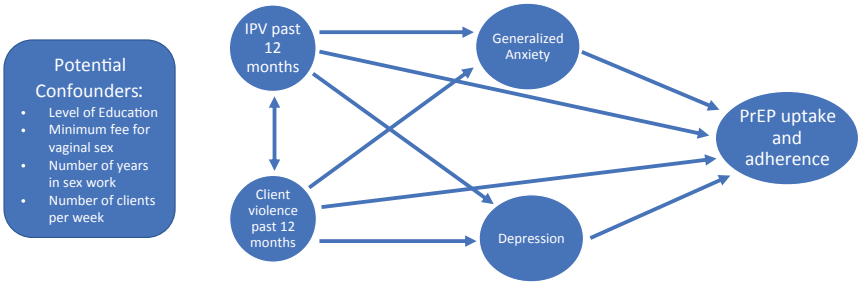

Figure 1. Model of associations tested. Conceptual model of the associations between gender-based violence, mental health symptomatology, and use of PrEP medication. IPV, intimate partner violence; PrEP, pre-exposure prohylaxis

sexual, emotional). The items were asked once for perpetration of violence by an intimate partner (husband or boyfriend), once for the perpetration of violence by clients, and once for any other perpetration of violence. An overall variable was also created to represent any violence, which included any form (emotional, physical, sexual) perpetrated by any of an intimate partner, client or other in the past 12 months. The VAWI has demonstrated good internal validity (Cronbach's $\alpha = 0.88$) [27].

2.3 | PrEP medication use

PrEP use was operationalized into four categories determined by the following question series. Participants were asked "Have you ever used PrEP?" If no, they were categorized as "never used." If yes, participants were asked "Are you currently taking PrEP?" If no, they were categorized as a "past user." If yes, participants were asked "How often do you take your PrEP pill?" If participants responded with less than six to seven times per week, they were categorized as a "current sub-optimal user". If participants responded six to seven times per week they were catergorized as a "current optimal user."

2.4 | Depressive symptoms

Current levels of depressive symptoms were assessed using the nine-item self-reported Patient Health Questionnaire-9 (PHQ-9) to assess both diagnostic categories and severity of symptoms [20]. Participants rate the chronicity of symptoms using a four-point scale ranging from 0 (Not at all) to 3 (Nearly every day). Total scores of all items were summed, and participants were categorized as meeting criteria for moderate depression (PHQ-9 $\geq$ 10) or not meeting criteria (PHQ-9 < 10). The PHQ-9 has been utilized widely in both research and clinical settings and possesses strong psychometric properties [28,29]. Two large-scale validation studies in healthcare settings found excellent internal consistency for the measure (Cronbach's $\alpha = 0.86$ to 0.89) and support for strong test–retest reliability ($r = 0.84$) across a 48-h timeframe [30]. It has been validated among Kenyan HIV/AIDS populations ($\alpha = 0.78$), with acceptable test-retest reliability (ICC = 0.59) [31].

2.5 | Generalized anxiety symptoms

Current levels of anxiety symptoms were similarly measured using the seven-item self-reported Generalized Anxiety Disorder-7 (GAD-7) designed to assess for both presence and severity of symptoms of generalized anxiety disorder [32]. Participants rate the chronicity of symptoms using a four-point scale ranging from 0 (Not at all) to 3 (Nearly every day). Total scores of all items were summed, and participants were categorized as meeting criteria for moderate generalized anxiety (GAD $\geq$ 10) or not meeting criteria (GAD<10). The GAD-7 has demonstrated strong psychometric properties in validation studies including excellent internal consistency (Cronbach's $\alpha = 0.92$) and strong test–retest reliability ($r = 0.83$). It has been validated among Kenyan HIV/AIDS populations ($\alpha = 0.82$), with acceptable test–retest reliability (ICC = 0.70) [33].

2.6 | Statistical analysis

Categorical variables were reported as counts with percentages and analysed with chi-square or Fisher's exact test whenever appropriate. Dichotomous variables were reported with percentages. Continuous variables were assessed for normal distribution using a normal probability plot, and were reported as mean with standard deviation if normally distributed or median with interquartile range (IQR) if not normally distributed. Continuous variables were compared between groups using Welch's t-test if normally distributed or Mann–-Whitney U test if not normally distributed. There were no multiple imputations performed. Data were 99.9% complete.

The following three outcomes were evaluated with multivariable logistic regression models: depression (PHQ9 $\geq$ 10), anxiety (GAD7 $\geq$ 10) and use of PrEP (current use vs. past or no use). The following a priori covariates (chosen based on clinical relevance and parsimony) were included in the models: emotional IPV, physical IPV, sexual IPV, client emotional violence, client physical violence, client sexual violence, other emotional violence, other physical violence, other sexual violence, any violence, level of education (primary education or less, secondary education, postsecondary education), minimum fee for vaginal sex, number of years in sex work and number of clients per week. Participants with no intimate partner were excluded from multivariate models where IPV was a covariate. Measures of violence may be collinear, so we calculated the variance inflation factor for all multivariable models; all were <4. Beta-coefficients were exponentiated for clinical interpretability. Generalized estimating equations were used to assess for clustering by site, which was non-contributory. If using a Bonferroni correction for the nine different types of violence predictors, the significance level would become ($\alpha = 0.05/9 = 0.006$). Statistical analysis was performed in R (version 3.6.2).

3 | RESULTS

3.1 | Participant demographics and experiences of violence

In total, questionnaires were completed by 220 HIV-negative clinic attendees meeting the study criteria (Table 1).

The prevalence of probable depression was 56.8% (125/220). The prevalence of probable anxiety was 39.1% (86/220). Overall, 90% (198/220) of women reported a history of any violence in the past 12 months. 80.9% (178/220) reported client-perpetrated violence. When stratifying violence types, 73.6% (162/220) reported client-perpetrated emotional violence, 52.3% (115/220) reported client-perpetrated physical violence and 68.6% (151/220) reported client-perpetrated sexual violence. Of 164 women with an intimate partner, 78.7% (129/164) reported IPV in the past 12 months. 66.5% (109/164) reported emotional IPV, 57.7% (94/163, 1 missing data) reported physical IPV and 57.3% (94/163) reported sexual IPV. There were 49.5% (109/220) of women who reported violence by other perpetrators in the past 12 months. Of the 220 total participants, 42.3% (91/215, 5 missing data) were categorized as current optimal PrEP users.

3.2 | Recent experience of violence was associated with depression and anxiety

To explore the associations of violence with mental health, total depressive and generalized anxiety scores were first compared between participants who had and had not experienced IPV (emotional, physical and/or sexual). Overall, participants who reported having experienced any of these forms of IPV in the past 12 months reported significantly higher depression and generalized anxiety scores than those who did not (Table 2).

A similar analysis was then carried out to assess the association of client-perpetrated violence (emotional, physical and/or sexual) with mental health, and recent client-perpetrated violence was again associated with higher depression and generalized anxiety scores (Table 3).

Univariable and multivariable logistic regression models examining associations of violence with depression are presented in Table 4. Overall, any emotional IPV within the last 12 months and a secondary school education were each associated with an increased likelihood of probable depression (PHQ9≥10).

Univariable and multivariable logistic regression models examining associations of violence with anxiety were then assessed, and results are presented in Table 5. Overall, any emotional IPV within the last 12 months and a lower fee for sex work were associated with an increased likelihood of probable anxiety (GAD7 ≥ 10).

3.3 | Associations of PrEP use with partner violence and mental health

PrEP use was first assessed based on the experience of IPV in the past 12 months. While there was no association of PrEP with a recent experience of emotional IPV (Pearson $\chi^2 = 0.63$; $p = 0.43$) or physical IPV (Pearson $\chi^2 = 1.32$, $p = 0.25$), participants who had experienced sexual IPV were more likely to be taking PrEP (Pearson $\chi^2 = 6.08$, $p = 0.014$). While no univariable associations were found between PrEP use and emotional, physical or sexual violence initiated by casual clients (Pearson $\chi^2 = 0.02$, 1.14 and 2.32 respectively; all $p > 0.05$), subsequent multivariable logistic regression found that client-perpetrated physical violence was independently linked with PrEP use, and client-perpetrated emotional violence was independently linked with a lower likelihood of PrEP use (Table 6).

Table 1. Cohort demographics

Characteristic	Total = 220[a]
Age	32 (27 to 39)
Age started sex work	23 (19 to 29)
Years in sex work	7 (4 to 12)
Level of education	
Primary education or less	105 (47.7%)
Secondary education	89 (40.5%)
Postsecondary education	26 (11.8%)
Casual clients per week	4 (3 to 7)
Regular clients per week	5 (3 to 8)
Minimum fee for vaginal sex (KSH)	500 (200 to 925)
History of sexually transmitted infection	142 (64.8%)
IPV (past 12 months)	
Any IPV	129/164 (78.7%)
Emotional	109/164 (66.5%)
Physical	94/163 (57.7%)
Sexual	94/164 (57.3%)
Client violence (past 12 months)	
Any client violence	178 (80.9%)
Emotional	162 (73.6%)
Physical	115 (52.3%)
Sexual	151 (68.6%)
Other violence (past 12 months)	
Any other violence	109 (49.5%)
Emotional	108 (49.1%)
Physical	88 (40%)
Sexual	50 (22.7%)
Any violence overall (past 12 months)	198 (90.0%)
PHQ9	10 (8 to 14)
≥10	125 (56.8%)
GAD7	8 (6 to 13)
≥10	86 (39.1%)
PrEP use (*215)	
Current optimal user	91 (42.3%)
Current sub-optimal user	9 (4.2%)
Never used	84 (39.1%)
Past user	31 (14.4%)

Continuous variables are reported as median (interquartile range) unless otherwise specified. GAD7, Generalized Anxiety Disorder-7; IPV, intimate partner violence; KSH, Kenyan Shilling; PHQ9, Patient Health Questionnaire-9; PrEP, pre-exposure prophylaxis.
[a]Denominator is 220 unless otherwise specified.

Table 2. Demographics of FSW who experienced any IPV in the last 12 months versus FSW who have not experienced any IPV in the last 12 months

Characteristic	No recent IPV history (n = 35)	Recent IPV history (n = 129)	*p*-value
Age	32 (26.5 to 38.5)	31 (26 to 37)	0.371
Age started sex work	25 (22 to 30)	20 (18 to 26)	<0.001
Years in sex work	6 (3 to 9.5)	8 (4 to 13)	0.053
Level of education			
Primary education or less	17 (48.6%)	57 (44.2%)	0.211
Secondary education	11 (31.4%)	58 (45%)	
Postsecondary education	7 (20%)	14 (10.9%)	
Casual clients per week	4 (3 to 5.5)	4 (3 to 7)	0.382
Regular clients per week	5 (3.5 to 6)	5 (3 to 9)	0.947
Minimum fee for vaginal sex (KSH)	500 (300 to 1000)	500 (300 to 900)	0.654
History of sexually transmitted infection	16 (47.1%)	85 (65.9%)	0.07
Client violence (past 12 months)			
Any client violence	16 (45.7%)	113 (87.6%)	<0.001
Emotional	14 (40%)	100 (77.5%)	<0.001
Physical	8 (22.9%)	72 (55.8%)	0.001
Sexual	12 (34.3%)	98 (76%)	<0.001
Other violence (past 12 months)			
Any other violence	13 (37.1%)	66 (51.2%)	0.2
Emotional	12 (34.3%)	66 (51.2%)	0.114
Physical	9 (25.7%)	51 (39.5%)	0.191
Sexual	3 (8.6%)	31 (24%)	0.077
PHQ9	7 (5 to 10.50)	12 (9 to 14)	<0.001
≥10	11 (31.4%)	84 (65.1%)	0.001
GAD7	5 (3 to 9.5)	9 (6 to 13)	0.001
≥10	9 (25.7%)	55 (42.6%)	0.104
PrEP use			
Current optimal user	12 (35.3%)	55 (43.3%)	0.198
Current sub-optimal user	2 (5.9%)	5 (3.9%)	
Never used	18 (52.9%)	46 (36.2%)	
Past user	2 (5.9%)	21 (16.5%)	

Continuous variables are reported as median (interquartile range) unless otherwise specified. Continuous variables evaluated with Welch's t-test if normally distributed or Mann–Whitney U test if non-normally distributed. Categorical variables evaluated with chi-square or Fisher's exact test whenever appropriate. FSW, female sex workers; IPV, intimate partner violence; PHQ9, Patient Health Questionnaire-9; GAD7, Generalized Anxiety Disorder-7; PrEP, pre-exposure prophylaxis; KSH, Kenyan Shilling.

Next, we assessed associations of PrEP use with mental health based on total depressive and generalized anxiety scores. Depressive symptomatology did not differ between PrEP users ($\bar{x}$ = 10.48) and non-users ($\bar{x}$ = 11.38), nor did anxiety scores between PrEP users ($\bar{x}$ = 8.69) and non-users ($\bar{x}$ = 9.10), (both $p > 0.05$). Neither depression or anxiety significantly predicted PrEP use in subsequent multivariable logistic regression (Table 6).

4 | DISCUSSION

There is high HIV incidence and prevalence among FSW in sub-Saharan Africa [2], and PrEP is a highly effective HIV prevention tool [9,10]. However, the uptake of PrEP within these communities has been suboptimal [34]. Given the prior linkage of violence with both HIV acquisition and adverse mental health outcomes, the aim of our study was to explore the associations between specific types of IPV and client-perpetrated violence, mental health outcomes, and the uptake of effective HIV prevention services (PrEP) among FSW from Nairobi, Kenya. Our goal was to identify barriers to effective HIV prevention that may constitute targets for future interventions. We found that emotional, physical and sexual violence were very common among Nairobi FSW; participants who had experienced any of these forms of violence, regardless of the perpetrator, were more likely to experience depressive and generalized anxiety symptoms, although the strongest associations were with emotional IPV. A history of sexual IPV (but not other forms of violence) was associated with enhanced PrEP uptake; furthermore, client-perpetrated physical violence was linked to increased PrEP use, whereas client-perpetrated emotional violence was associated with decreased PrEP use. These findings suggest that interventions to reduce

Table 3. Demographics of FSW based on the experience of any client-perpetrated violence in the last 12 months

Characteristic	No recent client violence history (n = 42)	Recent client violence history (n = 178)	*p*-value
Age	32 (26.25 to 38.75)	32 (27 to 39)	0.759
Age started sex work	24 (20 to 30)	23 (18.25 to 28)	0.156
Years in sex work	6.5 (2 to 10)	7 (4 to 13)	0.147
Level of education			
Primary education or less	19 (45.2%)	86 (48.3%)	0.846
Secondary education	17 (40.5%)	72 (40.4%)	
Postsecondary education	6 (14.3%)	20 (11.2%)	
Casual clients per week	4 (3 to 5)	4 (3 to 7.75)	0.304
Regular clients per week	4.5 (3 to 6.75)	5 (3 to 8)	0.552
Minimum fee for vaginal sex (KSH)	500 (300 to 1000)	500 (200 to 500)	0.155
History of sexually transmitted infection	16 (39%)	126 (70.8%)	<0.001
IPV (past 12 months)			
Any IPV (past 12 months)	16 (45.7%)	113 (87.6%)	<0.001
Emotional	11 (31.4%)	98 (76%)	<0.001
Physical	10 (28.6%)	84 (65.6%)	<0.001
Sexual	6 (17.1%)	88 (68.2%)	<0.001
Other violence (past 12 months)			
Any other violence	6 (14.3%)	103 (57.9%)	<0.001
Emotional	5 (11.9%)	103 (57.9%)	<0.001
Physical	5 (11.9%)	83 (46.6%)	<0.001
Sexual	3 (7.1%)	47 (26.4)	0.013
PHQ9	7.5 (5 to 11.75)	11 (9 to 14)	<0.001
≥10	14 (33.3%)	111 (62.4%)	0.001
GAD7	5.5 (3 to 8.75)	9 (6 to 13)	<0.001
≥10	9 (21.4%)	77 (43.3%)	0.015
PrEP use			0.338
Current optimal user	17 (41.5%)	74 (42.5%)	
Current sub-optimal user	1 (2.4%)	8 (4.6%)	
Never used	20 (48.8%)	64 (36.8%)	
Past user	3 (7.3%)	28 (16.1%)	

Continuous variables are reported as median (interquartile range) unless otherwise specified. Continuous variables evaluated with Welch's t-test if normally distributed or Mann–Whitney U test if non-normally distributed. Categorical variables evaluated with chi-square or Fisher's exact test whenever appropriate. FSW, female sex workers; GAD7, Generalized Anxiety Disorder-7; IPV, intimate partner violence; KSH, Kenyan Shilling; PHQ9, Patient Health Questionnaire-9; PrEP, pre-exposure prophylaxis.

gender-based violence may independently enhance HIV prevention and reduce the mental health burden in this community.

The fact that FSW who used PrEP were more likely to have experienced sexual IPV, and that client-perpetrated physical violence was associated with increased PrEP use, is in keeping with a systematic review by Mugo and colleagues [22] who found that PrEP uptake, adherence and retention in Africa is enhanced in persons who perceive themselves to be at high risk for HIV infection. Clearly, women who have experienced sexual IPV may feel particularly vulnerable, given that sex is the most common route of HIV transmission [2], and FSW find it more difficult to use male condoms with their intimate partners compared to casual clients [35]. Indeed, it is likely due to these barriers that intimate partners have been found to contribute more to HIV transmission in FSW communities than casual clients [35,36]. Our results support independent modelling studies which suggested that the elimination of sexual violence alone would avert 17% of HIV infections in Kenya among FSW and their clients in the next decade [37]. Furthermore, client-perpetrated emotional violence in our community was independently linked to decreased PrEP use, supporting literature which suggest that different patterns of violence among FSW in Kenya are associated with distinct sexual risk outcomes [21]. Together, these findings have important implications for strategies aiming to reduce gender-based violence against FSW, not only as a fundamental human right but also to reduce the community spread of HIV/AIDS.

In our study, women who experienced intimate partner or client-perpetrated emotional, physical or sexual violence displayed higher levels of depressive and generalized anxiety symptoms. This is in accordance with a recent study by Roberts and colleagues [21] in Mombasa, Kenya which found that women with severe gender-based violence had higher scores for depressive symptoms, post-traumatic stress disorder

Table 4. Univariable and multivariable logistic regression models of probable depression among FSW

	Univariable		Multivariable v1 n = 163		Multivariable v2 n = 220	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
IPV emotional	7.36 (3.55, 15.3)	<0.0001	7.52 (2.76, 20.5)	<0.0001		
IPV physical	2.49 (1.31, 4.73)	<0.01	0.71 (0.28, 1.82)	0.48		
IPV sexual	2.41 (1.28, 4.56)	<0.01	0.83 (0.32, 2.18)	0.7		
Client emotional violence	3.5 (1.86, 6.57)	<0.0001	1.39 (0.46, 4.18)	0.56		
Client physical violence	2.41 (1.39, 4.16)	<0.01	1.95 (0.73, 5.2)	0.18		
Client sexual violence	2.21 (1.24, 3.94)	<0.01	0.87 (0.3, 2.47)	0.79		
Other emotional violence	2.41 (1.39, 4.16)	<0.01	1.25 (0.37, 4.29)	0.72		
Other physical violence	2.4 (1.36, 4.23)	<0.01	1.23 (0.34, 4.52)	0.75		
Other sexual violence	3.46 (1.66, 7.21)	<0.001	2.24 (0.62, 8.07)	0.22		
Secondary education	3.11 (1.71, 5.65)	<0.001	3.86 (1.63, 9.16)	<0.01	3.41 (1.81, 6.44)	<0.001
Postsecondary education	2.05 (0.85, 4.94)	0.11	1.48 (0.4, 5.53)	0.56	2.01 (0.73, 5.54)	0.18
Minimum fee vaginal sex (per 100 KSH)	1.02 (0.99, 1.06)	0.17	1.01 (0.97, 1.05)	0.77	1.02 (0.98, 1.06)	0.34
Years in sex work	0.99 (0.95, 1.03)	0.68	0.99 (0.93, 1.06)	0.76	0.99 (0.95, 1.04)	0.71
Casual clients per week	0.98 (0.93, 1.03)	0.35	0.96 (0.89, 1.02)	0.17	0.98 (0.93, 1.03)	0.38
Any violence	7.07 (2.31, 21.7)	<0.001			9.39 (2.9, 30.4)	<0.001

FSW, female sex workers; IPV, intimate partner violence; KSH, Kenyan Shilling.

Table 5. Univariable and multivariable logistic regression models of probable anxiety among FSW

	Univariable		Multivariable v1 n = 163		Multivariable v2 n = 220	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
IPV emotional	3.27 (1.56, 6.87)	<0.01	3.61 (1.33, 9.76)	0.01		
IPV physical	1.48 (0.78, 2.83)	0.23	0.72 (0.3, 1.71)	0.46		
IPV sexual	1.97 (1.02, 3.78)	0.04	1.21 (0.49, 2.96)	0.68		
Client emotional violence	2.24 (1.15, 4.35)	0.02	1.67 (0.58, 4.83)	0.34		
Client physical violence	1.47 (0.85, 2.55)	0.16	0.88 (0.36, 2.17)	0.78		
Client sexual violence	1.73 (0.94, 3.17)	0.08	0.73 (0.26, 2.01)	0.54		
Other emotional violence	2.13 (1.23, 3.7)	<0.01	0.57 (0.17, 1.91)	0.36		
Other physical violence	2.52 (1.44, 4.41)	<0.01	3.4 (0.97, 12)	0.06		
Other sexual violence	2.46 (1.29, 4.67)	<0.01	1.25 (0.42, 3.66)	0.69		
Secondary education	2.04 (1.13, 3.67)	0.02	1.53 (0.72, 3.29)	0.27	2.21 (1.21, 4.04)	<0.01
Postsecondary education	1.96 (0.81, 4.69)	0.13	3.58 (0.99, 12.9)	0.05	3.12 (1.16, 8.44)	0.02
Minimum fee vaginal sex (per 100 KSH)	0.98 (0.95, 1.01)	0.26	0.95 (0.91, 1)	0.04	0.97 (0.93, 1.01)	0.09
Years in sex work	1 (0.97, 1.05)	0.82	0.98 (0.92, 1.04)	0.49	1 (0.96, 1.04)	0.95
Casual clients per week	1 (0.95, 1.05)	0.88	0.98 (0.92, 1.04)	0.48	0.99 (0.94, 1.04)	0.62
Any violence	3.18 (1.04, 9.75)	0.04			3.47 (1.1, 10.9)	0.03

FSW, female sex workers; IPV, intimate partner violence; KSH, Kenyan Shilling.

symptoms and disordered alcohol use, and concluded that PrEP would be an important HIV prevention tool in the community. While our own study found mental health to be more strongly linked with emotional IPV specifically, other recent research also suggests that emotional IPV may be a particularly important contributor to adverse mental health outcomes [38]. This may be especially true in FSW who often depend on their intimate partners for basic survival needs [39]. Our study extends these findings by defining specific associations between mental health and both perpetrator and violence type, and by assessing associations of generalized anxiety symptoms, which were also extremely prevalent among our participants.

Table 6. Univariable and multivariable logistic regression models of current PrEP use among FSW

	Univariable		Multivariable v1 n = 160		Multivariable v2 n = 160	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
IPV emotional	1.31 (0.67, 2.54)	0.43	0.95 (0.38, 2.36)	0.9	1.2 (0.45, 3.21)	0.71
IPV physical	1.45 (0.77, 2.74)	0.25	1.31 (0.57, 3.04)	0.52	1.29 (0.55, 3)	0.55
IPV sexual	2.23 (1.17, 4.25)	0.01	1.99 (0.82, 4.82)	0.13	2.03 (0.83, 4.96)	0.12
Client emotional violence	0.95 (0.52, 1.75)	0.88	0.23 (0.07, 0.71)	0.01	0.24 (0.08, 0.74)	0.01
Client physical violence	1.34 (0.78, 2.3)	0.29	3.01 (1.16, 7.81)	0.02	3.2 (1.22, 8.41)	0.02
Client sexual violence	1.58 (0.88, 2.84)	0.13	1.75 (0.64, 4.81)	0.28	1.7 (0.62, 4.7)	0.31
Other emotional violence	1.27 (0.74, 2.18)	0.38	0.45 (0.14, 1.48)	0.19	0.44 (0.13, 1.46)	0.18
Other physical violence	1.54 (0.89, 2.66)	0.12	2.49 (0.73, 8.48)	0.15	2.7 (0.78, 9.35)	0.12
Other sexual violence	1.64 (0.87, 3.11)	0.13	1.54 (0.51, 4.65)	0.44	1.7 (0.55, 5.18)	0.35
Secondary education	0.97 (0.55, 1.72)	0.91	1 (0.47, 2.12)	0.99	1.16 (0.53, 2.55)	0.71
Postsecondary education	1.52 (0.63, 3.66)	0.35	2.45 (0.68, 8.79)	0.17	2.7 (0.74, 9.8)	0.13
Minimum fee vaginal sex (per 100)	0.98 (0.95, 1.01)	0.19	0.97 (0.93, 1)	0.08	0.96 (0.93, 1)	0.08
Years in sex work	1.02 (0.98, 1.06)	0.42	0.95 (0.9, 1.01)	0.08	0.95 (0.89, 1)	0.06
Casual clients per week	1 (0.95, 1.05)	0.99	0.97 (0.91, 1.03)	0.32	0.96 (0.9, 1.02)	0.23
Depressive symptoms	0.67 (0.39, 1.16)	0.15			0.62 (0.25, 1.55)	0.3
Anxiety symptoms	0.82 (0.47, 1.42)	0.48			0.78 (0.33, 1.84)	0.58

FSW, female sex workers; IPV, intimate partner violence; KSH, Kenyan Shilling.

Although our study did not find depression or anxiety to be associated with PrEP use, mental health concerns were still very prevalent in this community. Others have demonstrated that depression, but not anxiety, decreased antiretroviral treatment adherence among women living with HIV [40], but our findings are important in the context of antiretrovirals for prevention, particularly given the very high rates of depression and generalized anxiety in this sex worker community. While interventions exist that focus on integrating culturally sensitive mental health services into Kenyan communities [41-43], these services may be failing to reach key vulnerable populations. A recent systematic review and meta-analysis on mental health in FSW in low- and middle-income countries did not find any single intervention that was designed to address mental disorders among FSW [16]. Research in this field is urgently needed in order to provide effective evidence-based mental healthcare to this key population. Specific programmes have been shown to be effective in reducing violence against women in Uganda and Tanzania [44,45], as well as violence against FSW in South India, and these may serve as the basis for developing programmes targeting FSW in Kenya [46]. In addition, existing programmes in Nairobi, Kenya that have demonstrated success in reducing violence against girls through empowerment, such as the IMPower/SOS programme, could be adapted for use in FSW populations [47].

Despite these important findings, our study has potential limitations. Questionnaires were only administered to FSW attending KACP clinics, and data could only be assessed from those attendees who agreed to participate. Therefore, it remains unknown to what extent the results apply to FSW not in care, who accessed other services, or who declined the questionnaire. In addition, the use of a facility-based convenience sample may have led to our study having an enriched enrolment of FSW taking PrEP. Our study is cross-sectional in design, and so the direction of causation cannot be defined for the associations that we describe. Furthermore, reporting bias (overreporting of PrEP and/or underreporting of violence) may have skewed associations. Our results may have been confounded by other unmeasured factors, such as adverse childhood experiences, violence predating the 12-month time frame, indirect cost of accessing services, or other non-measured reasons for non-adherence to PrEP such as fear of side effects. Nonetheless, our results have clear implications for quality improvement within the programme and merit broader consideration within female sex worker clinics elsewhere.

5 | CONCLUSIONS

In summary, this study demonstrates that among FSW attending KACP clinics in Nairobi, Kenya, those who experience sexual IPV were more likely to use PrEP, whereas client-perpetrated violence differentially affected the use of PrEP medication. Women who experienced any form of emotional, physical or sexual violence currently had greater symptomatology for depression and generalized anxiety, with emotional IPV particularly associated with mental health symptomatology. These findings stress the importance of developing targeted strategies aimed at addressing gender-based violence for FSW, while also providing mental health support services particularly to women who have suffered from these abuses.

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COMPETING INTERESTS

The authors declare no conflicts of interest exist.

AUTHORS' CONTRIBUTIONS

ML, MM, TB, RK and JK designed and conceived the study. AK[1] and LS performed the data analyses. ML and AK[1] wrote the manuscript. ML, MM, AK[2] and JK coordinated data collection and management. All authors critically reviewed, edited and approved the final manuscript.

ABBREVIATIONS

FSW, female sex workers; GAD7, Generalized Anxiety Disorder-7; IPV, intimate partner violence; KACP, Kenya Aids Control Project; PHQ9, Patient Health Questionnaire-9; PrEP, pre-exposure prophylaxis; VAWI, Violence Against Women Instrument.

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REVIEW

Prevalence and factors associated with common mental disorders in young people living with HIV in sub-Saharan Africa: a systematic review

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Abstract

Introduction: Common mental disorders (CMDs) particularly depression and anxiety, are highly comorbid with HIV also in young people living with HIV (YLWH). In sub-Saharan Africa (SSA) where most YLWH reside, there are limited summary data on CMDs among these youths, yet there are previous systematic reviews summarizing data on CMDs among adults living with HIV. We conducted a systematic literature review on the prevalence and correlates of CMDs among YLWH, aged 10 to 24 years, from SSA.

Methods: We searched African Index Medicus, African Journals Online and five other electronic databases (from database inception up to 31 December 2020) for relevant studies published in English. The key search terms applied were as follows: "Depression OR Anxiety", "Young people", "HIV infections" and "sub-Saharan Africa".

Results and discussion: Out of 3989 articles, 31 studies were included in the review. The prevalence of CMDs in YLWH widely varied ranging between 16.0% and 40.8% for major depression, 4.4% and 52.6% for depressive symptoms and 2.2% and 25.0% for anxiety symptoms. Anxiety disorder was estimated at 45.6%. Four of the five included studies with a comparison group of HIV-negative young people reported significantly higher prevalence estimates of depressive disorders among YLWH. Several sociodemographic, psychosocial and HIV-related correlates of CMDs were reported but most lacked consensus across studies. Nevertheless, female sex, older age, fewer schooling years, HIV-positive status, bullying, sexual abuse, HIV-related stigma, social support and poor antiretroviral therapy adherence were frequently reported (in ≥2 studies) as significant correlates of depressive symptoms among YLWH. Higher social support was the only frequent significant correlate of anxiety symptoms.

Conclusions: The burden of CMDs among YLWH from SSA is substantial and appears to be significantly higher when compared with HIV-negative peers, particularly for depressive disorders. However, more comparative research is needed. Importantly, screening for CMDs at the youth HIV-clinics should be prioritized especially for YLWH at high risk of CMDs, to facilitate early management or referral for treatment. Furthermore, youth-friendly psychological interventions addressing CMDs in YLWH should urgently be piloted in SSA, incorporating contextual components that may directly or indirectly reduce symptoms of CMDs among YLWH, such as social support.

Keywords: young people; HIV infections; depression; anxiety; correlates; sub-Saharan Africa

Additional Supporting information may be found online in the Supporting Information tab for this article.

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1 | INTRODUCTION

Globally, there are over 1.8 billion young people aged 10 to 24 years, the majority residing in low- and middle-income countries [1]. The term "young people" generally combines the overlapping terms of "adolescents," that is individuals in the 10- to 19-year age group and "youths," that is the 15- to 24-year age group [2] and will be used to refer to both age groups in this work. Young people represent a significant proportion of people living with HIV. As of 2018, 1.6 million young people aged 10 to 19 years were living with HIV globally [3], whereas 3.9 million young people aged 15 to 24 years

lived with HIV worldwide by 2014 [4]. Most of these young people were infected through vertical transmission and live in sub-Saharan Africa (SSA) [5,6].

Common mental disorders (CMDs), herein referring to depressive and anxiety disorders or their symptoms, are very frequent in people living with HIV [7-9] and the risk is two to three times higher than the general population [10]. Among young people living with HIV (YLWH), global reviews [5,11,12] report the prevalence of comorbid CMDs as high as 44.0% for depressive disorders and 48.2% for anxiety disorders. In recent reviews on the burden of psychiatric disorders among YLWH aged 10 to 19 years in SSA [13,14], depressive and anxiety symptoms ranged from 14% to 53% and 15% to 25% respectively. The burden of CMDs may also be higher in YLWH than their peers without HIV [15] or even other vulnerable groups of young people, such as those in juvenile detention [16]. The higher risk of CMDs in people living with HIV, including the youth, may be caused by side effects of antiretroviral therapy (ART) [17,18], persistent HIV-related stigma in the community [19,20], the direct and indirect neurologic effects of HIV on the brain [21] and the fear of premature death [22]. There are detrimental consequences when CMDs co-occur with HIV including worsened prognosis of HIV infection [23], increased risk of suicidality [24], non-adherence to ART [25], poor quality of life [26] and alteration of economic productivity of people living with HIV [23].

Previous global reviews [5,11,12] and one recent review from SSA [13] have reported on factors associated with CMDs among YLWH, but there is little or no consensus across individual studies included in these reviews. Notably, most of the studies included in the global reviews have been conducted in Western countries (Europe and North America). Only four out of the 14 studies included in the review from SSA reported a few correlates of CMDs. Nevertheless, female sex [16,27], older age [28-30], poor adherence to ART [31,32], stressful life events [33,34], parental or caregiver mental health status [15,27,35], maternal HIV-positive status [15,29], low cluster of differentiation-4 (CD4) cell count [27,36] and history of AIDS-defining illness [36,37] appear important correlates of CMDs in YLWH as they are reported by more than one study in the aforementioned reviews. Extrapolating findings from especially reviews of global nature to inform interventions seeking to address the mental health of YLWH from settings such as SSA may be problematic because of contextual differences (especially where very few of the studies included are from the setting targeted for intervention). With the increasing research effort towards an understanding of the mental health of people living with HIV from SSA [38], including the youth [39-41], there is a need for a greater understanding of context-specific factors associated with CMDs among people living with HIV from this setting.

The increasing mental health issues among YLWH is an emerging public health concern with the potential of burdening the already busy healthcare systems and the scarce human resources in mental healthcare in resource-limited settings like those of SSA [7,23]. Hitherto, no study has extensively summarized data on the burden and contextual determinants of CMDs among YLWH from SSA, a region where most of these HIV-positive young people reside. While there have been several global reviews trying to understand the burden of mental health problems among YLWH [5,11,12], most of the studies included have been conducted outside SSA, limiting the generalizability of their findings to the African context. Past systematic reviews on the burden of CMDs among people living with HIV from SSA [9,38,42] have only considered studies recruiting adults living with HIV sidelining YLWH who currently represent a considerable percentage of people living with HIV. The recent systematic reviews involving YLWH from SSA [13,14] are limited to young people aged 10 to 19 years only and broadly focus on many psychiatric disorders. For the current systematic review, the overall objective was to summarize the available evidence on the prevalence and factors associated with CMDs among YLWH aged 10 to 24 years from SSA. The specific objectives of this review were:

1 To systematically summarize the existing literature on the prevalence of CMDs, specifically depressive and anxiety disorders, or their symptoms, among YLWH aged 10 to 24 years from SSA alongside information on measurement tools used and their contextual reliability and/or validity.
2 To systematically identify the factors associated with CMDs, specifically depressive and anxiety disorders or their symptoms, among YLWH aged 10 to 24 years from SSA.

The added value of this review is two-fold. First, by extending the review age range, we include young people regarded as adults (societally and/or by law) who are expected to take care of themselves, most often outside the family context, with implications for an arrangement of mental health support. Second, although the recent reviews from SSA give important information on the prevalence and range of mental disorders in YLWH, the review by Olashore *et al.* [14] only addresses the association of these disorders with ART adherence. In both reviews [13,14], their approach limits the possibility to understand which contextual factors importantly relate to CMDs, the most frequent of the psychiatric disorders. This review addresses this gap.

2 | METHODS

2.1 | Search strategy

The Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [43] informed the design and reporting of this systematic review. The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42020160806. Structured electronic searches were initially conducted in African Index Medicus, African Journals Online, Google Scholar, PsycArticles, PsycInfo, PubMed and Web of Science Core collection databases between 3 and 24 December 2019. The search was later updated in January 2021 to capture publications up to 31st December 2020. Where applicable, databases were searched from the time of their inception. The key search terms included "Depression/Anxiety", "Young people", "HIV infections" and "sub-Saharan Africa" which were combined by the Boolean operator "AND". Synonyms for each of the key search terms were combined using the "OR" Boolean operator. Where applicable, Medical Subject Headings (MeSH) terms were used. (Additional file S1) provides the search string used in the PubMed database,

which was modified to meet the specifications for other databases.

The search was restricted to studies published in the English language, where a database could allow this filter. All the retrieved references were exported and managed in EndNote version 7. An additional search for relevant articles was conducted by scanning the reference lists of included articles and any relevant systematic reviews captured in the initial search.

2.2 | Screening of articles by inclusion and exclusion criteria

For potential inclusion, all the articles returned from the database searches were screened in two steps: i) based on title and abstract and ii) by full text. The first author (ET) screened the articles for eligibility. To reduce bias that may arise from human error, two other reviewers (CN and MKN) independently repeated 10% of the study screening at every stage through a systematic random selection of articles divided into two halves, each for the independent reviewers. Rates of agreement between each of the independent reviewers and the first reviewer were consistently high, and minor disagreements were settled through consensus. To be included for review, studies had to fulfil a pre-determined inclusion and exclusion criteria as shown in Table 1.

2.3 | Data extraction

ET and MKN independently extracted the following data from included studies using a standardized Microsoft Excel data abstraction form: (i) Article details – name of the first author, title and publication year; (ii) Study details – country of origin, study design, study setting, data collection period and response rate (where reported) and the reported study limitations; (iii) Study participant characteristics – HIV-related data (mode of acquisition, time since diagnosis, ART regimen and duration on ART treatment), sample size, sampling method, source of the sample, age (mean, median, or range) and sex (proportion of male vs. female); (iv) Outcome and measures – prevalence of depression and anxiety, or their symptoms, measurement tool used, cut off score applied (for screening tools), information on local tool validation, factors associated with depression and anxiety or their symptoms (alongside the reported measure of effect and precision estimate).

2.4 | Quality assessment

ET and MKN independently assessed the risk of bias of each included study using the Newcastle–Ottawa Scale [44]. These authors then held a meeting to resolve any disagreements in quality rating. Using this tool, studies were assessed based on three domains: the selection of participants, comparability of study groups and the ascertainment of exposure (for case–control studies) or outcome of interest (for cohort and cross-sectional studies). A star-grading system was used, with each domain item receiving one or two stars if appropriate methods were reported. A maximum of nine stars was awarded for cohort and case–control studies, and a maximum of 10 stars for cross-sectional studies. Studies were classified as unsatisfactory, satisfactory, good and very good if they had a total of 0 to 4, 5 to 6, 7 to 8 and 9 to 10 stars respectively.

Table 1. Study selection criteria

Inclusion criteria	Exclusion criteria
Population	
- Studies with HIV-positive young people from SSA. - Studies with participants aged 10 to 24 years or with mean/median age within this age bracket.	- Studies involving HIV-positive young people outside SSA. - Studies involving HIV-negative young people or with HIV-positive participants outside the 10 to 24 age range. - Studies with unspecified age range, mean or median age of participants. - Studies with very specific subpopulations of young people e.g. pregnant women, out-of-school adolescents et cetera.
Outcome	
- Studies on depression or depressive symptoms and associated factors. - Studies on anxiety disorder or anxiety symptoms and associated factors.	- Studies on mental disorders other than depression or anxiety, or their symptoms. - Studies using measurement scales evaluating both anxiety and depression without providing separate data. - Studies where reported measurement scales do not evaluate depression or anxiety, or their symptoms.
Study designs	
- Cross-sectional studies - Case-control studies - Cohort studies	- Review articles e.g. narrative, systematic, scoping - Intervention studies - Case studies/reviews - Commentaries or editorials - Conference proceedings, symposia abstracts, or workshop publications - Qualitative studies - Books or book sections - Theses and dissertations

Studies with a comparison group of HIV-negative young people and providing disaggregated mental health data by HIV infection status were included. Studies duplicating similar project data to an already included main and more comprehensive article were excluded. SSA, sub-Saharan Africa.

2.5 | Data analysis

Because of the heterogeneous nature of measurement tools used across included studies, data were narratively summarized. Data on the prevalence of CMDs among YLWH were summarized by each homogeneous measurement tool used, whereas data on correlates of CMDs were summarized by the investigated outcome (depression or anxiety). We manually

calculated the odds ratio using the reported proportions from individual studies comparing the prevalence of CMDs between YLWH and their HIV-negative peers. In this review, only factors significantly associated with either depression or anxiety, or their symptoms at $p < 0.05$ in the multivariable analysis were considered and extracted as correlates. Basic descriptive statistics (frequencies with percentages) were used to summarize data on the region of SSA where each of the included studies was conducted.

3 | RESULTS AND DISCUSSION

The electronic search yielded 3988 hits from the different databases (African Index Medicus, n = 11, African Journals Online, n = 147, Google Scholar, n = 2137, PsycArticles, n = 8, PsycInfo, n = 865, PubMed, n = 302 and Web of Science, n = 518). A scan of the reference lists of included articles and relevant systematic reviews captured by the search yielded one additional article. After removing duplicates and screening articles based on the eligibility criteria, we included 31 studies in the review. Figure 1 shows the PRISMA flowchart for the systematic review process.

3.1 | Characteristics of included studies

(Additional file S2) presents in detail the characteristics of the 31 included studies. The reviewed studies were mostly conducted in Eastern (n = 13; 41.9%) or Southern (n = 13; 41.9%) African countries except four studies [45-48] that were conducted in a Western African country (12.9%) and one study (3.2%) from Central Africa [49]. The included studies enrolled a total of 9935 YLWH (individual study sample size ranging from 58 to 1088). Additionally, the studies with a comparison group enrolled 1000 HIV-negative young people (individual study sample size ranging from 44 to 600).

Many of the studies (n = 29) were cross-sectional in design and published after 2010, except two studies [47,50]. A review of the literature on depression among HIV-positive adults from SSA [38] also observed that most of the studies included were conducted after 2010. It is, therefore, encouraging to note that from the beginning of the last decade, there is an upsurge of research work towards an understanding of the mental health of people living with HIV in Africa with the potential to inform clinical practice and policy.

Many of the studies were conducted in urban settings of SSA (n = 20). Nearly all studies (n = 29) recruited YLWH from HIV-specialized clinics except one study [51] that recruited from the community. In one study [52], this information could not be retrieved because the study was only available in abstract form (see study quality section for details). YLWH were exclusively on ART in most studies (n = 17). Eight studies [46,53-59] recruited ART experienced (majority) and ART naïve participants, whereas six studies [45,48,60-63] did not provide information on participant ART-use status. In eight studies [52,55,59,61,64-67] YLWH were exclusively perinatally HIV-infected. Five studies [45,49,58,68,69] had a mixture of perinatally and behaviourally HIV-acquired youths; the rest (18 studies) did not provide information on the mode of HIV infection. Outside Africa, certain characteristics of YLWH like mode of HIV infection (behavioural vs. perinatal) [8,70] and ART-use status (ART naïve vs. ART experienced) [38] may influence their mental health experiences. In this review, none of the studies recruiting a mix of participants provided disaggregated mental health data by any of these characteristics. An in-depth investigation of this nature in the African context will require researchers working with a mixed sample of YLWH to collect and profile disaggregated mental health data by, for example mode of HIV infection or ART-use status. Additional data on CMDs among YLWH residing in rural settings of SSA are also needed, so far, research focus has been biased towards urban settings.

3.2 | Measurement tools for CMDs, their reliability and validity among YLWH from SSA

CMDs in YLWH from SSA were assessed using both diagnostic tools and symptom screeners. Diagnostic tools used in this study included the Mini-International Neuropsychiatric Interview for children and adolescents (MINI-KID) [71] used in three studies [45,46,64] to diagnose major depression and the tenth revision of the International Classification of Diseases (ICD-10) symptom checklist [72] used by Musisi and Kinyanda [50] to diagnose major depression and anxiety disorder. The other studies used different types of CMD symptom screeners. Kinyanda *et al.* [55] used the 5th edition of the Diagnostic and Statistical Manual (DSM) of mental disorders referenced Child and Adolescent Symptom Inventory-5 (CASI-5) [73] and the fourth revision of the Youth Inventory (YI-4R) [74] to assess symptoms of major depression, any anxiety disorder, generalized anxiety disorder, social and separation anxiety disorders. Buckley *et al.* [65] used the DSM (4th edition) referenced 84-item Patient Health Questionnaire for Adolescents (PHQ-A) [75] to assess symptoms of major depression and anxiety disorder (specifically panic disorder). Various screening tools based on different cut-off scores were also used to measure depressive (Table 2) or anxiety symptoms (Table 3). These screening tools included the 9-item patient health questionnaire [76] used in six studies [49,53,57,60,77, 78], the centre for epidemiologic studies depression scale [79] used in four studies [51,54,56,62], the child depression inventory [80] used in four studies [58,59,81,82], Beck's depression inventory [83] used in three studies [48,61,84], the revised children's depression rating scale [85] used by Kim *et al.* [28], the hospital anxiety and depression scale [86] used by Sale & Gadanya [47], Reynold's adolescent depression Scale [87] used by Paul *et al.* [63], National Institute of Health toolbox – Sadness module [88] used by Molinaro *et al.* [52], the Beck's youth inventory [89] used in two studies [66,67] and the revised children's manifest anxiety scale [90] used in two studies [58,59]. Most studies did not report information on the reliability and/or validity of these measurement tools among YLWH. In some studies, where this information was not provided, authors pointed out that the tool they used was previously validated in the study country or provided a reference to the tool validation process (see Tables 2 and 3). Where reported, information on tool reliability and/or validity was mostly limited to Cronbach's alpha, a measure of internal consistency of a scale, and values were above the acceptable threshold of 0.7.

For any meaningful epidemiological data that can inform appropriate interventions, there is a need for future studies

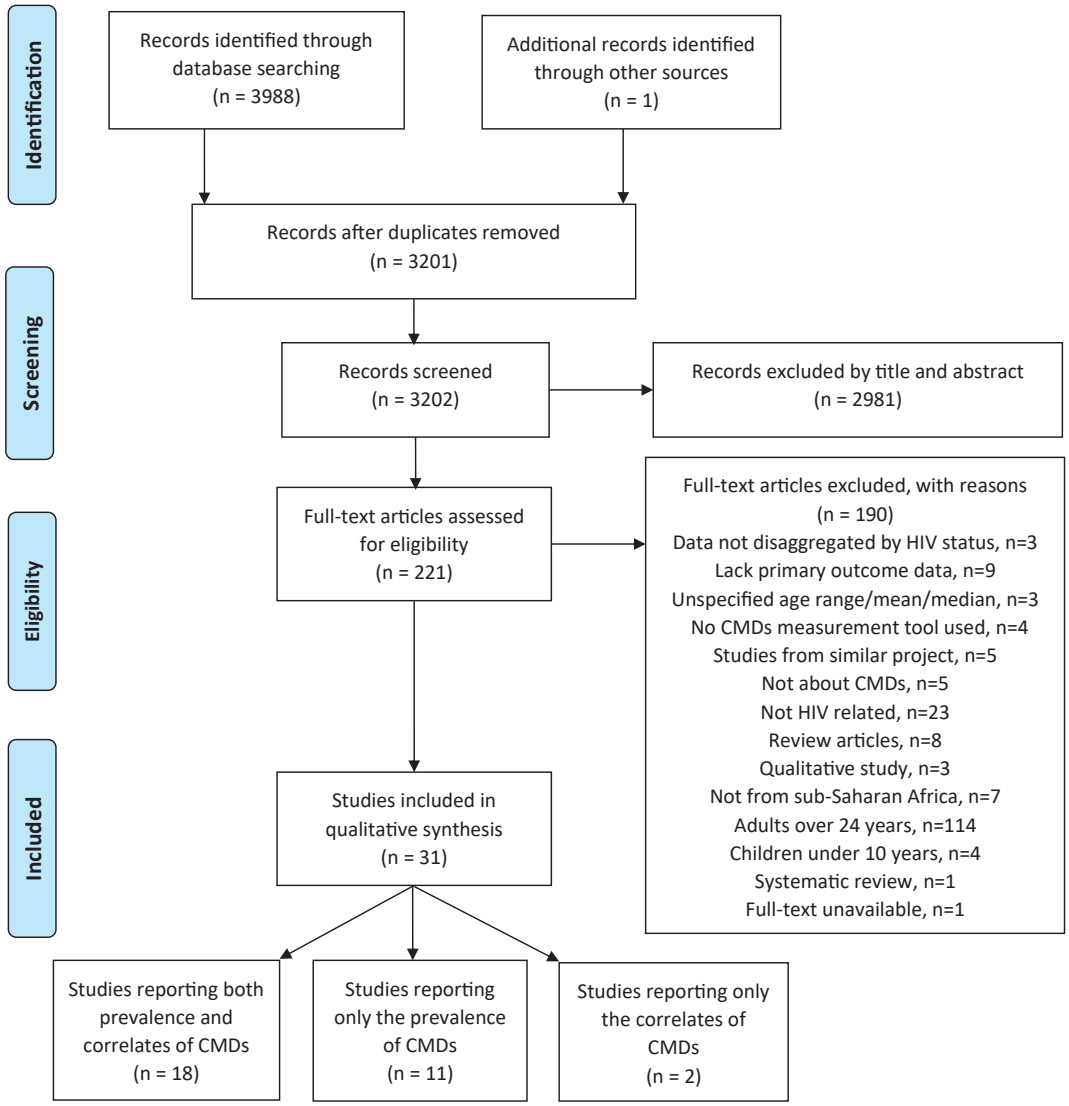

Figure 1. PRISMA flowchart for the systematic review process. CMDs, common mental disorders.

involving YLWH in SSA to measure CMDs using culturally appropriate and locally validated tools. Where feasible, validated mental health diagnostic measures should be administered concurrently to check the diagnostic accuracy of these mental health screening tools.

3.3 | Prevalence of CMDs among YLWH from SSA

Twenty-nine studies reported the prevalence of either major depression or depressive symptoms [45-67,77,78,81]. Of these, seven studies [50,55,58,59,65,66,78] additionally reported the prevalence of anxiety or its symptoms. No study investigated the prevalence of anxiety or its symptoms as a stand-alone mental disorder among YLWH. Tables 2 and 3 present the prevalence of depressive and anxiety disorders (or their symptoms according to the screening tool used), as reported from the above studies.

In summary, wide-ranging prevalence estimates of CMDs were reported among YLWH. The prevalence of major depression ranged between 16.0% and 40.8% [45,46,50,64]. A prevalence of 5.2% for symptoms of major depression was reported by a Ugandan study [55]. When comparing YLWH and their HIV-negative peers [65], the observed prevalence of symptoms of major depression was 6.2% and 7.4% respectively. Regardless of the screening tool used, depressive symptoms ranged between 4.4% and 52.6%. The prevalence of anxiety disorder among YLWH from Uganda was 45.6% [50]. When comparing YLWH and their HIV-negative peers [65], the observed prevalence of symptoms of panic disorder was 3.7% and 2.5% respectively. Regardless of the screening tool used, anxiety symptoms ranged between 2.2% and 25.0%. Wide-ranging CMD prevalence estimates have been documented in past reviews involving YLWH [11,12,91] but also adults living with HIV in SSA [9,38]. Differences in study context and population (like the conceptualization of mental health issues, exposure levels to triggers of mental health problems), study respondents (self vs. others) and use of heterogenous measurement tools (including different cut-off scores for similar measures) may contribute to the wide variation of the reported prevalence estimates. As a start point for

Table 2. Prevalence estimates for major depression and depressive symptoms among YLWH from SSA according to the measurement tool used

Author, year	Country	Outcome of interest	Sample size (n)	Assessment tool used	Cut-off score	Information on local tool validation	Prevalence estimates
The mini-international neuropsychiatric interview for children and adolescents (MINI-KID)							
Adeyemo *et al.*, 2020 [45]	Nigeria	Major Depression	201	MINI-KID	NA	–	16.9%
Ashaba *et al.*, 2018 [64]	Uganda	Major Depression	224	MINI-KID	NA	–	16.0%
Bankole *et al.*, 2017 [46]	Nigeria	Major Depression	75 HIV+ 75 HIV–	MINI-KID	NA	–	20.0% among HIV+ 6.7% among HIV– $p = 0.01$
International classification of diseases, tenth edition (ICD-10) symptom checklist							
Musisi & Kinyanda, 2009 [50]	Uganda	Major Depression	82	ICD-10	NA	–	40.8%
The youth inventory fourth revision (YI-4R) and the child and adolescent symptom inventory-5 (CASI-5)							
Kinyanda *et al.*, 2019 [55]	Uganda	Symptoms of Major Depression	479	YI-4R CASI-5	NR	Cronbach alpha of 0.88 and test–retest reliability of 0.2, $p < 0.01$ Cronbach alpha of 0.77 and test–retest reliability of 0.17, $p < 0.01$	5.2%
The patient health questionnaire for adolescents (PHQ-A)							
Buckley *et al.*, 2020 [65]	South Africa	Symptoms of Major Depression	81 HIV+ 81 HIV–	PHQ-A	NR	NR	6.2% among HIV+ 7.4% among HIV– $p = 0.99$
The 9-item patient health questionnaire (PHQ-9)							
Dow *et al.*, 2016 [53]	Tanzania	Depressive symptoms	182	PHQ-9	≥10	NR	12.1%
Dyer *et al.*, 2020 [60]	Kenya	Depressive symptoms	479	PHQ-9	≥5	NR	10.0%
Ekat *et al.*, 2020 [49]	DRC	Depressive symptoms	135	PHQ-9	≥9	NR	38.5%
Gaitho *et al.*, 2018 [77]	Kenya	Depressive symptoms	270	PHQ-9	≥1	NR	52.6%
Haas *et al.*, 2020 [78]	South Africa	Depressive symptoms	1088	PHQ-9	≥10	NR	4.4%
Ramos *et al.*, 2018 [57]	Tanzania	Depressive symptoms	280	PHQ-9	≥10	NR	20.4%
The centre for epidemiologic studies depression scale (CES-D)							
Fawzi *et al.*, 2016 [51]	Rwanda	Depressive symptoms	193	CES-D	≥30	Not provided in this study. However, the authors note that they used a CES-D previously validated in Rwanda	26.0%
Filiatreau *et al.*, 2020 [62]	South Africa	Depressive symptoms	334	CES-D	≥16	Cronbach alpha of 0.76	27.5%

(*Continued*)

Table 2. (*Continued*)

Author, year	Country	Outcome of interest	Sample size (n)	Assessment tool used	Cut-off score	Information on local tool validation	Prevalence estimates
Kemigisha *et al.*, 2019 [54]	Uganda	Depressive symptoms	336	CES-D	≥15	Cronbach alpha of 0.85	45.8%
Okawa *et al.*, 2018 [56]	Zambia	Depressive symptoms	190	CES-D (10-item)	≥10	Cronbach alpha of 0.74	25.3%
The child depression inventory							
Lwidiko *et al.*, 2018 [82]	Tanzania	Depressive symptoms	300 HIV+ 600 HIV−	CDI-II	≥12	Cronbach alpha of 0.7	27.0% among HIV+ 5.8% among HIV− $p < 0.001$
Cavazos-Rehg *et al.*, 2020 [81]	Uganda	Depressive symptoms	675	CDI-S (Short form)	≥3	Authors claim to have used culturally adapted tools	50.3%
West *et al.*, 2018 [58]	South Africa	Depressive symptoms	278	CDI-S (Short form)	≥7	Not provided in this study, but authors note that the tool was previously validated in South Africa	7.6%
Woollett *et al.*, 2017 [59]	South Africa	Depressive symptoms	343	CDI-S (Short form)	≥10	Not provided in this study, but authors say they used measures previously validated among youth in South Africa (Cronbach alpha >0.70)	14.0%
Beck's depression inventory-II (BDI-II)							
Abebe *et al.*, 2019 [84]	Ethiopia	Depressive symptoms	507	BDI-II	≥21	NR	35.5%
Earnshaw *et al.*, 2018 [61]	South Africa	Depressive symptoms	250	BDI-II	≥20	Cronbach alpha of 0.9	33.8%
Yarhere & Jaja, 2020 [48]	Nigeria	Depressive symptoms	58	BDI-II	≥11	NR	44.8%
Beck's youth inventory-II (BYI-II)							
Hoare *et al.*, 2019 [66]	South Africa	Depressive symptoms	204 HIV+ 44 HIV−	BYI-II (Depression inventory)	NR	NR	6.4% among HIV+ 2.3% among HIV− $p < 0.01$
Kikuchi *et al.*, 2017 [67]	Rwanda	Depressive symptoms	475	BYI-II (Depression inventory)	>55	Cronbach alpha of 0.84	22.1%
The revised children's depression rating scale (CDRS-R)							
Kim *et al.*, 2015 [28]	Malawi	Depressive symptoms	562	CDRS-R	≥55	Not provided in this study. Authors provide a reference for information on tool validation	18.9%

Table 2. *(Continued)*

Author, year	Country	Outcome of interest	Sample size (n)	Assessment tool used	Cut-off score	Information on local tool validation	Prevalence estimates
The hospital anxiety and depression scale (HADS)							
Sale & Gadanya, 2008 [47]	Nigeria	Depressive symptoms	162	HADS (Depression scale)	≥8	NR	39.5%
Reynolds adolescent depression scale-second edition (RADS-2)							
Paul *et al.*, 2015 [63]	Zambia	Depressive symptoms	100	RADS-2	≥76	NR	19.0%
NIH toolbox sadness module							
Molinaro *et al.*, 2019† [52]	Zambia	Depressive symptoms	200 HIV+ 200 HIV−	NIH	≥60	NE	24.0% among HIV+ 13.0% among HIV− $p = 0.03$

†This work was only available as a published abstract from an annual meeting with prevalence data within the abstract. DRC, Democratic Republic of Congo; NA, Not Applicable; NE, Not Extracted; NR, Not Reported.

possible quantification of the magnitude of CMDs among YLWH in SSA, researchers, perhaps from similar regions, should work towards the use of homogenous mental health measurement tools.

Compared to HIV-negative peers, YLWH from SSA appear to be experiencing higher CMDs, particularly depressive disorders. However, the evidence is limited to draw any conclusions. Only five studies in this review [46,52,65,66,82] compared CMDs between YLWH and their HIV-negative peers. Four of these studies reported significantly higher prevalence estimates of either major depression [46] or depressive symptoms [52,66,82] among YLWH (Table 2). In these studies, YLWH were 3.5- [46], 2.9- [66], 6.0- [82] and 2.1-times [52] more likely to have higher depression compared to their HIV-negative peers. Even though the odds of symptoms of major depression were 17% less likely among YLWH compared to HIV-negative peers in the fifth study [65], there was no significant between-group difference (Table 2). In the literature, individual empirical studies from other settings comparing for instance depressive symptoms among YLWH and their HIV-negative peers report mixed results. Some observe significant group differences [92], whereas others observe insignificant differences [27,93].

For anxiety, two of the five studies above [65,66] also compared the prevalence of anxiety symptoms between YLWH and their HIV-negative peers and reported slightly higher, but statistically insignificant, prevalence estimates among YLWH (Table 3). In these studies, even though insignificant, the odds of anxiety symptoms were 1.5 [65] and 1.3 times [66] higher in YLWH. In contrast, a study from Italy found significantly higher anxiety scores among YLWH compared to their HIV-negative peers [92]. For a clearer insight as to whether YLWH from SSA are at an elevated risk of CMDs compared to their HIV-negative peers, there is a need for more comparative research.

Despite the observed wide-ranging prevalence estimates, this review generally shows that the burden of CMDs among YLWH from SSA is high, and that rates may be two to six times higher when compared with HIV-negative youths, particularly for depressive disorders. However, caution must be taken when interpreting the reported prevalence estimates. Only four studies [45,46,50,64] used a mental health diagnostic interview based on either DSM or ICD criteria. Two studies [55,65] used DSM-referenced checklists to assess symptoms of major depression and an anxiety disorder. The rest collected mental health data of YLWH using screening tools, some with unknown reliability and/or validity. Most importantly, screening and early management or referral for treatment of CMDs among YLWH from SSA are urgently needed at the HIV clinics servicing these youths, more so because CMDs co-occurring with HIV are associated with worse HIV outcomes [23,25].

Overall, fewer studies in this review focussed on anxiety compared to depression. This under-investigation of anxiety disorders is of concern because previous research involving YLWH report higher rates of anxiety than depression [94]. Partly, the under-investigation could be due to the paucity of adequately validated measurement tools of anxiety [95]. To allow more research focus on anxiety among YLWH in the African context, as has depression, there is a need for adequate validation of measurement tools for anxiety, taking into

consideration contextual and cultural differences within the SSA setting.

3.4 | Correlates of CMDs among YLWH from SSA

To the best of our knowledge, this is the first review from SSA to comprehensively collate information about factors associated with CMDs in YLWH. Recent reviews from SSA involving YLWH provide an overview of some of these factors because of broadly covering multiple psychiatric disorders [13,14], focussing on only one correlate – ART adherence [14] or including HIV-positive young people up to 19 years only [13,14]. In this review, 19 studies reported the correlates of either major depression [64], symptoms of major depression [65] or depressive symptoms among YLWH [28,48,49,53,54,56,58,61,62,66,67,69,77,78,81,82,84]. Of these, four studies concurrently investigated correlates of anxiety symptoms [58,66,69,78]. One study [68] independently focused on the correlates of anxiety symptoms. There was limited consensus across studies for most of the reported correlates. Generally, the factors reported to be significantly associated with CMDs among YLWH from these studies can be categorized into sociodemographic, psychosocial and HIV-related clinical correlates and are presented as such in this paper.

3.5 | Correlates of major depression or depressive symptoms among YLWH from SSA

Table 4 presents in detail the identified correlates of major depression or depressive symptoms among YLWH as reported from the studies above. In summary, none of the studies reported any sociodemographic correlate of major depression. The sociodemographic factors that significantly increased the risk for higher depressive symptoms among YLWH included: older age [49,53,69,77,84], female sex [28,53], fewer schooling years [28,49], longer distance to the clinic [54], and HIV-positive status [66,82]. Similarly, but in the inverse direction, Haas *et al.* [78] report younger age as significantly lowering the risk for depressive symptoms. There appeared to be a consensus between two or more studies regarding older age, female sex, fewer schooling years and HIV-positive status as significant sociodemographic correlates of higher depressive symptoms, congruent with results from previous reviews involving YLWH [5,11, 12]. In contrast, one included study [81] reported older youth age as protective against depressive symptoms and male sex as a risk indicator for higher depressive symptoms. Better overall health [69], residing in rural areas [82], not being in a romantic relationship [28], not failing a term or class [28] and higher height for age z-scores [67] were the sociodemographic factors that significantly decreased the risk for depressive symptoms. However, there was a lack of consensus across studies for these correlates.

Females living with HIV from SSA could be at a higher risk of depressive symptoms because of additional experiences of traumatic events such as sexual abuse and intimate partner violence, some of which may have had a role in their acquisition of HIV infection [96,97]. Additionally, they are more likely to be stigmatized [98] and blamed for HIV transmission within families in patriarchal societies like those of SSA [99]. Older YLWH compared to younger ones are more likely to understand the threat posed by HIV infection to their own life [16], which may manifest as depressive symptoms. The awareness of HIV-related cognitive deficits [41] by a YLWH manifesting in ways like grade retention or poor performance may explain the association between fewer years of schooling and higher depressive symptoms. Although two studies in this review observed significant associations between HIV-positive status and higher depressive symptoms, Western empirical studies report non-significant associations [27,93]. In SSA where poverty is high [100], HIV-related adjustments such as recommended intake of a balanced diet with ART use and meeting the regular transportation costs for clinic appointments may be additional challenges to most families of YLWH. Such challenges may lead to psychiatric manifestations among YLWH.

Bullying was the only reported psychosocial correlate of major depression in the study examining the relationship between psychosocial factors and major depression [64]. Psychosocial factors that significantly increased the risk for higher symptoms of major depression among YLWH included living with someone who has anger/aggression problems and ever witnessing violence at home [65]. Psychosocial factors that significantly increased the risk for higher depressive symptoms among YLWH were as follows: bullying victimization [69], bullying for taking ART [28], caregiver depression [67], grandparent as primary caregiver [81], low social support [84], HIV-related stigma in its various forms such as perceived stigma [53,56,66,84], internalized stigma [61,69] and associative stigma [61], history of sexual [62,69], emotional [69] and physical abuse [62] or a combination of physical and/or sexual abuse [62], conflict in the household [78], unsatisfactory relationship with family or health workers [56], insomnia and suicidal ideation [48], negative clinic interactions [69], history of childhood deprivation [82] and stressful life events [66]. On the other hand, the following psychosocial factors significantly lowered the risk for depressive symptoms in YLWH: access to a clinic support group [69], positive parenting [69], higher socio-economic status [81], family cohesion [81], not being bereaved in the family [28], self-efficacy [69], satisfaction with physical appearance [28] and higher social support [58,69,81]. Among the reported psychosocial correlates of depressive disorders in YLWH, bullying, HIV-related stigma, history of sexual abuse and social support were consistently reported across two or more studies as significantly associated with depressive disorders, similar to previous review findings [5,11,12].

The negative effects of HIV-related stigma among YLWH including social devaluation and experience of injustices like restrictions in interacting with other people and being denied equal opportunities of enrolling or staying in school [20], may explain why HIV-related stigma (in its various forms) is associated with higher depressive symptoms in YLWH. HIV-related stigma can lead to depression manifesting as low self-worth, self-isolation, loss of hope in future plans or aspirations and poor ART adherence [20,84,101]. As previously emphasized [19,20], there is a need for continuously addressing HIV-related stigma in multiple settings within the community. Bullying can lead to negative outcomes such as humiliation, self-blame and shame [102] and coupled with living with HIV at a younger age, high levels of depressive symptomatology may be expected among YLWH. The finding that higher social support is associated with fewer depressive symptoms (or vice versa, low social support being associated with more depressive symptoms) supports the proposition of a buffering effect

Table 3. Prevalence estimates for anxiety disorder or its symptoms among YLWH from SSA according to the measurement tool used

Author, year	Country	Outcome of interest	Sample size	Assessment tool used	Cut-off score	Information on local tool validation	Prevalence estimates
International classification of diseases, tenth edition (ICD-10) symptom checklist							
Musisi & Kinyanda, 2009 [50]	Uganda	Anxiety disorder	82	ICD-10	NA	–	45.6%
The patient health questionnaire for adolescents (PHQ-A)							
Buckley *et al.*, 2020 [65]	South Africa	Anxiety disorder symptoms (Panic disorder)	81 HIV+ 81 HIV–	PHQ-A	NR	NR	3.7% among HIV+ 2.5% among HIV– $p = 0.99$
The revised children's manifest anxiety scale (RCMAS)							
West *et al.*, 2018 [58]	South Africa	Anxiety symptoms	278	14-item RCMAS	≥10	Not provided in this study, but authors say tools were previously validated in South Africa	6.7%
Woollet *et al.*, 2017 [59]	South Africa	Anxiety symptoms	343	28-item RCMAS	NR	Not provided in this study, but authors say they used measures previously used with youth in South Africa (Cronbach alpha >0.75)	25.0%
The youth inventory fouth revision (YI-4R) and the child and adolescent symptom inventory-5 (CASI-5)							
Kinyanda *et al.*, 2019 [55]	Uganda	Symptoms of: -Any anxiety disorder -GAD -SAD -SEAD	479	YI-4R CASI-5	NR	Cronbach alpha of 0.88 and test–retest reliability of 0.2, $p < 0.01$ Cronbach alpha of 0.77 and test–retest reliability of 0.17, $p < 0.01$	14.7% for Any anxiety disorder 7.2% for GAD 7.0% for SAD 5.4% for SEAD
The 7-item generalized anxiety disorder scale (GAD-7)							
Haas *et al.*, 2020 [78]	South Africa	Anxiety symptoms	1088	GAD-7	≥10	NR	2.2%
Beck's youth inventory-II (BYI-II)							
Hoare *et al.*, 2019 [66]	South Africa	Anxiety symptoms	204 HIV+ 44 HIV–	BYI-II (Anxiety inventory)	NR	NR	11.8% among HIV+ 9.1% among HIV– $p = 0.61$

GAD, Generalized Anxiety Disorder; NA, not applicable; NR, not reported; SAD, Social Anxiety Disorder; SEAD, Separation Anxiety Disorder.

of social support against psychological distress as described in the "buffering hypothesis" [103]. This hypothesis postulates that any form of social support (social companionship, emotional, informational, or instrumental support) proffers protection to individuals facing stressful life events (in this case, HIV infection adversity) and assists them in coping with distress. The persistent psychological distress among sexually abused YLWH can be addressed through continued counselling and appropriate support mechanisms.

The following HIV-related clinical factors significantly increased the risk for elevated depressive symptoms among YLWH: poor adherence to ART [49,53,77,84], history of opportunistic infections [84], experiencing ART side effects [69] and taking efavirenz-based ART [67]. On the other hand, better immunological stage [28] or increasing CD4 cell count [48] were associated with fewer depressive symptoms among YLWH. See Table 4 for effect sizes reported from individual studies. Of these correlates, only poor adherence to ART was consistently reported across four studies, a finding that has also been observed in past global reviews involving YLWH [5,11,12]. Non-optimal adherence to ART can lead to viral non-suppression [104], and patients may experience psychological distress when informed of a poor prognosis. This may explain the observed consistent significant association between poor ART adherence and elevated depressive symptoms among YLWH from SSA [49,53,77,84]. However, depression can also be an antecedent to poor ART adherence [25], thus there is uncertainty on the temporality of the significant associations reported in the above four cross-sectional studies.

3.6 | Correlates of anxiety symptoms among YLWH from SSA

Table 5 presents in detail the identified correlates of anxiety symptoms among YLWH. The study that diagnosed anxiety disorder [50] did not report any correlation. Younger age [78] and better overall health among YLWH [69] were the only significant sociodemographic correlates of anxiety symptoms. The following psychosocial factors significantly increased the risk for anxiety symptoms among YLWH: internalized stigma [69], anticipated stigma [69], history of sexual abuse or emotional abuse in the past year [69], bullying victimization [69], poor parental monitoring [69], history of physical violence [78] and stressful life events [66]. Conversely, higher social support [58,68], self-efficacy [69], positive parenting [69] and access to a clinic support group [69] were the factors that significantly decreased the risk for anxiety symptoms among YLWH from SSA. Experiencing ART side effects was the only significant HIV-related clinical correlate of anxiety symptoms among YLWH reported by one South African study [69].

Similar to what was observed for depressive symptoms, social support was also a significant correlate of anxiety symptoms reported across two studies [58,68]. As earlier noted, social support may also provide a buffering effect against anxiety symptoms [103].

3.7 | Quality of included studies

(Additional file S3) shows the quality scores of included studies according to their study designs, based on the Newcastle-Ottawa risk of bias assessment tool. Two studies were graded to be of very good quality [55,69], twelve of good quality [28,53,54,58,64-67,77,78,82,84], nine of satisfactory quality [45,49-51,56,61,62,68,81] and seven of unsatisfactory quality [46-48,57,59,60,63]. One study [52], available only as an abstract publication, provided relevant mental health data for this review. This study was rated as unclear of high risk of bias because of a lack of feedback from authors when contacted (on three attempts) with a request for data that would enable assessment of the quality of the entire study.

Even though most of the studies reporting on correlates of CMDs among YLWH were of low risk of bias, they were cross-sectional in design. This study design limits inferences on causality. Therefore, the summarized significant correlates of CMDs among YLWH in this review should be interpreted with caution. For better decisions on priority intervention areas, future studies from this setting should seek to substantiate the causal direction of the identified correlates, using, for instance longitudinal study designs.

3.8 | Study limitations

This review has several limitations worth highlighting. First, the review does not provide pooled prevalence estimates of CMDs among YLWH from SSA because measurement tools used across studies were highly heterogeneous. Relatedly, because a meta-analysis could not be performed, we are unable to report on publication bias. Second, the review deliberately focused on SSA. Even though the region has predominantly low- to middle-income countries, findings may not necessarily be generalizable to other low- and middle-income countries outside this context. Relatedly, across the different countries in SSA, there is diversity in aspects such as language, religious and cultural practices which may make the results ungeneralizable to some communities within the region. Lastly, the review search strategy was biased as only publications in English were considered. It may be that we left out important work reported in a language other than English.

3.9 | Implications of the findings for future research, policy and practice

The limitations notwithstanding, this study has important implications for future research, policy and practice. There is a need to invest in mental health awareness as one of the primary prevention strategies aiming at preventing the occurrence of CMDs at high rates among YLWH in SSA. This can entail psychoeducating YLWH about CMDs, that is what they are, the signs and symptoms, when and where to seek help, and providing them with self-help tips or quick guides through forums such as peer-to-peer meetings. The high burden of CMDs in YLWH from SSA highlights the urgent need to test youth-friendly psychological and psychosocial interventions that address CMDs faced by African youths living with HIV. Adaptation of available interventions such as those identified in a scoping review by Okonji *et al.* [105] may be a good starting point. The high burden also calls for the integration of mental healthcare into the existing HIV care packages offered to YLWH in this setting. Successful integration requires training of primary health care personnel at the HIV clinics on how to manage CMDs (using, e.g. the World Health Organization's mhGAP intervention guide [106]), adequate infrastructure

Table 4. Sociodemographic, psychosocial and HIV-related correlates of major depression or depressive symptoms among young people living with HIV from SSA

Author, year	Outcome	Measure of effect (precision)	Sociodemographic correlates		Psychosocial correlates		HIV-related correlates	
			Risk indicators	Protective indicators	Risk indicators	Protective indicators	Risk indicators	Protective indicators
Abebe *et al.*, 2019 [84]	Depressive symptoms	AOR (95% CI)	-Older age: 2.20 (1.33 to 3.62)	NR	-Low social support: 2.74 (1.42 to 5.27) -HIV-related stigma: 2.06 (1.35 to 3.14)	NR	-Poor ART adherence: 1.73 (1.13 to 2.64) -History of opportunistic infections: 1.94 (1.15 to 3.27)	NR
Ashaba *et al.*, 2018 [64]	Major depression	AOR (95% CI)	NR	NR	-Bullying: 1.09 (1.00 to 1.20)	NR	NR	NR
Boyes *et al.*, 2018 [69]	Depressive symptoms	β (Se)	-Older age: 0.07 (0.02)	-Better overall health: −0.18 (0.08)	-Internalized stigma: 0.29 (0.05) -Negative clinic interactions: 0.06 (0.02) -Emotional abuse 0.56 (0.14) -Sexual abuse: 0.83 (0.25) -Bullying victimisation: 0.04 (0.02)	-Self-efficacy: −0.04 (0.02) -Higher social support: −0.11 (0.020) -Access to a clinic support group: −0.32 (0.10) -Positive parenting: −0.04 (0.01)	-ART side effects: 0.49 (0.12)	NR
Buckley *et al.*, 2020 [65]	Symptoms of Major Depression	AOR (95% CI)		NR	-Living with someone with aggression or anger problems: 2.80 (1.05 to 7.44) -Ever witnessing violence at home: 4.34 (1.65 to 11.46)	NR	NR	NR
Cavazos-Rehg *et al.*, 2020 [81]	Depressive symptoms	AOR (95% CI)	-Male sex: 1.62 (1.15 to 2.27)	-Older age: 0.87 (0.77 to 0.98)	-Grandparent as primary caregiver: 1.83 (1.16 to 2.88)	-Higher social support (from friends): 0.96 (0.91 to 0.998) -Higher socio-economic status (additional assets and employment): 0.85 (0.74 to 0.99) -Family cohesion: 0.94 (0.91 to 0.96)	NR	NR
Dow *et al.*, 2016 [53]	Depressive symptoms	MR (95% CI)	-Older age: 1.08 (1.03 to 1.14) -Female sex: 1.52 (1.11 to 2.09)	NR	-HIV-related stigma: 1.08 (1.04 to 1.11)	NR	-Poor ART adherence: 1.52 (1.07 to 2.18)	NR
Earnshaw *et al.*, 2018 [61]	Depressive symptoms	ARR (95% CI)		NR	-Internalized stigma: 1.23 (1.13 to 1.34) -Associative stigma: 1.59 (1.37 to 1.84)	NR	NR	NR

(*Continued*)

Table 4. (*Continued*)

Author, year	Outcome	Measure of effect (precision)	Sociodemographic correlates		Psychosocial correlates		HIV-related correlates	
			Risk indicators	Protective indicators	Risk indicators	Protective indicators	Risk indicators	Protective indicators
Ekat *et al.*, 2020 [49]	Depressive symptoms	APR (95% CI)	-Older age: 2.07 (1.06 to 4.04) -Stopping education: 1.60 (1.06 to 2.42)	NR	NR	NR	-Poor ART adherence: 2.06 (1.23 to 3.45)	NR
Filiatreau *et al.*, 2020 [62]	Depressive symptoms	APR (95% CI)	NR	NR	-History of physical violence: 2.02 (1.43 to 2.84) -History of sexual violence: 2.25 (1.58 to 3.19) -History of physical or sexual violence: 2.01 (1.43 to 2.83) -History of physical and sexual violence: 3.01 (2.06 to 4.39)	NR	NR	NR
Gaitho *et al.*, 2018 [77]	Depressive symptoms	AOR (95% CI)	-Older age: 2.34 (1.40 to 4.00)	NR	NR	NR	-Poor ART adherence: 1.84 (1.08 to 3.10)	NR
Haas *et al.*, 2020 [78]	Depressive symptoms	AOR (95% CI)	NR	-Younger age: 10 to 12 years age group vs. 16 to 19 years age group = 0.05 (0.01 to 0.21) 13 to 15 years age group vs. 16 to 19 years group = 0.18 (0.08 to 0.40)	-Conflict in the household: 3.76 (1.97 to 7.17)	NR	NR	NR
Hoare *et al.*, 2019 [66]	Depressive symptoms	β (95% CI)	-HIV+ status: 5.08 (1.35 to 8.82)	NR	-Stressful life events: 0.83 (0.57 to 1.08) -HIV-related stigma: 9.93 (2.88 to 16.98)	NR	NR	NR
Kemigisha *et al.*, 2019 [54]	Depressive symptoms	AOR (95% CI)	-Travelling > 30 minutes for routine clinic care: 1.66 (1.02 to 2.70)	NR	NR	NR	NR	NR
Kikuchi *et al.*, 2017 [67]	Depressive symptoms	AOR (95% CI)	NR	-Higher height-for-age: 0.78 (0.62 to 0.99)	-Caregiver depression: 1.79 (1.13 to 2.7)	NR	-Taking efavirenz: 2.33 (1.21 to 4.50)	NR

Table 4. (*Continued*)

Author, year	Outcome	Measure of effect (precision)	Sociodemographic correlates		Psychosocial correlates		HIV-related correlates	
			Risk indicators	Protective indicators	Risk indicators	Protective indicators	Risk indicators	Protective indicators
Kim *et al.*, 2015 [28]	Depressive symptoms	β (95% CI)	-Female sex: 2.13 (0.82 to 3.43) -Fewer years of schooling: 3.84 (1.71 to 5.98)	-Not failing a school term/class: −1.46 (−2.76 to −0.17) -Not being in a romantic relationship: −2.38 (−4.35 to −0.41)	-Being bullied for taking ART: 5.31 (3.19 to 7.43)	-No death in the family: −1.77 (−3.15 to −0.39) -Satisfaction with physical appearance: −0.93 (−1.74 to 0.11)	NR	-No immune suppression: −2.58 (−4.29 to −0.87)
Lwidiko *et al.*, 2018 [82]	Depressive symptoms	AOR (95% CI)	-HIV+ status: 1.96 (1.1 to 3.45)	-Rural residence: 0.61 (0.39 to 0.96)	-History of childhood deprivation: 4.76 (2.79 to 8.13)	NR	NR	NR
Okawa *et al.*, 2018 [56]	Depressive symptoms	AOR (95% CI)	NR	NR	-Unsatisfactory relationship with family: 3.01 (1.20 to 7.56) -Unsatisfactory relationship with health workers: 2.68 (1.04 to 6.93) -HIV-related stigma: 2.99 (1.07 to 8.41)	NR	NR	NR
West *et al.*, 2018 [58]	Depressive symptoms	APR (95% CI)	NR	NR	NR	-Higher social support: 0.25 (0.10 to 0.59)	NR	NR
Yarhere & Jaja, 2020 [48]	Depressive symptoms	β (t)	NR	NR	-Insomnia: 5.61 (2.94) -Suicidal thoughts: 4.64 (3.39)	NR	NR	Higher CD4 count: −0.001 (2.74)

AOR, Adjusted odds ratio; APR, Adjusted prevalence ratio; ART, Antiretroviral therapy; CD4, Cluster of Differentiation-4; CI, Confidence interval; MR, Mean ratio; NR, None reported; Se, Standard error; t, t statistic; β, Beta coefficients (adjusted).

Table 5. Sociodemographic, psychosocial and HIV-related correlates of anxiety symptoms among young people living with HIV from SSA

			Sociodemographic correlates		Psychosocial correlates		HIV-related correlates	
Author (year)	Outcome	Measure of effect (precision)	Risk indicators	Protective indicators	Risk indicators	Protective indicators	Risk indicators	Protective indicators
Besthorn *et al.* (2018) [68]	Anxiety symptoms	β (Se)	NR	NR	NR	-Higher social support: −0.16 (0.06)	NR	NR
Boyes *et al.* (2018) [69]	Anxiety symptoms	β (Se)	NR	-Better overall health: −0.18 (0.08)	-Internalized stigma: 0.54 (0.07) -Past year emotional abuse: 1.17 (0.19) -History of sexual abuse: 1.08 (0.34) -Bullying victimisation: 0.15 (0.02) -Poor parental monitoring: 0.02 (0.01) -Anticipated stigma: 0.30 (0.08)	-Self-efficacy: −0.06 (0.02) -Positive parenting: −0.05 (0.01) -Access to clinic support group: −0.43 (0.14)	-ART side effects: 0.51 (0.17)	NR
Haas *et al.*, 2020 [78]	Anxiety symptoms	AOR (95% CI)	NR	-Younger age: 10 to 12 years age group vs. 16 to 19 years age group = 0.05 (0.01 to 0.37) 13 to 15 years age group vs. 16 to 19 years group = 0.19 (0.06 to 0.56)	-History of physical violence: 2.74 (1.09 to 6.85)	NR	NR	NR
Hoare *et al.* (2019) [66]	Anxiety symptoms	β (95% CI)	NR	NR	-Stressful life events: 0.72 (0.44 to 1.01)	NR	NR	NR
West *et al.* (2018) [58]	Anxiety symptoms	APR (95% CI)	NR	NR	NR	-Higher social support: 0.30 (0.13 to 0.71)	NR	NR

APR, Adjusted prevalence ratio; ART, Antiretroviral therapy; CI, Confidence interval; NR, Not reported; Se, Standard error; β, Beta coefficients (adjusted).

(including the availability of psychotropic medication), followed by regular supervision and support from mental health specialists using a task-shifting approach [107,108].

Many of the included studies were cross-sectional in design, did not compare the burden of CMDs between YLWH and their uninfected peers, and focused more on depression than anxiety. Alternative study designs that ascertain causal relationships are recommended for future investigations of factors associated with CMDs among YLWH in SSA. Where feasible, future studies seeking to understand CMDs in YLWH should include an appropriate comparison group of HIV-negative peers to clearly describe the burden. Finally, more research on anxiety among YLWH from SSA is needed. Currently, this data remains limited.

4 | CONCLUSIONS

According to this review, the prevalence of CMDs in YLWH from SSA is substantially high despite the wide variation of reported estimates. From studies that recruited a comparison group of HIV-negative peers, it appears YLWH are at a higher risk of experiencing CMDs particularly depressive symptoms, but more comparative research is needed to draw definite conclusions. The mental health experience of YLWH in SSA is not any different compared to that of YLWH from other settings, all are reporting high rates of CMDs. However, some of the factors associated with CMDs among YLWH in SSA are context-specific and may require contextualized intervention approaches. YLWH at an elevated risk of CMDs in SSA such as females, older youths, those with fewer schooling years, with a history of sexual abuse, reporting ART adherence issues, being bullied or experiencing HIV-related stigma may benefit from early management or referral for treatment using a stepped care approach [109] if at least targeted screening for CMDs is done at the youth HIV clinics. Social support may lower the risk for CMDs among YLWH in SSA and can be an important component to consider when designing youth-friendly intervention packages for YLWH with comorbid CMDs.

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COMPETING INTERESTS

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

MKN, AA and CRJCN conceived the study. ET, MKN, AA, CRJCN designed the study. CN, HK, PC contributed to the design of the study. ET did the initial screening of the articles, whereas MKN and CN independently checked the quality of data screening. ET and MKN independently extracted data and assessed the risk of bias for the included studies. ET and MKN wrote the first draft of the manuscript. AA, CN, CRJCN, HK and PC critically reviewed subsequent versions of the manuscript. All the authors have approved the submission of this final version.

ABBREVIATIONS

ART, antiretroviral therapy; CASI-5, child and adolescent symptom inventory – fifth edition; CD4, cluster of differentiation-4; CMDs, common mental disorders; DSM, diagnostic and statistical manual of mental disorders; ICD-10, international classification of diseases – tenth edition; MINI-KID, mini international neuropsychiatric interview for children and adolescents; PRISMA, preferred reporting items for systematic reviews and meta-analysis; PROSPERO, the international prospective register of systematic reviews; SSA, sub-Saharan Africa; YI-4R, Youth inventory – fourth revision; YLWH, young people living with HIV.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:
Additional file S1. Search string used in PubMed database.
Additional file S2. Characteristics of included studies.
Additional file S3. Quality scores of the included studies.

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RESEARCH ARTICLE

The longitudinal association between depression, anxiety symptoms and HIV outcomes, and the modifying effect of alcohol dependence among ART clients with hazardous alcohol use in Vietnam

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Abstract

Introduction: Mental health disorders may negatively impact HIV outcomes, such as viral suppression (VS) and antiretroviral (ART) adherence among people with HIV (PWH) with hazardous alcohol use. This study evaluates the longitudinal association between depression, anxiety symptoms, VS and complete ART adherence among ART clients with hazardous alcohol use in Vietnam; and examines alcohol dependence as a modifier in this association.

Methods: This was a secondary data analysis of a trial for hazardous drinking ART clients in Thai Nguyen, Vietnam. From March 2016 to May 2018, 440 ART clients with an Alcohol Use Disorders Identification Test-Concise (AUDIT-C) score ≥4 for men and ≥3 for women were enrolled. Individuals were randomized to either a combined intervention, a brief intervention or a standard of care. Data on sociodemographics, depression, anxiety symptoms, alcohol use, VS and ART adherence were collected at baseline, three, six, and twelve months. Generalized estimating equation models controlling for intervention exposure were used to estimate time-lagged associations. Risk ratios were estimated using Poisson regression with robust variance estimation.

Results: The mean age of participants was 40.2. The majority was male (96.8%), had at least some secondary school education (85.0%) and had a history of injection drug use (80.9%). No overall effect of depression and anxiety symptoms on VS was observed. When stratified by time, increased anxiety symptoms at six months were associated with VS at 12 months (adjusted risk ratio (aRR) = 1.09; 95% CI 1.02 to 1.17). An increase in depression or anxiety symptoms was associated with a decreased probability of complete ART adherence (depression symptoms: aRR = 0.95; 95% CI: 0.91 to 0.99; anxiety symptoms: aRR = 0.93; 85% CI: 0.88 to 0.99). The negative effects of anxiety symptoms on ART adherence were stronger among participants with alcohol dependence, compared to those without.

Conclusions: Depression and anxiety symptoms had no overall effect on VS, although they were associated with a lower probability of complete ART adherence. Interventions focusing on mental healthcare for PWH with hazardous alcohol use are needed, and integration of mental healthcare and alcohol reduction should be implemented in HIV primary care settings.

Keywords: mental health; depression; anxiety; HIV; hazardous alcohol use; viral suppression; adherence; Vietnam

Additional Supporting information may be found online in the Supporting Information tab for this article.

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1 | INTRODUCTION

People with HIV (PWH) are disproportionately affected by depression and anxiety disorders [1-3]. Indeed, PWH are 1.6 to 4 times more likely to be diagnosed with depression and anxiety disorders than HIV-negative individuals [4-9]. For example a global systematic review reported a prevalence of depression among PWH ranging from 15% to 44%, depending on the region [10,11]. The presence of anxiety or depression symptoms among PWH has numerous implications for HIV outcomes. The Transactional Model of Stress and Coping suggests that the experience of stress can have a negative impact

on physical health and functional status through direct physiological impacts on health or through indirect effects via maladaptive behaviours, such as non-adherence to medications [12]. Depression and anxiety symptoms among PWH are associated with poor viral load outcomes [3,13-16] and lower odds of achieving antiretroviral therapy (ART) adherence [17-19]. PWH with depression and anxiety symptoms generally have faster progression to AIDS and higher mortality rates [20-24].

Hazardous drinking is defined as the quantity and pattern of alcohol consumption that increases adverse health outcomes, while alcohol dependence – a higher level of alcohol use disorder – is defined as a strong desire to consume alcohol, difficulties in controlling its use, and persistent use despite harmful consequences [25,26]. An estimated 25% to 50% of PWH are hazardous drinkers [27-29], and about 10.6% of PWH had both depression symptoms and harmful levels of alcohol use [30]. PWH with hazardous alcohol use are even more vulnerable to mental disorders than PWH without drinking issues [31], and they may have unique challenges that make abstinence difficult. For example a study among PWH in Vietnam showed that participants were particularly susceptible to alcohol abstinence stigma, which was also associated with higher levels of alcohol use [32]. Therefore, it is essential to understand how depression and anxiety symptoms affect viral suppression (VS) and ART adherence among PWH with hazardous alcohol use. However, there is a dearth of research on the associations between depression, anxiety and HIV outcomes among this subgroup of PWH.

According to the Syndemics Theory, the co-existence and synergistic interaction of more than one adverse condition in a patient can produce worse health outcomes than each condition independently [33,34]. While mental health symptoms are independently associated with poorer HIV outcomes, alcohol use can also accelerate HIV progression through a number of mechanisms. High levels of alcohol use do not only negatively impact ART adherence and response to medication but can also lead to compromised liver function and liver diseases [35-42]. Therefore, mental health symptoms and high levels of alcohol use can substantially increase the risk of treatment failure among PWH [43]. The interrelationship between these comorbidities and HIV outcomes among PWH remains largely unknown. The understanding of how these comorbidities interact will shed light on the need for a more holistic approach to addressing psychological and substance use comorbidities for PWH.

In Vietnam, alcohol is accessible and affordable, and excessive alcohol consumption is common during social and business gatherings [44,45]. A study among 1016 PWH in Vietnam found that 30.1% of PWH had hazardous alcohol use [46]. Vietnamese PWH are also commonly affected by mental health disorders such as depression and anxiety [47,48]. Using data from a randomized controlled trial of two alcohol reduction interventions among PWH with hazardous alcohol use in Vietnam, we aim to [1] evaluate the longitudinal association between mental health symptoms (depression and anxiety symptoms) and two HIV outcomes (VS and complete ART adherence) among ART clients with hazardous alcohol use in Vietnam; and [2] determine whether alcohol dependence modifies the longitudinal association between depression, anxiety symptoms and HIV outcomes (conceptual model shown in Figure S1).

2 | METHODS

2.1 | Study design and study population

This research is a secondary data analysis of the parent study, *Reducing Hazardous Alcohol Use & HIV Viral Load: A Randomized Controlled Trial in Antiretroviral Treatment (ART) Clinics in Vietnam* [REDART; NCT02720237]. REDART is a three-arm RCT conducted from March 2016 to May 2018 among ART clinic patients with hazardous alcohol use in Thai Nguyen – a mountainous, multi-ethnic province located in Northeast Vietnam [49]. Mirroring Vietnam's broader epidemic, HIV transmission in Thai Nguyen is primarily driven by injection drug use, with an HIV prevalence among people who inject drugs of 31.2% [50].

The main goal of the parent study was to understand the relative effectiveness of two interventions based on Motivational Enhancement Therapy (MET) and Cognitive Behavioral Therapy (CBT) in improving alcohol- and HIV-related outcomes [49]. Four hundred and forty PWH with hazardous alcohol use were randomly assigned to receive either a combined intervention, a brief intervention or a standard of care assessment control (Figure 1). Participants were recruited from six ART community clinics and 1 ART hospital clinic. The World Health Organization (WHO) Alcohol Use Disorders Identification Test-Concise (AUDIT-C) survey, which had been utilized in previous studies in Vietnam [46,51-54], was used to assess eligibility [55]. Men and women who scored ≥4 (men) or ≥3 (women) on the AUDIT-C were considered eligible [55]. Additional inclusion criteria were as follows: (1) being a current ART client; (2) being ≥18 years of age and (3) planning to reside in Thai Nguyen for the next 24 months. Exclusion criteria were as follows: (1) inability to provide informed consent due to cognitive impairment or having threatening behaviour (study staff assessed sobriety); (2) unwilling to provide locator information or (3) currently participating in other HIV, drug use or alcohol programme, study or intervention. Survey data, along with viral load data were collected at baseline, three, six and twelve months after the intervention. All questionnaires were administered in Vietnamese. The study was reviewed and approved by the University of North Carolina at Chapel Hill's Institutional Review Board (IRB) and the IRB at the Thai Nguyen Center for Preventive Medicine.

The combined and brief interventions were associated with a significant improvement of the primary outcome – percent days abstinent, compared to the standard of care group at 12 months. VS (<20 copies of HIV-1 RNA per millilitre) at 12 months was also higher after the brief intervention than the standard of care. Details of the main trial were published elsewhere [49].

2.2 | Measurements

2.2.1 | Depression and anxiety symptoms

At all visits, depression symptoms were assessed with the Patient Health Questionnaire-9 (PHQ-9) scale [56] and anxiety symptoms were assessed with the Generalized Anxiety Disorder-7 (GAD-7) scale [57,58]. In Vietnam, the PHQ-9 scale has shown good convergent validity, construct validity as well as reliability [59], and has been used for a range of

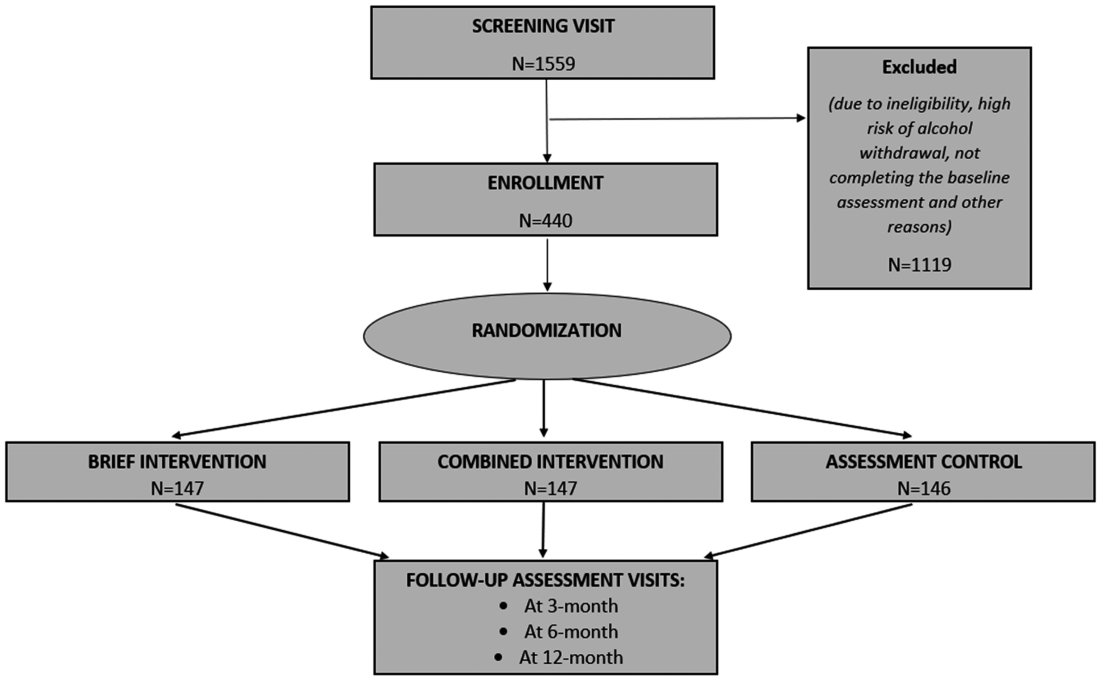


Figure 1. Study design of REDART intervention (Reducing Hazardous Alcohol Use & HIV Viral Load).

populations, including PWH [60-62]. Nine items assess how often depression symptoms including loss of interest or pleasure in doing things or feeling down or depressed occurred in the last two weeks. The GAD-7 scale has not been formally validated in Vietnam but has been used in different Vietnamese populations to measure anxiety [63,64]. This scale has seven items that evaluate the frequency of symptoms such as feeling nervous, anxious, or on edge or not being able to stop or control worrying. For both the PHQ-9 and GAD-7, a cut-off score of 5 can be interpreted as having mild levels of symptoms that are consistent with depression and anxiety respectively [56,65]. The maximum scores for depression and anxiety symptoms were 27 and 21 respectively. Since classifying continuous data into binary data can result in a loss of power and binary data are less sensitive to change [66], the original continuous scores of depression and anxiety symptoms were used in this study. Depression and anxiety symptoms were rescaled so that the reported estimates of association reflect the change in outcome associated with a 5-unit change in the continuously measured PHQ-9 or GAD-7 score. We performed this rescaling because a 1-unit change in each score is not clinically meaningful, whereas a 5-unit change is considered potentially clinically significant, implying that a participant has moved from one level of severity to the next [67,68]. This rescaling method has been used in other studies using continuous measures of depression and anxiety symptoms [69,70].

2.2.2 | *Alcohol dependence*

Alcohol dependence was evaluated with the Mini International Neuropsychiatric Interview (MINI) questionnaire [71] – a 7-item structured diagnostic psychiatric interview in which endorsing three or more items indicates alcohol dependence [72].

2.2.3 | *VS and ART adherence*

Viral load was measured by HIV-1 ribonucleic acid (RNA) levels using the in vitro nucleic acid amplification test (COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test). VS was defined as having less than 20 copies/ml. Complete ART adherence (self-reported) was defined as no missed pills in the past three months. Both HIV viral load and self-reported adherence were measured at baseline, three-, six- and twelve-month follow-ups. Since ART adherence is subject to social desirability bias [73], VS was considered the primary outcome of interest in this study.

2.2.4 | *Demographics and other covariates*

Standard demographics were collected at baseline (e.g. age, marital status, education, employment). Based on the literature, the following covariates were chosen a priori as potential confounders: age, sex, education, marital status, employment, alcohol dependence, non-injection drug use, injection drug use, social support, HIV stigma and intimate partner violence [16,74-81]. Participants were asked if they had used any types of non-injection drugs (including heroin, methamphetamines, etc.) in the last three months and if they had ever injected drugs in the past. Social support was measured with a 5-question modified version of the Medical Outcomes Study Social Support Instrument [82] used previously by our research group among PWH in Vietnam [83]. Based on the distribution of the social support score at baseline, the social support level was classified into four quartiles. To evaluate HIV stigma, participants were asked to state their levels of agreement with four statements indicating internalized, experienced or anticipated HIV stigma. They were classified as having HIV stigma if they reported any level of agreement with

Table 1. Participants' baseline characteristics, stratified by viral suppression and ART adherence at baseline

Characteristics N (%)	Complete ART adherence at baseline		Viral suppression at baseline		Total (N = 440)
	Yes (N = 334)	No (N = 103)	Yes (N = 370)	No (N = 70)	
Age (years) (mean ± SD)	40.8 ± 5.6	38.2 ± 5.8	40.3 ± 5.6	39.9 ± 6.6	40.2 ± 5.8
Male	322 (96.4)	101 (98.1)	361 (97.6)	65 (92.9)	426 (96.8)
Education					
Primary school or less	51 (15.3)	14 (13.6)	55 (14.9)	11 (15.7)	66 (15.0)
Some secondary school	191 (57.2)	53 (51.5)	201 (54.3)	45 (64.3)	246 (55.9)
Some high school	66 (19.8)	20 (19.4)	76 (20.5)	10 (14.3)	86 (19.6)
Some technical training, college or university	26 (7.8)	16 (15.5)	38 (10.3)	4 (5.7)	42 (9.6)
Marital status					
Not married	54 (16.2)	25 (24.3)	67 (18.1)	12 (17.1)	79 (18.0)
Married	245 (73.4)	57 (55.3)	261 (70.5)	44 (62.9)	305 (69.3)
Widowed, divorced or separated	35 (10.5)	21 (20.4)	42 (11.4)	14 (20.0)	56 (12.7)
Employment (Yes)	273 (81.2)	81 (78.6)	297 (80.3)	60 (85.7)	357 (81.1)
History of injection drug use (Yes)	267 (80.0)	87 (84.5)	301 (81.4)	55 (78.6)	356 (80.9)
Non-injection drug use in the past three months (Yes)	125 (37.4)	46 (44.7)	145 (39.2)	27 (38.6)	172 (39.1)
Alcohol dependence (Yes)	55 (16.5)	36 (35.0)	82 (22.2)	11 (15.7)	93 (21.1)
Ever experienced, internalized or anticipated HIV stigma (Yes)	200 (59.9)	68 (66.0)	230 (62.2)	40 (57.1)	270 (61.4)
Ever experienced intimate partner violence (Yes)[a]	111 (33.5)	51 (50.5)	140 (38.3)	23 (33.3)	163 (37.5)
Social support (mean ± SD)	64.6 ± 28.9	61.1 ± 29.6	64.4 ± 29.2	60.7 ± 28.6	63.3 ± 29.27
Depression symptoms (mean ± SD)	2.6 ± 3.5	3.8 ± 4.2	2.9 ± 3.7	2.9 ± 3.9	2.9 ± 3.70
Anxiety symptoms (mean ± SD)	1.3 ± 2.5	2.4 ± 3.6	1.5 ± 2.8	1.9 ± 3.1	1.6 ± 2.85

ART, antiretroviral therapy; SD, standard deviation.
[a]Five participants had missing data on intimate partner violence at baseline.

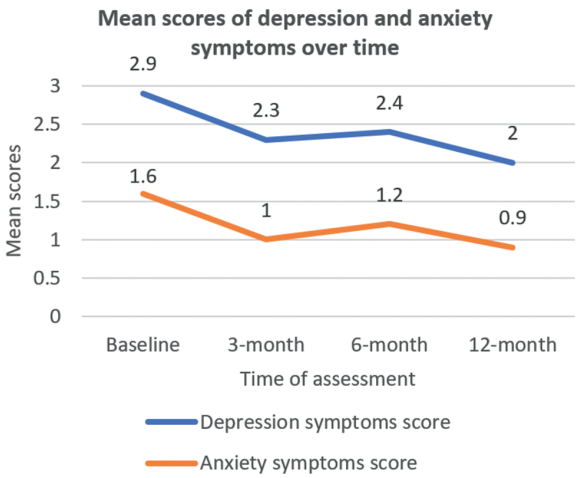
any of the four statements. Participants were classified as having ever experienced intimate partner violence if they had ever been a victim of physical, emotional or sexual abuse in an intimate relationship.

2.3 | Statistical analysis

Means (standard deviations [SD]) of continuous variables and proportions of categorical variables were reported. Generalized estimating equations (GEE) models were used to estimate the time-lagged associations between depression, anxiety symptoms and two HIV outcomes: VS and complete ART adherence. We conducted lagged analyses of the association between mental health symptoms at a given visit and HIV outcomes at the following visit. In this paper, time refers to the time of outcome assessment, which included: three-month, six-month or twelve-month follow-up visits. We estimated risk ratios (RR) of VS and ART adherence associated with a 5-unit change in scores of depression and anxiety symptoms, as other studies have [69,70]. Since depression and anxiety symptoms were highly correlated in our sample, for each outcome, separate models with the same set of covariates were run for depression or anxiety symptoms as the main predictor. Since HIV outcomes in the sample were very common (Table 1), the associations were explored using Poisson regression with robust variance estimation to avoid biases associated with inflated odds ratios [84]. Exchangeable covariance matrix between repeated measures was selected because it did not have convergence issues and had the smallest Quasi-likelihood Information Criterion (QIC) [85].

We assessed whether alcohol use modified the associations between mental health symptoms and HIV outcomes by adding interaction terms (e.g. depression symptoms × alcohol dependence) to the model. Similarly, the interactions between assessment time point and mental health symptoms were tested (e.g. depression symptoms × three-month visit). Since the longitudinal effects of mental health symptoms on VS may vary by baseline VS, baseline VS was also examined as a potential effect modifier. Interactions with product terms not significantly different from 0 (at $p < 0.05$ using the Wald test) were not included in the multivariable regression models. Significant modification effects were further explored by probing the associations of interest within the stratum of the effect modifiers (controlling for confounders). Only covariates associated with the outcome at $p < 0.1$ in the univariable models and meaningfully changed the main estimates of association (by more than 10%) were included in the final models [86,87]. Intervention exposure and time were kept in multivariable models regardless of statistical significance and meaningful change of the main estimates. Multiple imputations were used to accommodate missingness of depression, anxiety symptoms, VS and adherence data at follow-ups [88,89].

Statistical analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).



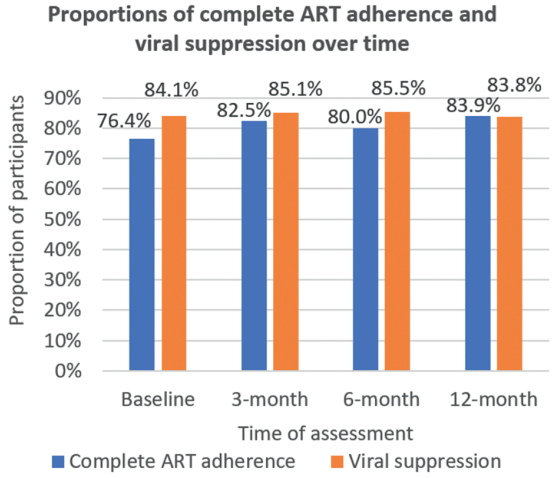


Figure 2. Changes in depression, anxiety symptoms, viral suppression and complete ART adherence of the sample over time. ART, antiretroviral therapy.

Table 2. Associations between depression, anxiety symptoms and HIV outcomes at the next visit[a]

	Viral suppression[b]			ART adherence[c]		
	aRR	95%CI	*p*-values	aRR	95%CI	*p*-values
Depression symptoms	1.00	0.96 to 1.03	0.94	0.95	0.91 to 0.99	0.03
Anxiety symptoms	1.00	0.95 to 1.05	0.98	0.93	0.88 to 0.99	0.02

ART, antiretroviral therapy; aRR, adjusted risk ratio; CI, confidence interval.
[a]Each multivariable model has only one mental health predictor, either depression symptoms or anxiety symptoms; models with the same outcome have the same set of covariates. aRRs were associated with a 5-point increase in scores of depression or anxiety symptoms at the previous time point; [b]models predicting viral suppression controlled for age, viral suppression at baseline, intervention exposure and time; [c]models predicting adherence controlled for marital status, alcohol dependence at baseline, adherence at baseline, intervention exposure and time

3 | RESULTS

3.1 | Sample characteristics at baseline

The mean age of enrolled participants (n = 440) was 40.2 years old (SD = 5.8) (Table 1). Almost all participants were male (96.8%), and 85% had at least some secondary school education. More than two-thirds (69.3%) were married, and 81.1% were employed at baseline. Most participants had a history of injection drug use (80.9%), and 39.1% had used non-injection drugs in the past three months. Alcohol dependence based on the MINI score was identified among 21.1% of participants. More than half had ever experienced HIV stigma (61.4%), and 37.5% had ever experienced intimate partner violence. The mean social support score was 63.3 (SD = 29.3, scale 0 to 100).

At baseline, 84.1% were virally suppressed and 76.4% had not missed an ART pill in the last three months. There was no difference in depression symptoms between participants with and without VS at baseline. A slightly lower score for anxiety symptoms was observed among those with VS (Table 1). Those who completely adhered to their ART regimen at baseline had lower depression and anxiety symptoms scores, compared to those without complete adherence.

3.2 | Distribution of depression, anxiety symptoms and HIV outcomes over time

Figure 2 shows changes in mental health symptoms, VS and ART adherence of the whole sample over time. There is a decrease in observed depression and anxiety symptoms from baseline to 12-month follow-up. There were no significant changes in VS over time, whereas complete ART adherence increased from 76.4% at baseline to 84.8% at the last follow-up.

3.3 | Associations between depression, anxiety symptoms and HIV outcomes

Overall, there were no associations between mental health symptoms and VS. However, a 5-point increase in depression or anxiety symptoms score was associated with a lower probability of complete ART adherence at the next visit (depression symptoms: adjusted risk ratio (aRR) = 0.95; 95% CI: 0.91 to 0.99; anxiety symptoms: aRR = 0.93; 85% CI: 0.88 to 0.99) (Table 2).

There was a significant effect modification by time, and the strength and significance of the associations between anxiety symptoms and HIV outcomes varied across study time points. Estimates of the full models with *p*-values of interaction terms are presented in Supplementary File, Table S1. When being

Table 3. Associations between depression, anxiety symptoms and HIV outcomes at the next visit, stratified by time of outcome assessment[a]

	Models predicting viral suppression[b]			Models predicting complete ART adherence[c]		
Time of outcome assessment	**aRR**	**95%CI**	***p*-values**	**aRR**	**95%CI**	***p*-values**
Main predictor: depression symptoms						
At three-month visit	0.99	0.94 to 1.04	0.66	0.90	0.84 to 0.97	0.005
At six-month visit	0.97	0.91 to 1.03	0.31	0.96	0.89 to 1.03	0.28
At twelve-month visit	1.05	1.00 to 1.10	0.09	1.01	0.94 to 1.09	0.69
Main predictor: anxiety symptoms						
At three-month visit	0.96	0.89 to 1.03	0.30	0.87	0.79 to 0.96	0.005
At six-month visit	0.96	0.86 to 1.07	0.50	0.90	0.79 to 1.03	0.14
At twelve-month visit	1.09	1.02 to 1.17	0.02	1.04	0.96 to 1.13	0.36

ART, antiretroviral therapy; aRR, adjusted risk ratio; CI, confidence interval.
[a]Each multivariable model has only one mental health predictor, either depression symptoms or anxiety symptoms at the previous time point. Models with the same outcome have the same set of covariates. Time presented in the first column is the time of assessment of viral suppression and ART adherence. aRRs were associated with a 5-point increase in scores of depression or anxiety symptoms at the previous time point; [b]models predicting viral suppression control for age, viral suppression at baseline, intervention exposure, time, interaction of time × depression/anxiety symptoms; [c]models predicting adherence control for marital status, alcohol dependence at baseline, adherence at baseline, intervention exposure, time, interaction of time × depression/anxiety symptoms

stratified by time, both baseline depression and anxiety symptoms were associated with a lower probability of complete ART adherence at three months (depression symptoms: aRR = 0.90; 95%CI: 0.84 to 0.97; anxiety symptoms: aRR = 0.87; 85%CI: 0.79 to 0.96), though no association was seen with VS. At subsequent follow-up visits, there was no association between symptoms of depression and anxiety with either VS or complete ART adherence, except for a signal of higher VS at 12 months associated with a 5-point increase in anxiety symptoms at six months (aRR = 1.09; 95%CI 1.02 to 1.17) (Table 3). Baseline VS was not a significant modifier of the associations between depression, anxiety and VS (Tables S2.1 and S2.2).

3.4 | Associations between depression/anxiety symptoms and HIV outcomes: Possible modification role of alcohol dependence

Alcohol dependence at baseline significantly modified the association between anxiety symptoms and complete ART adherence (*p*-value for interaction term = 0.02). Anxiety symptoms at baseline and lower probability of complete adherence at three months were more strongly related among participants with alcohol dependence, compared to those without (Table 4). Anxiety symptoms only predicted poor adherence at six months among those with alcohol dependence. At 12 months, there was no association between anxiety at the previous time point and adherence for all participants. The interactions between alcohol dependence and mental health symptoms in the remaining associations (depression predicting both HIV outcomes and anxiety predicting VS) were not significant at $p < 0.05$ and were not further explored.

Table 4. Associations between anxiety symptoms and complete ART adherence at the next visit, stratified by alcohol dependence and time since baseline

Time of outcome assessment	**aRR[a]**	**95%CI**	***p*-values**
At three-month visit			
Alcohol dependence	0.80	0.68 to 0.94	0.008
No alcohol dependence	0.90	0.82 to 0.99	0.04
At six-month visit			
Alcohol dependence	0.82	0.68 to 0.99	0.05
No alcohol dependence	0.93	0.82 to 1.06	0.33
At twelve-month visit			
Alcohol dependence	0.95	0.81 to 1.12	0.57
No alcohol dependence	1.08	1.00 to 1.17	0.08

aRR, adjusted risk ratio; CI, confidence interval
[a]Models controlling for marital status, alcohol dependence at baseline, adherence at baseline, intervention exposure, time, interaction of time × anxiety symptoms, interaction of alcohol dependence × anxiety symptoms. aRRs were associated with 5-point increase in scores of anxiety symptoms at the previous time point.

4 | DISCUSSION

Among a sample of 440 ART clients with hazardous alcohol use, we did not find an overall effect of depression and anxiety symptoms on VS, but observed a decreased probability of complete ART adherence associated with increased depression and anxiety symptoms. The magnitude and significance of the associations varied by the time of outcome assessment. Negative effects of anxiety symptoms on ART adherence were significantly worse among participants with alcohol dependence at baseline, compared to those without alcohol dependence.

While there was no effect of mental health symptoms on VS when all time points were taken into account, we found that anxiety symptoms were associated with a small increase in the probability of VS at the last follow-up. This was an

unexpected finding, although one study among PWH in Russia also reported that a greater state of anxiety was positively associated with better adherence [16]. Previous studies reported a Hawthorne effect, which refers to the alteration of behaviour of subjects due to awareness of being observed in a study [90,91]. Moreover, an inverted U-shaped association between arousal, anxiety and performance [92,93] has been demonstrated. By participating in multiple rounds of interviews, participants with milder anxiety symptoms might become more aware of and worried about their health's status, and therefore more motivated to take action to improve their overall health. Participants with more severe anxiety were more likely to be lost to follow-up in this study (data not shown) – therefore at 12-month follow-up, participants with lower levels of anxiety might comprise a greater proportion of the sample.

Our results are similar to other studies that examined the association between mental health symptoms and ART adherence in the general population of PWH [17,19]. However, the magnitudes of the associations in our study were smaller than those reported by previous studies. Participants in our sample had a high proportion of VS and ART adherence at baseline, which leaves fewer opportunities for enhancement of HIV outcomes. Due to the Hawthorne effect mentioned above, being a participant in REDART over time might have also attenuated the effects of mental health problems on adherence and viral suppression to some extent, regardless of which intervention arm the participant belonged to. This might help explain why stratification by time only showed significant associations between mental health symptoms and ART adherence at the three-month visit.

We also found that the negative effects of anxiety symptoms on ART adherence at earlier time points were modified by alcohol dependence such that the associations appeared to be stronger among those with alcohol dependence. Previous studies among PWH reported that a higher number of syndemic conditions was associated with higher HIV viral load and lower ART adherence [94,95], although the authors did not examine the specific interaction of alcohol use and mental health symptoms. PWH can use alcohol as a coping strategy, which may help improve mood to an extent [44]. However, since hazardous alcohol use independently decreased ART adherence [96,97], high levels of alcohol use such as alcohol dependence among PWH with anxiety symptoms may pose greater challenges than benefits to adherence.

Our analyses have several limitations. First, self-reported measures of adherence are more likely to produce measurement errors, as compared to objective measures such as electronic medication packaging devices [73]. In order to minimize this limitation, we also analysed the associations between mental health symptoms and HIV VS – a biological outcome not subject to such biases. Second, our study was not immune to loss to follow-up – a common issue affecting longitudinal analyses. We had missing data for key predictors and outcomes at the follow-up visits, ranging from 7% to 12% (Table S3). In this study, we used multiple imputations to impute missing values of depression, anxiety symptoms, VS and adherence for the sample, as recommended for GEE analyses of longitudinal data [88,89]. Third, our sample was not a random sample of ART clients. The majority of our participants were men and had a history of injection drug use. HIV transmission in Thai Nguyen is primarily driven by injection drug use [50] – a behaviour more commonly seen among men in Vietnam [98,99]. Other studies among PWH in Vietnam also reported overwhelming proportions of participants being male with drug use behaviours [46,53]. Finally, in this study, we reported aRRs associated with a 5-unit change in depression and anxiety symptoms. We acknowledge that there are alternative ways to analyse PHQ-9 and GAD-7 scores, which might result in different estimates of the associations between mental health symptoms and HIV outcomes than ours.

Our findings suggest that increased depression or anxiety symptoms over time are associated with decreased ART adherence among PWH with hazardous alcohol use, and support a modifying effect of alcohol dependence on the association between anxiety symptoms and ART adherence in this group. We recommend that future interventions aim to raise awareness about mental health problems among PWH, especially those with alcohol use disorders. Mental health services such as screening, counselling or medication treatment are also imperative to improve HIV outcomes for PWH with hazardous alcohol use. These mental health services can be integrated into alcohol use interventions or into existing HIV primary care clinics in Vietnam. It is also important that these interventions are tested for efficacy and cost-effectiveness in low-resource settings such as Vietnam.

5 | CONCLUSIONS

Depression and anxiety symptoms had no overall effect on VS, although anxiety symptoms at six months were associated with a mild increase in the probability of VS at 12 months. Increased depression and anxiety symptoms were associated with a lower probability of complete ART adherence, and participants with both alcohol dependence and anxiety symptoms had the lowest adherence. Interventions focusing on mental healthcare for PWH with hazardous alcohol use are much needed, and optimal models integrating mental healthcare and alcohol reduction should be implemented and tested in HIV primary care clinics in low-resource settings.

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COMPETING INTEREST

The authors have declared no conflict of interest.

AUTHORS' CONTRIBUTIONS

V.G., C.L., H.H., G.C., K.L., T.S., H.T. and D.D. performed the research. V.G., C.L., H.H., G.C., K.L., D.D. and C.F. designed the research study. M.N. analysed the data and wrote the paper. V.G., H.L.R., B.P. K.M., C.L., D.D., H.H., G.C. and K.L.

revised it critically for important intellectual contents. All authors have given final approval of the manuscript to be published.

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SUPPORTING INFORMATION

Additional Supporting information may be found online in the Supporting Information tab for this article.

Figure S1. Conceptual model and mapping of underlying theories

Table S1. Associations between depression, anxiety symptoms and HIV outcomes at the next visit, taking into account the effect modification by time (Models with interaction terms)

Table S2. Effect modification of baseline viral suppression on the associations between depression, anxiety symptoms and viral suppression

Table S3. Missing data of depression, anxiety symptoms and HIV outcomes at follow-up visits

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REVIEW

Interventions to address the mental health of adolescents and young adults living with or affected by HIV: state of the evidence

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Abstract

Introduction: Adolescents and young adults (AYA) remain vulnerable to HIV-infection and significant co-morbid mental health challenges that are barriers to treatment and prevention efforts. Globally millions of AYA are living with HIV (AYALH) and/or have been affected by HIV in their families (AYAAH), with studies highlighting the need for mental health programmes. With no current guidelines for delivering mental health interventions for AYALH or AYAAH, a scoping review was undertaken to explore current evidence-based mental health interventions for AYALH and AYAAH to inform future work.

Methods: The review, targeting work between 2014 and 2020, initially included studies of evidence-based mental health interventions for AYALH and AYAAH, ages 10 to 24 years, that used traditional mental health treatments. Given the few studies identified, we expanded our search to include psychosocial interventions that had mental health study outcomes.

Results and discussion: We identified 13 studies, seven focused on AYALH, five on AYAAH, and one on both. Most studies took place in sub-Saharan Africa. Depression was targeted in eight studies with the remainder focused on a range of emotional and behavioural symptoms. Few studies used evidence-based approaches such as Cognitive Behaviour Therapy; psychosocial approaches included mental health treatments, group-based and family strengthening interventions, economic empowerment combined with family strengthening, group-based mindfulness and community interventions. Eleven studies were randomized control trials with four pilot studies. There was variation in sample size, treatment delivery mode (individual focus, group-based, family focus), and measures of effectiveness across studies. Most used trained lay counsellors as facilitators, with few using trained mental health professionals. Eleven studies reported positive intervention effects on mental health.

Conclusions: Despite the need for mental health interventions for AYALH and AYAAH, we know surprisingly little about mental health treatment for this vulnerable population. There are some promising approaches, but more work is needed to identify evidence-based approaches and corresponding mechanisms of change. Given limited resources, integrating mental health treatment into healthcare settings and using digital health approaches may support more standardized and scalable treatments. Greater emphasis on implementation science frameworks is needed to create sustainable mental health treatment for AYALH and AYAAH globally.

Keywords: HIV; mental health; adolescents and young adults; psychosocial interventions

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1 | INTRODUCTION

In 2019, 1.7 million people were newly infected with HIV, with 460,000 of these new infections in adolescents and young adults (AYA), ages 10 to 24-years [1,2]. The number of new AYA infections is largely driven by horizontal transmission and 9% of new infections still occur in children 14 years and older, primarily through vertical transmission [2]. Moreover, improvements in antiretroviral therapy (ART) have resulted in children with perinatally acquired HIV (PHIV) surviving into adolescence and adulthood. AYA with PHIV experience unique challenges to those with behaviourally acquired HIV, including developmental delays, neurocognitive issues, and not finding out their diagnosis until older. Furthermore, sub-populations of AYA experience unique vulnerabilities, for example, adolescent girls and young women accounted for 25% of new infections in sub-Saharan Africa in 2019, despite making up about 10% of the total population [1]. In the United States (USA), young men who have sex with men, followed by young transgender women are at greatest risk for HIV-infection, particularly Black and Latinx populations. These same groups are also at high risk in many Asian and Pacific countries [3]. While many countries are reporting excellent progress towards HIV prevention, recent data confirm a bleak picture globally for AYA. Older adolescents and younger adults (15 to 24 years) compared to children and young adolescents (0 to 14 years)

and older adults (25+ years) have the lowest chance of knowing their status and the lowest likelihood of HIV viral suppression – along with the highest HIV incidence [4]. These data are being hidden in health information systems which pool figures in all those over the age of 14, and in those which merge older and younger adolescents [5]. Given the high burden of HIV among AYA, addressing the differential emotional and behavioural needs and complex vulnerabilities of AYA living with HIV (AYALH) is critical to treatment and prevention.

Mental health challenges are a critical barrier to ending the HIV epidemic across contexts and populations, given that they increase the risk of non-adherence to ART, poor engagement in care and sexual and substance use risk behaviours for HIV transmission [6-9]. Studies from multiple countries increasingly show high rates of various mental health problems in AYALH ranging from psychosocial distress and symptoms of emotional and behavioural problems to actual psychiatric disorders [7,9-14], with some studies finding higher rates of mental health problems in youth compared to those with PHIV [15,16].

Importantly, addressing mental health problems early in AYA development is crucial for the wellbeing of those impacted [17] given that more than 50% of adult mental health disorders appear before the age of 14 years globally [18-20]. During this period, AYA experience extensive physical, hormonal, neurocognitive and psychosocial transformations. These changes are challenging to manage in the context of living with a chronic, life-threatening, stigmatized and sexually transmissible virus, that can have significant neurological effects [7,21,22].

Unfortunately, understanding the role of HIV and other pathways of influence on mental health has been difficult to determine. Studies of AYALH have often utilized comparison groups of AYA affected by HIV (AYAAH) - including those who lost one or both parents to AIDS, or who are living in households with caregivers or family members living with HIV, and those who were perinatally HIV exposed, but uninfected (PHEU) as they share many of the same psychosocial and contextual vulnerabilities. Results show that AYAAH are also at increased risk for mental health problems [23,24], with some studies suggesting that they are at even greater risk than AYALH [11,14,16]. For example, in one study, AYAAH were more likely to be depressed, anxious and report internalized stigma, suicidal ideation and excessive substance use than AYALH [16]. Importantly, both groups have shown higher rates of mental health problems than the general population [8,25,26]. In low-resource contexts, where the majority of AYALH and AYAAH reside, limited availability of psychosocial supports adds to the challenges of coping with poor mental health [7,27-29].

There are numerous individual, familial, social and environmental risks that can profoundly influence life trajectories and mental health in both AYALH and AYAAH [7,27]. Both groups typically face ongoing and cumulative psychological stressors exacerbated by adverse environments including poverty, violence, discrimination, familial and environmental substance abuse or mental illness, as well as HIV-related illness and loss of caregivers. Both groups also confront stigma associated with familial HIV. All these factors have been associated with behavioural problems and psychiatric disorders, including post-traumatic stress disorder, depression and severe anxiety [30], which in turn may increase sexual risk behaviours, putting AYAAH at risk of HIV infection, and putting AYALH at risk for non-adherence to treatment, poor health outcomes, and secondary transmission to others. For these reasons, it is imperative to consider mental health interventions for both groups.

Fortunately, over the past 20 years, substantial advances in evidence-based mental health treatment for AYA in the general population could be a basis for intervention work with AYALH and AYAAH. Evidence-based mental health treatment, that is a treatment approach supported by a body of research evidence relating to its efficacy, include Cognitive-Behavioural Therapy (CBT) [31,32], Interpersonal Psychotherapy (IPT) [33,34], Dialectical Behavioural Therapy (DBT) and Acceptance and Commitment Therapy [35]. Most of these treatments have been evaluated with AYA in multiple trials in multiple contexts, although primarily in resource-rich countries, led by professional therapists. Although limited, increasingly trials are being conducted for use by lay counsellors in low- and middle-income countries (LMIC) [36].

Relatedly, multiple reviews have documented that even fewer trials have tested interventions which target the mental health needs AYALH or AYAAH, particularly in LMIC, with mixed findings [9,24,29,37,38]. Due to the lack of sufficient evidence, the World Health Organization guidelines on mental health treatment and prevention for adolescents (Helping Adolescents Thrive) concluded that despite the priority of delivering mental health interventions to AYALH, no recommendations could be made and highlighted a need for high-quality research on psychosocial interventions promoting AYALH mental health [39]. A similar need has been advocated for AYAAH including uninfected AYA with PHEU given the high rates of mental health problems and potential risks of perinatal exposure to ART, as well as similar psychosocial and contextual risks as AYALH [40]. Given the research gap, a scoping review was undertaken to explore current evidence-based mental health interventions for AYALH and AYAAH (including uninfected AYA with PHEU) and to explore how research gaps could be addressed to inform evidence-based interventions for this population.

2 | METHODS

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines for scoping reviews [41], searching data in August and September 2020 using online electronic databases, including PubMed (which includes Medline), the following EBSCO databases Psycharticles, Socindex, Academic Search Complete, Family and Society Studies Worldwide; CINAHL; Web of Knowledge Social Science and Emerging sources databases; EMBASE; Proquest; Scopus; Cochrane Reviews; Epistemonikos (evidence-based healthcare database); CT.gov (http://apps.who.int/trialsearch) and the International Clinical Trials Registry Platform (https://clinicaltrials.gov). In addition, we examined the National Institute for Health databases and the AIDS 2020 Virtual Conference Oral Abstracts and E-posters conference proceedings. Lastly, additional hand searching, and citation tracking was done.

Given previous reviews [6-9,24,29,37,38,42], we focused our search on 2014 to 2020. We predefined our search using

Population, Intervention, Comparison, Outcome and Study (PICOS).

a. Population: AYALH or AYAAH, aged 10 to 24 years. Although adolescence is typically defined as ages 10 to 19 years, there is inconsistency in the definition across agencies and contexts. Additionally, in many clinical HIV settings, AYA remain in paediatric HIV care into their twenties (19 to 24 years). While it is recognized that several stages of development exist within adolescence itself (early – 10 to 13 years; middle – 14 to 16 years; late – 17 to 19 years), many studies do not distinguish between these stages, and thus we included studies using a broader definition of adolescence. This broad range ensured inclusion of a larger number of studies, with the recognition that younger and older adolescents may require different approaches.
b. Intervention: any mental health treatment approach, or psychosocial intervention that has promotion of mental health or reduction of mental health distress as an outcome. This could include a range of modalities, including school-based, social and family support, community and economic interventions, etc.
c. Comparison group: any choice of comparison group including no comparison group.
d. Outcome: any mental health outcome variable including psychiatric disorders, general mental illness or specific mental health problems (e.g. depression, anxiety); also included were the following: psychological or emotional wellbeing, psychosocial capital or resilience, or mental or emotional health; psychological distress or emotional distress or trauma.
e. Study design: any research study design that included a mental health-related intervention. Clinical notes or reports or case-based descriptions of mental health interventions were excluded.
f. Geographic location: all global locations were included. Even though a majority of AYALH and AYAAH live in sub-Saharan Africa, given the global epidemiology of HIV in women which in turn affects youth, we included evidence-based mental health treatments from across the globe.

The first author (AB) undertook the scoping review of databases described above using the above criteria and the search terms described in Appendix S1. Following the search, any duplicates were removed. The remaining titles were imported into Rayyan software to scan titles and abstracts for selection [43]. A second author (PK) independently searched 25% of the same list of titles and abstracts. This review process did not find discrepancies or additional titles for inclusion. Importantly, in the first review search, only four studies were identified using more traditional evidence-based mental health interventions (e.g. CBT, IPT). Thus, we expanded the review to include mental health promotion interventions or interventions that targeted mental health outcomes, including psychosocial, school-based, family strengthening and economic empowerment interventions [24,29,38].

For presentation, we organized the studies into several categories of interventions: individual mental health treatment; group and family strengthening; family based economic strengthening; group-based mindfulness training; and a community-based intervention. An analysis of the review results focuses on providing a detailed description of the mental health interventions, describing the targeted mental health conditions, the specific outcome measures used, the type of evidence-based intervention that was used, the setting in which this intervention was applied, the training and level of expertise required to deliver the intervention, and the outcomes of the mental health intervention.

3 | RESULTS AND DISCUSSION

Our database search identified 1335 records. After removing duplicates, the remaining 1145 titles were screened. The majority did not meet study criteria as most were descriptive or clinical accounts of individuals living with or affected by HIV and focused on social, demographic and clinical characteristics rather than interventions. Only 20 titles remained for full-text evaluation with 13 studies meeting inclusion criteria. The remainder did not have a mental health outcome, did not measure the effects of a mental health intervention, or focused on adult participants (Figure 1).

3.1 | Evaluation of risk of bias

An evaluation of the bias risk of the 13 studies in this review was done to establish the relative strength of evidence of mental health interventions for AYALH and AYAAH using the Method for Evaluating Research Guideline Evidence (MERGE) [44]. MERGE provides a simple and well-defined way of evaluating public health interventions. Each of the 13 articles reviewed were independently coded by two authors (AB, AP) based on criteria relevant to evaluating intervention study characteristics. An agreement of 85% was achieved with differences in scoring (two cases) resolved through discussion. Table 1 shows the overall rating for each study using MERGE guidelines. Of the 13 studies, six were very unlikely or unlikely to change in outcome, with seven likely or very likely to have changed outcomes as a function of design flaws (Table 1).

3.2 | General characteristics

Among the 13 studies, eight focused on AYALH [45-52], five on AYAAH [53-57] and one on both [58] (See Table 2). Nine studies took place in sub-Saharan Africa, three in Asia (China, Myanmar, Thailand), and two in North America (both USA).

Depression was the most common mental health problem studied (N = 9) [45-48,51,54,56-58], with various depression scales used, including the Patient Health Questionnaire (PHQ-9) [45,48], the Center for Epidemiologic Studies Depression Scale for Children [58], the Child Depression Inventory [47,51,54], the Zung Self-Rating Scale [57] and the Depression Anxiety Stress Scale [56]. Only one study used a formal depression diagnostic tool, the Quick Inventory of Depressive Symptomatology-Clinician, since depression was an inclusion criterion for study participation [46].

Five studies utilized a general measure of emotional and behavioural symptoms, the Strengths and Difficulties Questionnaire (SDQ) [45,47,48,53,54], two studies assessed hopelessness [51,55], one focused on emotional regulation [49], and one study focused on self-esteem, self-worth, stigma (not

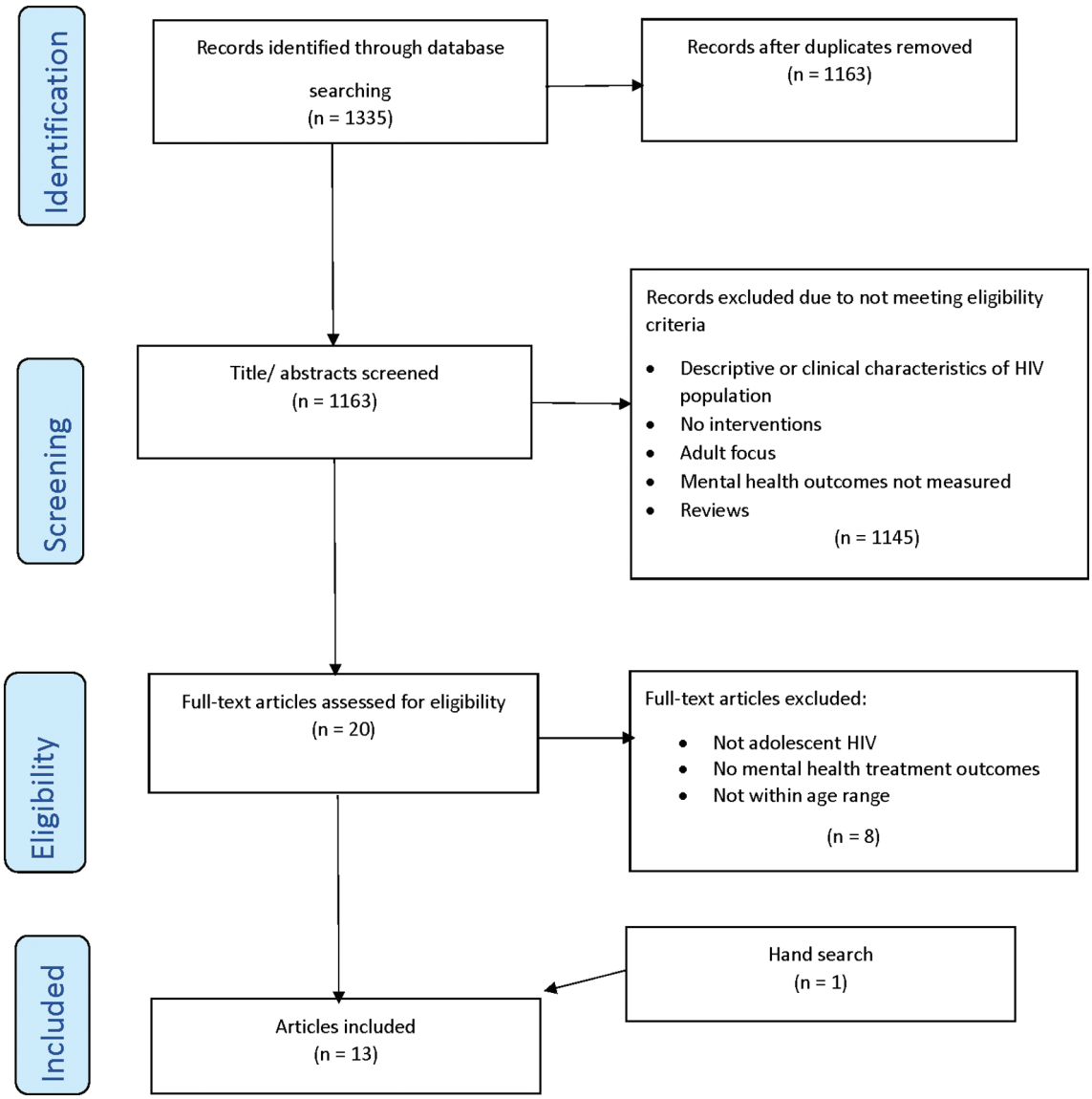

Figure 1. (Scoping Review) PRISMA Guide.

defined) and quality of life as indicators of mental health [50]. Apart from two studies [46,49], the measures in all others were adapted/translated to suit local needs in terms of language and meaning. None of the studies undertook any formal validation of the measures used.

Importantly, the 13 studies reflect a range of intervention strategies, including CBT, IPT, motivational interviewing (MI), family strengthening, economic empowerment, mindfulness, problem-solving and disclosure as presented below. Although mental health had to be an outcome for our review, it was not necessarily the only outcome – adherence, stigma and disclosure, for example were other outcomes in the studies. Moreover, the interventions were implemented by a range of facilitators from trained masters and doctoral-level therapists with enhanced CBT skills to community adolescent treatment supporters, trained lay health workers and skilled mindfulness instructors. All the interventions included some form of facilitator training and supervision.

3.3 | Individual mental health treatment interventions

As noted, only one study used a mental health diagnosis for study inclusion criteria [46]. This study examined the influence of depression treatment on adherence and health outcomes among eight AYALH in the USA diagnosed with depression. The intervention used CBT that included problem solving, mood monitoring, behavioural activation and cognitive restructuring to decrease obstacles to adherence and increase wellness (self-acceptance, positive relations with others, autonomy, environmental mastery, purpose in life and personal growth). Training in emotional regulation, social skills, assertiveness and relaxation was also provided. This study found that at 24 weeks post-baseline, the criteria for remission were met with a depression mean score of 1.5 compared to a score of 16 at baseline. Adherence improved from 74.3% to 90.5%. Although promising, with only eight participants, no

Table 1. Risk of bias analysis

Author and year	Comments	Overall assessment of bias	Rating	Outcomes
Betancourt *et al* (2017)	Contamination of community samples	Low-moderate risk	B1	Unlikely to change
Cavazos-Rehg *et al* (2020)	Well-controlled study	Low risk of bias	A	Very unlikely to change
Dow *et al* (2020)	Some bias due to lack of blinding and differences in treatment approach	Low-moderate risk	B1	Unlikely to change
Kennard *et al* (2014)	Case control study; small sample, no control group	High risk of bias	C	Very likely to change
Li *et al* (2014)	Small sample and potential bias in randomization process	Moderate-High risk	B2	Likely to change
Mon *et al* (2016)	Randomized only some groups; measurement bias	Moderate-high risk	B2	Likely to change
Nestadt *et al* (2019)	Small sample size, well controlled study	Low-moderate risk	B1	Unlikely to change
Puffer *et al* (2016)	Potential contamination and temporal effects of stepped-wedge design	Low-moderate risk	B1	Unlikely to change
Ssewamala *et al* (2016)	Well controlled study	Low-moderate risk	B1	Unlikely to change
Thurman *et al* (2018)	Biased sampling, no randomization and no control group	High risk of bias	C	Very likely to change
Vreeman *et al* (2019)	Only sites randomized, not individual allocations	Moderate-high risk	B2	Likely to change
Webb *et al* (2018)	Small sample size and 25% loss to follow-up	Moderate-high risk	B2	Likely to change
Willis *et al* (2019)	Small sample size and 32% loss to follow-up	Moderate-high risk	B2	Likely to change

comparison group and multiple components, a larger trial is needed to evaluate intervention efficacy.

Another study, based in Kenya, examined a counselling intervention to enhance HIV disclosure among AYALH randomized to intervention or control. This disclosure intervention comprised intensive counselling with trained counsellors and resulted in increased disclosure over 24 months, but with no statistically significant group differences in depression and SDQ scores [48].

3.4 | Group and family strengthening interventions

One study used an randomized control trial (RCT) and stepped-wedge design to evaluate a combined individual (2 sessions) and group-based (10 sessions) mental health intervention for AYALH [45]. The intervention, delivered by trained young adult group leaders who were either living with HIV and/or had prior mental health research experience, addressed mental health challenges through teaching strategies to improve coping and family support, and reduce internal stigma. The intervention was adapted for AYALH, in part, from a CBT intervention for bereaved orphans in Tanzania and included components of IPT and MI. Depression and SDQ scores improved overall, but with no statistically significant group differences. Scores on internalized stigma (effect size 2.11), externalized stigma (effect size 1.5) and self-reported adherence scores (effect size 7.29) all improved significantly in the intervention arm compared to standard of care.

A group-based intervention for AYAAH in Kenya was evaluated through a cluster RCT with families attending various churches [54]. The intervention sought to improve overall family communication particularly in relation to economic, emotional and HIV-related topics. While the intervention resulted in significant improvements in family communication compared to the comparison group, there was no significant impact on AYAAH mental health.

A few studies, all in LMIC, used family strengthening interventions. One pilot RCT with 88 families in Rwanda found that AYAAH and AYALH had significantly fewer symptoms of depression after receiving a family home-based intervention to support mental health and promote parent–child relationships compared to controls [58]. Another study used an adapted version of the Collaborative HIV and Adolescent Mental Health Program (CHAMP), an evidence-based intervention originally developed for youth at risk for HIV in the USA and validated in a large-scale clinical trial [59], and then adapted for AYAAH and AYALH in multiple contexts including the USA, South Africa, and Thailand (also called CHAMPSA, CHAMP+, CHAMP+Asia and VUKA) [52]. CHAMP is a developmentally timed intervention which aims to prevent HIV infection and promote mental health in adolescents through promoting family and peer support, adolescent and caregiver skill building, and promotion of resilience [59-62].

Several RCT pilot studies with early adolescents living with HIV, adapted this multiple family group-based intervention, CHAMP+ [47,61-63]. The most recent work, CHAMP+Asia took place in several HIV clinics in Thailand and focused on the promotion of mental health and ART adherence and prevention of sexual and drug-use risk behaviours in AYALH and can be delivered by lay counsellors, masters level psychologists or social workers. Six-month post baseline, AYALH in CHAMP+ condition had significantly improved adherence and mental health scores on the SDQ, but not on the Child Depression Inventory, compared to the comparison group [63].

Table 2. Study characteristics

Author, year and country	Study population		Intervention focus and facilitators	Study design & inclusion criteria	Mental health outcomes only	Summary of mental health findings only
	HIV status-and other criteria	Total N; gender and age				
Betancourt *et al* (2017) Rwanda No MH requirement	AYAAH and AYALH living with one HIV positive caregiver	82 families N = 170 AYAAH (7 to 17 years, mean= 11) (48% female) (12% HIV positive; n = 21) N = 123 caregivers	FSI-HIV (Family Strengthening Intervention) to promote mental health and improve parent–child relationships in families with caregivers living with HIV Manualized, delivered by: Bachelor level counsellors; 90-minute weekly home visiting; 8 sessions	Pilot RCT	• Depression • Conduct problems • Functional impairment	At 3 months, AYAAH in FSI-HIV showed fewer symptoms of depression compared to controls by self and parent report No significant differences by group on conduct problems, functional impairment
Cavazos-Rehg *et al* (2020) Uganda No MH requirement	AYALH	N = 702 (10 to 16 years, mean=12.42) (56.4% female)	Family level economic strengthening intervention includes 4 financial management sessions, support for ART, microenterprises for family income over 24 months + 12 educational sessions and adherence counselling Delivered by lay counsellors in ART adherence + finance mentor	Repeated measures RCT	• Hopelessness • Depression • Self-Concept Hopelessness • Depression • Self-Concept	At 24 months, treatment arm reported lower hopelessness score and at 36 months, lower depression scores
Dow *et al* (2020) Tanzania No MH requirement	AYALH	N = 128 AYALH (12 to 24 years, mean= 18) (51% female) (84% perinatally acquired)	Two individual and ten group-based intervention sessions with elements of CBT, IPT, MI, Trauma counselling lasting 90 minutes Delivered by young adults (23 to 30 years) living with HIV and/or prior experience with mental health research	RCT – stepped wedge design	• Depression • Emotional and behavioural problems • Stigma • Post-traumatic stress	At 6 months, no significant differences in mental health scores for depression, emotional and behavioural problems and stigma compared to the control arm
Kennard *et al* (2014) USA MH requirement	AYALH diagnosed with depression	N = 8 (16 to 24 years, mean= 21) (13% female) (88% behaviourally acquired)	14 planned, 60-minute sessions over 6 months using health and wellness CBT intervention with elements of MI; psychotropic medication; and psychoeducation Delivered by masters/ doctoral level therapists trained in CBT	Treatment group at two treatment sites – with no control group	• Depression	At 6 months, depression improved

(*Continued*)

Table 2 . (*Continued*)

Author, year and country	Study population		Intervention focus and facilitators	Study design & inclusion criteria	Mental health outcomes only	Summary of mental health findings only
	HIV status-and other criteria	Total N; gender and age				
Li *et al* (2014) China No MH requirement	AYAAH	N = 79 (6 to 12 years, 13 to 18 years (47% female)	A multilevel family intervention focusing on the family's capacity overcome impact of living with HIV small group session, home-based family activities and community events to promote social integration	Cluster RCT	• Self-esteem • Problem behaviour • Depression	At 6 months, improved self-esteem among 6 to 12-year-old children, but not 13 to 18 years; decrease in problem behaviour in controls
Mon *et al* (2016) Myanmar No MH requirement	AYAAH	N = 160 AYAAH (10 to 16 years) (58.8% female)	Mindfulness training group intervention sessions over 3 months for a total of 8 sessions lasting 120 minutes each Delivered by trained mindfulness leader	Cluster RCT	• Emotional and Behavioural Problems	At 6 months, emotional and behavioural problems improved; no effect on social behaviour
Nestadt *et al* (2019) Thailand No MH requirement	AYALH; on ART	N = 88 dyads of caregiver and AYALH AYALH (9 to 14 years, mean= 12) (49% female) (100% perinatally infected)	11 weekly sessions using structured manualized intervention, including a cartoon-based curriculum, follow-up activities and facilitated discussion over 6 months Delivered by a social worker or counsellor	Pilot RCT	• Depression • Emotional and Behavioural Problems	At 6 months, statistically significant improvements in emotional and behavioural problems, sustained at 9 months, but not on depression
Puffer *et al* (2016) Kenya No MH requirement	AYAAH	124 families N = 237 AYAAH (10 to 16 years, mean= 12) (51% female) N = 203 caregivers	Church-based intervention for families of 9 sessions of 120 minutes each delivered in churches Delivered by 4 lay facilitators who received 5-day training and weekly preparation (no prior training in MH or HIV prevention)	Cluster RCT – stepped wedge design	• Self-esteem • Depression • Anxiety • Emotional and Behavioural Problems	At 3 months, no effects on mental health outcomes
Ssewamala *et al* (2016) Uganda No MH requirement	AYAAH; (Orphans)	N = 346 (12 to 16 years, mean= 13) (65% female)	Family level economic strengthening that included one mentorship meeting per month, managing a savings account and ten, 1 to 2 hours microenterprise skills over 12 months Delivered by lay counsellors and finance mentor	Two-arm cluster RCT	• Hopelessness • Self-concept	At 24 months, the treatment arm reported lower-levels of hopelessness, and high-levels of self-concept compared to the control arm

(*Continued*)

Table 2 . (*Continued*)

Author, year and country	Study population		Intervention focus and facilitators	Study design & inclusion criteria	Mental health outcomes only	Summary of mental health findings only
	HIV status-and other criteria	Total N; gender and age				
Thurman *et al* (2018) South Africa No MH requirement	AYAAH	N = 105 AYAAH (12 to 17 years) (60% female) N = 95 caregivers	A structured curriculum building core HIV knowledge and behavioural skills (Let's Talk) comprising 19 caregiver and 14 adolescent sessions over 90 minutes. Includes CBT elements Delivered by trained facilitators who received three one-week training sessions	Pilot study (Pre-post no control group)	• Depression • Anxiety	At 3 months, both caregivers and adolescents demonstrated improved mental health including depression and anxiety
Vreeman *et al* (2019) Kenya No MH requirement	AYALH	N = 285 dyads of caregiver and AYALH (10 to 14 years, mean = 12) (52% female)	Disclosure intervention comprises access to intensive group and one-on-one counselling; pamphlets and videos over 2 years Delivered by trained counsellors	Cluster RCT	• Depression • Emotional and Behavioural Problems	At 24 months, no significant differences between groups on depression or emotional and behavioural problems
Webb *et al* (2018) USA No MH requirement	AYALH	N = 72 AYALH (14 to 22 years, mean = 18.7) (45% female)	Mindfulness stress reduction programme (MBSR) of nine sessions, including CBT elements (present-focus, rumination and future concerns) as well health education covering nutrition, exercise and puberty Delivered by instructors trained in MBSR over 8 weekly sessions and extensive experience teaching mindfulness and by health education instructors trained over 3 hours on curriculum and had health education experience.	Pilot RCT	• Mindful Attention and Awareness • Perceived Stress • Coping • Aggression • Emotional regulation	At 3 months, significant improvement in mindfulness: positive mental health (mindfulness; problem solving coping; life satisfaction; and aggression) No significant differences in perceived stress, rumination, distraction, anxiety or cognitive flexibility
Willis *et al* (2019) Zimbabwe No MH requirement	AYALH; on ART	N = 94 AYALH (10 to 15 years) (59% female)	Improving linkage to services through Community Adolescent Treatment Supporters trained and mentored in adherence and psychosocial support; Weekly home visits Delivered by youth aged 18 to 24 trained and mentored in adherence and psychosocial support counselling	RCT	• Self-confidence • Self-esteem • Self-worth	At 12 months, significant improvements in psychosocial wellbeing (confidence, self-esteem, and self-worth); quality of life

CBT, cognitive behaviour therapy; FSI, family strengthening intervention; IPT, interpersonal psychotherapy; MH, Mental health; MI, motivational interviewing.

Another randomized pilot study in China evaluated a family strengthening programme, Together for Empowerment Activities, a multilevel intervention that focuses on a family's capacity to overcome the impacts of living with HIV. It incorporates group and home-based family activities as well as community events to promote parent–child communication and improve AYAAH self-esteem and reduce any problem behaviour [57]. Group differences were noted in self-esteem for children 6 to 12 years of age at three months, but not at six months, and not for adolescents [13-18]. Both age groups showed significant group differences in the level of parental care at six months. The groups did not differ significantly on reduction in problem behaviours. A second family centred programme to mitigate HIV risk (knowledge, self-efficacy) and promote mental health among AYAAH in South Africa, focused on building core HIV knowledge and behavioural skills in a one group pretest–posttest design [56]. Elements of the intervention incorporated CBT components (goal-setting, challenging negative thoughts, problem-solving skills) for adolescents and caregivers. Significant improvements were noted concerning AYAAH mental health outcomes (depression and anxiety symptoms) on the Depression Anxiety Stress Scale as well as other outcomes (e.g. HIV transmission, condom knowledge).

3.5 | Family based economic strengthening interventions

Another approach to family based interventions involves economic strengthening. SUUBI (Hope) has been delivered in Ugandan school settings and was originally designed for AYAAH. Evaluated through a large-scale cluster RCT [55], the SUUBI intervention group had significantly lower levels of hopelessness and improved self-concept compared to the control group who received usual care. SUUBI, delivered by lay counsellors, has been found to be effective in reducing sexual risk behaviour and promoting emotional wellbeing in multiple countries in sub-Saharan Africa [64,65]. SUUBI+Adherence was adapted for AYALH, and evaluated in a RCT in multiple clinics in Uganda, with both the intervention and comparison groups also receiving bolstered psychosocial support, using a cartoon-based curriculum on disclosure, adherence and coping similar to that used in CHAMPSA and VUKA in South Africa [60,66,67]. The SUUBI+Adherence trial found significant intervention effects on hopelessness and depression, at 24-month post intervention [51].

3.6 | Group-based mindfulness interventions

Group-based mindfulness interventions were tested in two studies, one in Myanmar and one in the USA. Mindfulness is increasingly being used in many contexts as part of mental health treatments, for example DBT [35] and on its own or as part of CBT [31,32]. Derived from the Buddhist way of meditation, mindfulness is described in one of the studies as a state of consciousness in which there is enhanced attention of moment-to-moment experience." (Pp 2) [53]. In the Myanmar study, structured mindfulness training delivered by an experienced mindfulness instructor and two investigators included elements of family strengthening (involving parents/ guardians in the process and to monitor homework as well as meditation. In a cluster RCT, significant improvements in three domains of psychological behaviours (emotional [effect size 1.8], conduct and social behaviour [effect size 0.81]) at six months were noted among AYAAH who received the intervention component relative to the comparison group. In the USA study, a clinic-based pilot RCT was delivered by instructors with extensive experience in teaching mindfulness. They provided mindfulness-based stress reduction intervention over at least eight weekly sessions with didactics on and experiential practice of various mindfulness techniques (meditation, yoga) and application of mindfulness to everyday life. Significant improvement in the intervention group in mindfulness, problem-solving coping styles, life satisfaction, reducing aggression and lower HIV viral load was noted among African American AYALH [49].

3.7 | Community-based intervention

The last RCT, community-government partnerships were leveraged to enhance linkage and retention in care for AYALH. This programme recruited young adults from the local community to be peer counsellors. Known as Community Adolescent (18 to 24 years) Treatment Supporters, they were trained and mentored by the Zimbabwean Health and Child Care Ministry [50]. The study found significant increases in psychological wellbeing (self-confidence, self-esteem, self-worth), lower stigma and quality of life care, as well as improved adherence to ART and linkage to care, but not retention in care compared to controls.

In this review, in the past six years, 13 intervention studies were identified, with most conducted in sub-Saharan Africa where the majority of AYALH and AYAAH reside. The majority of these studies (n = 10) demonstrated positive intervention effects on some component of mental health [46,47,49-51,53,55-58], with only two studies of AYALH [45,48] and 1 of AYAAH [54] showing no effect of the intervention on mental health outcomes. However, the limited number of studies with full scale trials of mental health (four studies were pilot studies), the diversity of interventions and measures used, the diversity of age groups, study periods and contexts, the different types of facilitators, and the extreme limit in evidence-based treatments for specific mental health problems, make it very difficult to discern best practices. The risk of bias analysis indicated that seven of the 13 studies [46,49,50,53,56,57] were likely to have outcomes that would probably change because of the bias introduced by small sample sizes or flawed randomization procedures. Furthermore, while all the interventions used trained facilitators, there was great variation in training and previous facilitator experience, ranging from highly skilled CBT therapists to lay counsellors with varying levels of supervision and training.

In three of the four studies that used evidence-based mental health treatment [45,49,53], participants did not need to meet criteria for a mental disorder diagnosis, making it difficult to assess impact on those most vulnerable to psychiatric illness. Only one study included a formal diagnosis of participant mental health before undertaking the intervention [46]. Furthermore, studies used varying post-intervention periods, from immediately post-intervention to 24-month post-intervention, making comparisons difficult. The most commonly used measure of mental health was the SDQ which is not a diagnostic tool but a symptom checklist of emotional and behavioural difficulties and strengths. The most common

specific mental health problem was depression, but different measures were used across studies.

The SUUBI economic strengthening intervention was one of the most effective approaches in promoting mental health in AYALH [51,55]. This finding supports the increasing awareness that poverty is one of the key social determinants of poor mental health and that economic strengthening approaches can be helpful [68]. Additionally, studies focused on family strengthening interventions showed promise in addressing mental health outcomes among adolescents affected by HIV in their families [53-57]. The studies of mindfulness are also encouraging; mindfulness is increasingly recognized as an evidence-informed intervention for mental health as part of other treatments such as DBT and CBT or on its own, although testing and adaptation are needed in African countries at the centre of the HIV epidemic. For interventions to have a chance of being scalable, they need to be culturally appropriate and deliverable by non-mental health specialists, given the dearth of mental health providers in many contexts. We did not find any studies examining the capacity of lay counsellors to provide mental health treatment to AYALH or AYAAH with mental health disorders.

In Zimbabwe, a study currently underway is testing problem-solving therapy, an evidence-based transdiagnostic intervention for common mental disorders in youth, in a setting of high HIV prevalence, modelled on the Friendship Bench [69]. More studies are needed of transdiagnostic or simple evidence-based interventions such as problem-solving therapy or behavioural activation, that can be delivered by health workers, in order to promote feasibility in LMIC where capacity for psychiatric diagnosis may be limited [70].

Implementing mental health interventions in LMIC, particularly using evidence-based mental health treatment, is challenging given the limits on funding and available professionally trained staff to conduct screening, diagnostic evaluation and the treatment itself. For example in South Africa, there is only one psychiatrist per an estimated 357,143 people [71]. As a result, many studies reviewed here utilized lay counsellors and interventions that did not require specialized professional experience and training. It has been suggested that digital technology-based interventions could be helpful in resource-constrained contexts in standardizing treatment and reducing training costs as well as the need for professional providers [72,73]. A recent review suggested that digital psychological interventions (mostly with depression and substance use) are superior to control conditions and moderately effective in LMIC [74]. Mental health interventions that leverage digital technology may also provide increased access for AYA who heavily use social media and other text-based and internet-based platforms and be well suited for rapid scale-up with ongoing studies offering insights for the future development and scale-up of technology-based mental health interventions tailored to AYALH [75,76]. That said, many AYA in resource-constrained contexts in particular do not own mobile phones or share phones with others, and those who do own phones may have limited access to airtime, the internet and reliable electricity [77-80], requiring different approaches to treatment. Regardless of how interventions are delivered, studies to determine lay counsellor capacity, training and supervision required, and the potential role of digital technology in supporting them are needed.

Almost none of the 13 projects included descriptors of possible mediators promoting change, and most studies used multicomponent interventions. This leaves us unable to clearly identify mechanisms of change or make definitive statements about what worked and why. An analytic framework that may be useful in unpacking interventions that seek to influence complex systems is the use of realist reviews. By making explicit the underlying assumptions (programme theories) about how an intervention is meant to work with what impact, realist reviews may help in providing an explanatory analysis as to what works for whom, in what circumstances, in what way and how [81].

The risk of bias identified in many of the studies reviewed provides an opportunity for future work to ensure adequate sample size and randomization considerations in study recruitment and treatment in addressing the mental health needs of AYALH and AYAAH. It is likely that there is not a one-size-fits-all approach given that mental health has multiple biological, psychological and social causes, and context is critical to what is acceptable, accessible and feasible. Implementation science research approaches may help improve our understanding of what works for whom and under what conditions [82] and can also promote scale up and sustainability of mental health interventions beyond the life span of research projects. In low-resource contexts, the design of delivery systems using implementation science principles may close the mental health implementation gap [83]. A renewed focus on the barriers and enablers of the implementation of an intervention is called for, as well as the health or mental health impact of the intervention itself [84]. Moreover, use of community-based participatory research methods that involve community stakeholders at every step of the intervention research process can help ensure not only that interventions address the most critical problems for communities, but also that stakeholders are involved in sustainability of the programmes themselves.

Importantly, mental health problems are one of the leading causes of the loss of disability adjusted life years globally [85]. While health agencies are calling for global investment in mental health [86] and a mental health treatment gap has been identified particularly in LMIC [87], the current review suggests this mental health treatment gap may be even wider for young people living with or affected by HIV. Furthermore, this gap among youth persists in low-, middle- and high-income contexts. Integrating screening of mental disorders that can be used by non-specialists is recommended as one way of improving access to mental healthcare [6]. This strategy could be impactful for the mental health and wellbeing of AYALH, particularly those who experience challenges with linkage and retention to HIV care.

Given the stigma of HIV, those affected are likely not to seek care outside of HIV clinics. Hence, policies that promote the integration of mental healthcare into HIV care settings may be most effective for serving the needs of AYALH in need of mental health treatment [7,8,88], while also ensuring the quality of mental healthcare [89]. One promising example promoting the integration of mental health within a chronic care platform (including HIV) is the scale up of the Mental Health Integration Programme (MhINT) using an implementation science framework to identify what works for whom and under what conditions [90]. Another is the work of the Hub

Accelerating Achievement for Africa's Adolescents (Accelerate) to promote high-quality evidence generated in a series of randomized trials to improve the lives of adolescents across multiple Sustainable Development Goals [91]. But importantly, resources, policies and research to provide a sufficient evidence base are urgently needed to address the emotional wellbeing of adolescents and young adults living with and affected by HIV globally.

This study has some limitations. First, as a scoping review, we may have missed mental health interventions in our search of the literature. Given that much of the work described in this scoping review tends to reflect work done in LMIC because of the HIV burden in these regions, this unintended bias should be noted. Second, we used a broad definition of adolescence (10 to 24 years), as many studies assess adolescences in this age range. However, we recognize that several stages of development exist within this range and note that future studies should explore the differences between these stages and design developmentally tailored mental health interventions. Lastly, there are mental health interventions for adult populations affected by HIV, as well as populations of adolescents and young adults not living with or affected by HIV or living with other chronic conditions that could be useful in the context of AYALH and AYAAH, that did not form part of this review process.

4 | CONCLUSIONS

Given the heavy burden of disease associated with HIV, the staggering numbers of adolescents living with or affected by HIV and the high rates of mental health problems previously identified in this population, there is still a substantive need for evidence-based mental health treatment for AYALH and AYAAH. There is a need for simple brief transdiagnostic evidence-based interventions, which are likely to be feasible in low-resource settings that utilize lay counsellors and that are possibly supported through digital technology. Measurement tools for mental health research in AYA need to be locally validated in the contexts in which they are applied. Future research must develop implementation theory and look at implementation outcomes such as feasibility, acceptability and fidelity, as well as effectiveness, to ensure that interventions found to be effective become part of integrated mental health services for adolescents and young adults living with and affected by HIV globally.

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COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHORS' CONTRIBUTIONS

AB, PK, AP, MA and CAM were involved in conceptualizing and drafting the manuscript. All authors have read and approved the final manuscript.

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REVIEW

Mental health interventions for persons living with HIV in low- and middle-income countries: a systematic review

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Abstract

Introduction: Addressing the intersection between mental health and HIV is critical for the wellbeing of persons living with HIV (PLWH). This systematic review synthesized the literature on mental health interventions for PLWH in low- and middle-income countries (LMICs) to determine intervention components and explore their relationship with intervention effectiveness.

Methods: We included only controlled clinical trials of interventions aiming to improve the mental health of PLWH. We conducted a search in the following databases: PubMed, CINAHL, PsycINFO and EMBASE for eligible studies describing the evaluation of interventions for mental health problems among PLWH in LMICs published through August 2020. Two reviewers independently screened references in two successive stages of title/abstract screening and then full-text screening for references meeting title/abstract criteria.

Results: We identified a total of 30 eligible articles representing 6477 PLWH who were assigned to either the intervention arm (n = 3182) or control arm (n = 3346). The mental health interventions evaluated were psychological (n = 17, 56.67%), pharmacological (n = 6, 20.00%), combined psychological and pharmacological (n = 1, 3.33%) and complementary/alternative treatments (n = 6, 20.00%). The mental health problems targeted were depression (n = 22, 73.33 %), multiple psychological symptoms (n = 1, 3.33%), alcohol and substance use problems (n = 4, 13.33%), post-traumatic stress disorder (n = 1, 3.33%) and HIV-related neuro-cognitive impairment (n = 2, 6.67%). Studies of interventions with significant effects had significantly a higher number of active ingredients than those without significant effects [3.41 (2.24) vs. 1.84 (1.46) Mean (SD)] [Mean difference = −1.56, 95% CI = −3.03 to −0.09, p = 0.037].

Conclusions: There continue to be advances in mental health interventions for PLWH with mental illness in LMICs. However, more research is needed to elucidate how intervention components lead to intervention effectiveness. We recommend scale up of culturally appropriate interventions that have been successfully evaluated in low- and middle-income countries.

Keywords: mental health; psychotherapy; psychotropic; HIV/AIDS; anti-retroviral therapy theory of change; low- and middle-income countries

Additional Supporting information may be found online in the Supporting Information tab for this article.

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1 | INTRODUCTION

Mental health problems in people living with HIV (PLWH) were recognized early in the AIDS epidemic as a key factor affecting HIV treatment outcomes in high-income countries [1,2]. However, mental health of PLWH has only recently received the attention it deserves in low- and middle-income countries (LMICs) [3]. Despite the fact that mental health is a universal human right, the mental wellbeing of those living with HIV and mental illness is often neglected [4]. A call for global action to improve responses to non-communicable diseases has increased focus towards mental health promotion, prevention and treatment of mental health conditions across the world [5].

The relationship between HIV and mental health is bidirectional. On one hand, pre-existing mental health conditions increase the risk for HIV infections. Indeed, in some LMICs depression rates are more than 30% in PLWH [6]. In such cases, the risk for infection may be associated with poverty, transactional sex, sexual violence, sharing drug injection

equipment, inconsistent condom use or with psychiatric symptoms that can impair cognition and judgment [7,8]. On the other hand, PLWH are at increased risk of developing mental health conditions ranging from acute stress reactions to neurocognitive disorders [9,10] which can undermine health-seeking behaviours, reduce adherence to treatment [11] and lead to higher rates of mortality [12-14]. Also, some antiretrovirals can cause neuropsychiatric side effects for up to half of those using them [15]. Zidovudine and abacavir have been associated with mania and psychosis, whereas nevirapine and efavirenz have been associated with mood changes and vivid dreams [16]. HIV policy makers now acknowledge the importance of addressing the intersection between mental health and HIV, and the need to adopt a human rights-based approach to improve the quality of life of PLWH [17].

In 2015, HIV care and treatment guidelines were updated to require the identification and management of depression among PLWH [18]. In 2018, the UNAIDS Programme Coordinating Board addressed the topic of "Mental Health and HIV/AIDS" for the first time in its history [19]. These developments indicate that it is now common knowledge that the HIV epidemic cannot end without addressing the mental health problems of PLWH [20]. Since mental health problems lie along a continuum that extends from mild distress to persistent and severe symptoms [21], mental health promotion, prevention and treatment of such conditions is crucial.

Systematic reviews of mental health interventions for PLWH, which come predominately from high-income countries, show that these interventions lead to improvements in mental health, quality of life, adherence to medication and viral suppression [22,23]. However, in LMICs, data are sparse. In past reviews of intervention trials for depression and anxiety among PLWH in LMICs, the majority were preliminary studies, and few demonstrated efficacy [24]. Mental health researchers recommended further development and adaptation of mental health interventions for resource-limited settings to improve effectiveness.

Mental health interventions are complex. In pharmacological interventions, the component of the intervention responsible for therapeutic action is the active ingredient. However, in non-pharmacological interventions, active ingredients may be more than the sum of the intervention components and include the context, expertise and behaviours of stakeholders, beneficiaries and providers [25]. The Medical Research Council guidance calls for more detailed and standardized descriptions of complex interventions in published reports to facilitate the exchange of knowledge and to encourage the synthesis of results from similar studies [26].

Integrating the theory of change into the Medical Research Council framework has been proposed as an effective way to evaluate such interventions as it takes into account multiple causal pathways [27]. It is, therefore, necessary to understand how interventions relate to and interact with components of the system to produce an effect. Previous researchers have used the Theory of Change within the Medical Research Council framework to provide a set of indicators to evaluate all stages of the causal pathway through which a mental health intervention may achieve impact [27]. These include involving stakeholders, training and supervision of intervention deliverers, creating community awareness about the intervention, caseload of the intervention deliverer, adherence to the intervention and the active ingredients in either the pharmacological or non-pharmacological intervention used.

This systematic review synthesizes the literature on evaluated mental health interventions for PLWH, examines intervention components that may moderate causal mechanisms and tentatively explores their relationship to intervention effectiveness.

2 | METHODS

2.1 | Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [28,29]. We systematically searched the PubMed, CINAHL, PsycINFO and Embase databases for eligible studies describing the evaluation of interventions for mental health problems among PLWH in LMICs published through August 2020. We conducted our search by combining keywords and database-specific subject headings for the following concepts: (1) The population: HIV, AIDS; (2) The outcome: mental health, psychology, depression, anxiety, substance use, alcohol use, drug use, smoking behaviour, suicide, post-traumatic stress disorder and neurocognitive impairment; (3) The study location: developing countries, low resource, middle income or low income; (4) Mental health intervention: anti-depressive agents, anti-psychotic agents, psychotherapy, counselling, exercise therapy, relaxation meditation; (5) Study designs: quasi-experimental studies, controlled before-after studies, randomized controlled trials and controlled clinical trials. The full search strategy with adapted terms for each database is included in Figure S1. The protocol for the systematic review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020219483).

2.2 | Eligibility criteria

We reviewed abstracts and full texts of retrieved articles according to the following inclusion criteria: (1) studies written in English; (2) conducted with adults living with HIV; (3) residing in LMICs based on the classification of the World Bank during the financial year in which the study was published; (4) Randomized controlled trials or quasi-experimental studies that described the evaluation of mental health interventions in adults (≥18 years) living with HIV; (5) described a mental health treatment for mental health problems which lie along a continuum that extends from mild distress to persistent and severe symptoms. Studies describing mental health interventions were excluded if they were described as pilot studies, prospective cohort studies, conference abstracts or studies of children or adolescents (<18 years).

2.3 | Selection process

Two reviewers independently screened all titles and abstracts and assessed full-text articles against the inclusion criteria. A third reviewer was engaged to resolve discrepancies between the two reviewers at any point in the screening and

assessment process. The number of included and excluded full-text articles and reasons for exclusion are presented in the PRISMA flow chart (Figure 1).

2.4 | Narrative synthesis

We conducted a narrative synthesis based on guidelines produced by Popay et al [31] for the Economic and Social Research Council UK Methods Programme (2006), selecting and using the techniques applicable to our research question and included studies. A flow chart summarizing the synthesis process is presented in Figure 2. First, we adopted the Theory of Change Framework proposed by De Silva et al [27] to guide our synthesis.

Second, data were extracted using a standardized data extraction tool that included the following elements: (1) location of study (country), income category of the country, study sample size, mean age of participants, gender of the study population, duration of follow-up, type of mental health intervention, study design, and mental health problem targeted. We extracted data on the nature of study outcomes reported (e.g. immediate-, short- and long-term outcomes), indicators of intervention response reported (e.g. type of intervention deliverer, case load, treatment adherence, number and type of active ingredients) strategies to achieve outcomes (e.g. stakeholder & public involvement, community awareness, training and supervision of intervention deliverers). All data were extracted by two researchers and differences were resolved through discussions between the two reviewers or discussing with a third researcher.

Third, studies were clustered according to the characteristics in the data extraction tables, such as type of mental health intervention, targeted mental health problem, setting, gender, delivery format (individual vs. group approach), intervention effects (significant versus non-significant), etc.

Fourth, we assessed relationships between the various study clusters and intervention effectiveness. Specifically, we assessed relationships between intervention type, intervention deliverer's case load, treatment adherence and number of intervention active ingredients and intervention effectiveness. We also explored associations between stakeholder and public involvement, community awareness, training and supervision of intervention deliverers and intervention effectiveness.

Lastly, we examined the quality of the synthesis by assessing the methodological rigour of each study reviewed using the Effective Public Health Practice Project (EPHPP) Quality

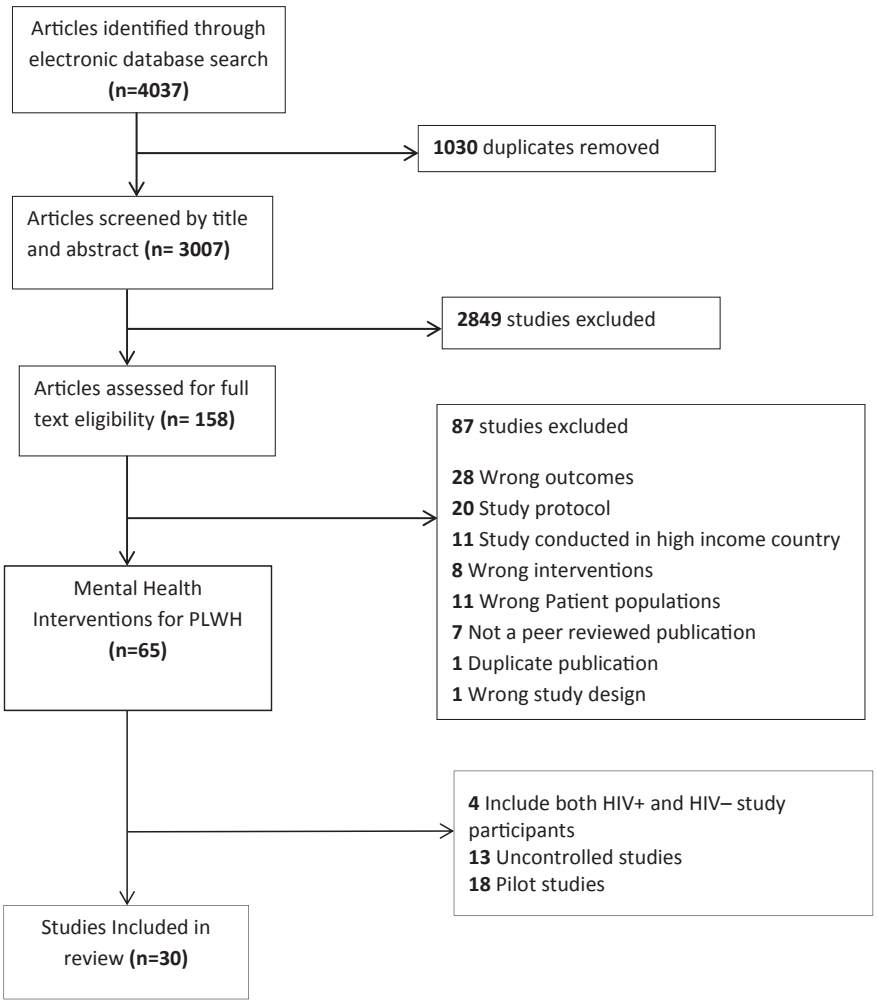

Figure 1. PRISMA flowchart. PLWH, people living with HIV.

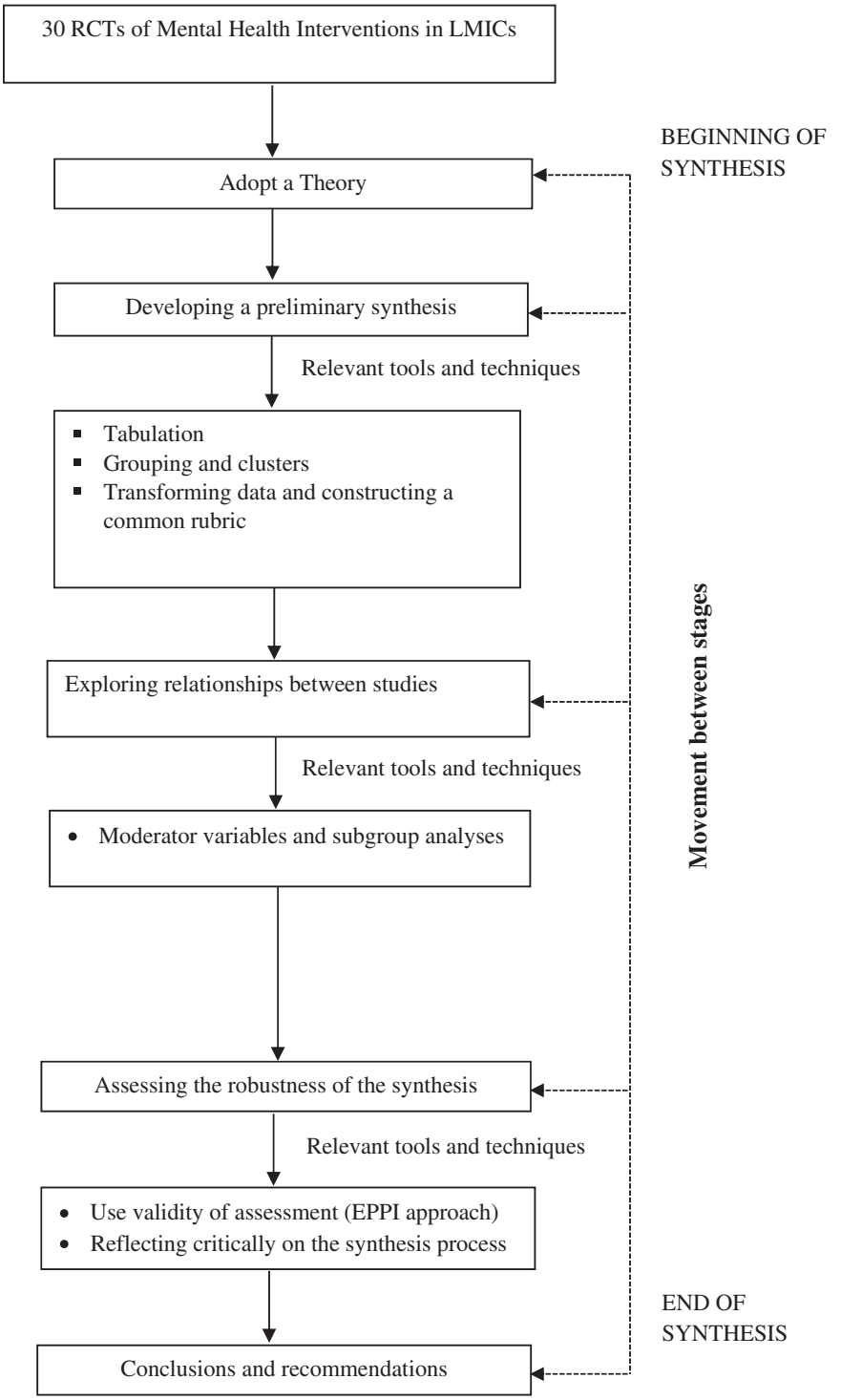

Figure 2. Narrative synthesis process. RCTs, randomized control trials; LMICs, low-and-middle-income countries.

Assessment Tool [32]. Methodological rigour for the EPHPP tool produces a global rating of "'strong," "moderate" or "'weak" for each study based on evaluations of two independent reviewers (EN-M and CMS). Differences of opinion were resolved through discussions between the two reviewers or brought to a third independent individual to consider and make a final decision.

3 | RESULTS

3.1 | Search and study selection

Our electronic search yielded 4,037 articles: 1,003 duplicate articles and 2,849 irrelevant articles were excluded. We assessed 158 full-text articles for eligibility. Thirty controlled

studies published through August 2020 were included in this systematic review. Figure 1 presents the flow chart of our study selection and the frequency of reasons for exclusion.

3.2 | Characteristics of studies

Half of the reviewed studies were conducted in the African region (n = 15), and the other half in the Eastern Mediterranean Region (n = 7) and South-East Asia Region (n = 8). The study's total sample size ranged from 32 to 1140, intervention sample sizes ranged from 19 to 578 and control group sample sizes ranged from 13 to 562. The majority of studies (n = 22, 73.33 %) reported on interventions for depression [33-55]. Major depressive disorder was confirmed using diagnostic interviews such as SCID or MINI in three studies [34-36]. One study (3.33 %) described an intervention for multiple psychological symptoms assessed with Symptom Check List-90 (SCL-90) [56]. Mental health Interventions for alcohol and substance use disorders were described in four studies (13.33 %) [57-60], post-traumatic stress disorder (PTSD) in one study (3.33 %) [61] and HIV neuro-cognitive impairment in two studies (6.67 %) [62,63]. Among the reviewed studies, four types of mental health interventions were described including psychological interventions (n = 17), pharmacological interventions (n = 6), combination of psychological and pharmacological (n = 1) and complementary and alternative interventions (n = 6). Detailed study characteristics are shown in Tables 1 and 2.

3.3 | Psychological interventions

The majority of studies described psychological interventions (n = 18). Of these, 13 targeted depression. These included six cognitive behavioural therapy (CBT) based interventions [35,38,47,53,55,61], two problem solving-based interventions [43,50], one rational emotive behavioural therapy [48] and four psychosocial support groups [39,41,51,54]. One study described a mindfulness-based intervention targeting multiple psychological symptoms [56]. Other studies described trauma-focused CBT for post-traumatic stress disorder (n = 1) [61], brief alcohol interventions (n = 2) and rational emotive behavioural therapy (n = 1) targeting alcohol use problems [57,59,60]. Only 11 (61.1%) of the 18 studies of psychological interventions reported significant effects.

3.4 | Pharmacological interventions

This review found six studies which evaluated pharmacological interventions for depression (N = 4) and HIV-related neurocognitive impairment (N = 2). One study evaluated the effect of minocycline on depression [42], whereas three evaluated the effect of antidepressants, including trazodone [45], citalopram [34] and escitalopram [36] on depression. Two studies examined the treatment efficacy of minocycline and lithium for neurocognitive impairment [61,62]. Only the two studies evaluating minocycline and trazadone reported significant effects. Other pharmacological interventions had no benefit over placebo. This review also revealed a single study which evaluated fluoxetine in combination with problem-solving therapy where the intervention did not have significant effects [43].

Table 1. Characteristics of reviewed articles (N = 30)

	Total N = 30 N (%)
Location of study	
Africa Region (AFRO)	15 (50.00)
Eastern Mediterranean Region (EMRO)	7 (23.33)
South-East Asia Region (SEARO)	2 (6.67)
Western Pacific Region(WPRO)	6 (20.00)
Latin American Region (LAR)	0 (0.00)
Incomes of countries	
Upper middle income	17 (56.67)
Lower middle income	8 (26.67)
Lower income	5 (16.67)
Study design	
Cluster randomized clinical trial	1 (3.33)
Individual randomized clinical trial	25 (83.33)
Pre-test & Post-test design	4 (13.33)
Gender of study population	
Females only	8 (26.67)
Males only	4 (13.33)
Both males & females	18 (60.00)
Age of study participants	
Mean (SD)	34.23 (4.60)
Median	35
Range	(26 to 41)
Type of mental health intervention	
Psychological intervention	17 (56.67)
Pharmacological intervention	6 (20.00)
Both psychological and pharmacological intervention	1 (3.33)
Complementary /alternative intervention	6 (20.00)
Outcomes	
Immediate outcomes	14 (46.67)
Short-term outcomes (<6 months)	4 (13.33)
Long-term outcomes (six to twelve months)	12 (40.00)
Significant Intervention Effects	
Yes	17 (56.67)
No	13 (43.33)

3.5 | Complementary and alternative interventions

This review revealed six studies which evaluated complementary and alternative interventions for depression. The interventions evaluated included omega-3 fatty acids [49,52], physical exercise [33] an herbal supplement [38] and yoga [37]. The study evaluating physical exercise and one study evaluating omega-3 fatty acids did not register any advantage over placebo.

3.6 | Association between intervention components and intervention effectiveness

We assessed the relationship between various intervention components and intervention effectiveness. The intervention

Table 2. Mental Health interventions for Persons Living with HIV in Low- and Middle-Income Countries

Intervention	Reference country	Mental disorder	Sample	Study design	Intervention characteristics	Active ingredients	Intervention strategies	Key findings
Group Support Psychotherapy	Nakimuli-Mpungu et al; 2020 [35] Uganda	Depression Tool:SRQ-20 MINI	Gender: M & F HIV:100% ART: 100%	CRCT GSP = 578 GHE = 562 Follow-up: twelve months	Sessions: 8 Lay Health Workers C:IF Ratio = 10:1 Adherence: 80%	Psych-education Venting Social Support Positive coping skills Problem solving Livelihood skills	Stakeholders: YES Community aware: YES Training IFs: YES Supervision IFs: YES Feasible: YES Acceptable: YES Fidelity: Assessed	Participants in GSP group had significantly lower cases of major depression than did those in the lower GHE group
Schema Focused Group Therapy	Jalali et al; 2019 [40] Iran	Depression Tool: BDI-II	Gender: M(Prisoners) HIV:100% ART: NS	Quasi Experimental SFGT = 21 CONTROL (WL) = 21 Follow-up: Post-test	Sessions: 11 Specialist delivered C:IF Ratio = 10:1 Adherence: 100%	Psych-education Social support Positive coping skills Cognitive restructuring	Stakeholders: YES Community aware: YES Training IFs: YES Supervision IFs: NA Feasible: YES Acceptable: YES Fidelity: Assessed	There was a significant difference in both pre- and post-test scores in the depression between the experimental and waiting list control groups
CBSM WeChat-based mobile health intervention	Guo et al; 2020 [47] China	Depression Tool: CESD-20	Gender: M& F HIV:100% ART:100%	RCT CBSM = 150 CONTROL(WL) = 150 Follow-up: Post-test	Sessions: 12 Self-administered C:IF Ratio = NA Adherence:55%	Psych-education Positive coping skills Cognitive restructuring Relaxation Meditation Behavioural activation Physical activity	Stakeholders: Not mentioned Community aware: Not mentioned Training IFs: NA Supervision IFs: NA Feasible: YES Acceptable: YES Fidelity: Assessed	There was a significant difference in depression symptoms between the experimental and control groups
Group Coping Enhancement Programme	Ye et al; 2018 [61] China	PTSD, PTG Tool: PTGI-21 & IES - 15	Gender: M HIV:100% ART:47%	RCT GCEP = 30 CONTROL = 30 Follow-up: Post-test	Sessions: 11 Specialist delivered C:IF Ratio = 10:1 Adherence:80%	Psych-education Venting Positive coping skills Cognitive restructuring Social support	Stakeholders: YES Community aware: YES Training IFs: YES Supervision IFs: NA Feasible: NS Acceptable: NS Fidelity: Assessed	The intervention group reported more improvement in problem-focused coping strategies, PTG, and PTSD than did the wait-list control groups
Group Behavioural intervention	Li et al; 2010 [53] Thailand	Depression Tool: DST-15	Gender: M& F HIV:100% ART: NS	RCT CBI = 260 CONTROL = 247 Follow-up: twelve months	Sessions: 13 Specialist delivered C:IF Ratio = 130:1 Adherence: NS	Cognitive restructuring Positive coping skills Physical activity Social support	Stakeholders: YES Community aware: YES Training IFs: NS Supervision IFs: NS Feasible: NS Acceptable: Assessed Fidelity: NS	The intervention did not have a significant effect on depression
Cognitive Behavioural Therapy	Nobakht et al; 2018 [55] Iran	Depression Tool: DASS-21	Gender: F HIV:100% ART:93%	RCT CBT = 33 CONTROL = 33 Follow-up: Post-test	Sessions: 6 Specialist delivered C:IF Ratio = 30:1 Adherence:91%	Psych-education Venting Social support Positive coping skills Cognitive restructuring	Stakeholders: Not mentioned Community aware: Not mentioned Training IFs: YES Supervision IFs: NA	There was a significant reduction in depression among the intervention group compared to the control group

Table 2. (*Continued*)

Intervention	Reference country	Mental disorder	Sample	Study design	Intervention characteristics	Active ingredients	Intervention strategies	Key findings
							Feasible: NS Acceptable: NS Fidelity: NS	
Group Cognitive Behavioural Therapy	Papas et al; 2012 [58] Kenya	Alcohol use disorder Tool: PDA, PDD	Gender: M &F HIV:53% ART:66% HIV:100% ART: 61%	RCT GCBT = 42 CONTROL = 33 Follow-up: three months	Sessions: 6 Specialist delivered C:IF Ratio = 21:1 Adherence: 93%	Psych-education Social support Positive coping skills Cognitive restructuring Livelihood skills Problem solving	Stakeholders: YES Community aware: YES Training IFs: YES Supervision IFs: YES Feasible: Assessed Acceptable: Assessed Fidelity: Assessed	Reported alcohol use at 3-month post-intervention alcohol was 69.4% in the CBT group and 37.5% in the control group
Single Brief Alcohol Reduction Intervention	Wandera et al; 2017 [57] Uganda	Alcohol use disorder Tool: AUDIT	Gender: M & F HIV:100% ART: 77%	RCT SBARI = 167 CONTROL = 170 Follow-up: six months	Sessions: 1 Specialist delivered C:IF Ratio = 83:1 Adherence:100%	Psych-education	Stakeholders: YES Community aware: YES Training IFs: YES Supervision IFs: YES Feasible: NS Acceptable: NS Fidelity: NS	The change in mean AUDIT scores was not statistically different between the intervention and control groups
Single Brief Alcohol Reduction Intervention	Huis in 't Veld et al.2019 [59] South Africa	Alcohol use disorder Tool: AUDIT	Gender: M & F HIV:100% ART: 85%	RCT SBARI = 267 CONTROL = 293 Follow-up: twelve months	Sessions: 1 Nurse delivered C:IF Ratio = 67:1 Adherence:100%	Psych-education	Stakeholders: YES Community aware: YES Training IFs: YES Supervision IFs: YES Feasible: NS Acceptable: NS Fidelity: Assessed	There was no significant difference in AUDIT scores between the intervention and control groups
Mindfulness-Based Stress Reduction Intervention	SeyedAlinaghi et al; 2012 [56] Iran	Multiple Psychological Symptoms Tool: SCL-90-R	Gender: M & F HIV:100% ART:0%	RCT MBSR = 120 CONTROL = 125 Follow-up: twelve months	Sessions: 8 Specialist delivered C:IF Ratio = 120:1 Adherence: 73%	Social support Relaxation Meditation Physical activity	Stakeholders: YES Community aware: YES Training IFs: YES Supervision IFs: NS Feasible: NS Acceptable: NS Fidelity: NS	There was no significant difference in mean SCL-90R scores between the intervention and control groups
Group Rational-Emotive-Behaviour-Based Therapy	Surilena et al; 2014 [48] Indonesia	Depression Tool: SRQ-20	Gender: F HIV:100% ART: 100%	RCT REBT = 72 CONTROL = 76 Follow-up: Post-test	Sessions: 8 Specialist delivered C:IF Ratio = 72:1 Adherence: NS	Psych-education Cognitive restructuring Behavioural activation Social support Positive coping skills	Stakeholders: Not mentioned Community aware: Not mentioned Training IFs: NS Supervision IFs: NA Feasible: NS Acceptable: NS Fidelity: NS	There was a greater reduction in the SRQ-20 mean scores in the intervention group compared to the control group.
Group Rational-Emotive-Behaviour-Based Therapy	Omeje et al; 2018 [60] Nigeria	Alcohol Use Tool: AUDS;AIBS	Gender: M & F HIV:100% ART: NS	Quasi Experimental REBT = 61 CONTROL = 63 Follow-up: one month	Sessions: 20 Specialist delivered C:IF Ratio = NS Adherence:100%	Psych-education Cognitive restructuring Behavioural activation Social support	Stakeholders: Not mentioned Community aware: Not mentioned Training IFs: YES	The intervention led to a significant reduction in AUDS % AIBS scores in the treatment group

Table 2. (*Continued*)

Intervention	Reference country	Mental disorder	Sample	Study design	Intervention characteristics	Active ingredients	Intervention strategies	Key findings
						Positive coping skills	Supervision IFs: NA Feasible: NS Acceptable: NS Fidelity: NS	compared to those in the control group
Friendship Bench-Problem Solving Therapy and Antidepressants	Stockton et al; 2020 [43] Malawi	Depression Tool: PHQ-9 TCA	Gender: M &F HIV:100% ART:100%	Quasi Experimental FBPST = 134 CONTROL = 290 Follow-up: six months	Sessions: 6 LHW delivered C:IF Ratio = 67:1 Adherence: FB = 42% TCA = 31%	Psych-education Problem solving Medication	Stakeholders: YES Community aware: YES Training IFs: YES Supervision IFs: YES Feasible: Assessed Acceptable: Assessed Fidelity: Assessed	The programme did not have a significant effect on depression
Group Problem Solving Psychotherapy	Kaaya et al; 2013 [50] Tanzania	Depression Tool: HSCL-15	Gender: F HIV:100% ART: 0%	RCT PST = 168 CONTROL = 163 Follow-up: Post-test	Sessions: 6 Specialist delivered C:IF Ratio = NS Adherence:56%	Psych-education Social Support	Stakeholders: YES Community aware: YES Training IFs: YES Supervision IFs: YES Feasible: NS Acceptable: NS Fidelity: NS	There was no significant difference in depression symptoms between the intervention and control groups
Telephone Support	Ross et al; 2013 [41] Thailand	Depression Tool: CESD-20	Gender: F (Pregnant) HIV:100% ART: NS	RCT TS = 20 CONTROL = 20 Follow-up: Post-test	Sessions: 8 Nurse delivered C:IF Ratio = 10 Adherence: NS	Venting Social Support	Stakeholders: Not mentioned Community aware: Not mentioned Training IFs: YES Supervision IFs: YES Feasible: NS Acceptable: NS Fidelity: NS	Depression symptoms decreased significantly more in the intervention than in the control group
Community Home-Based Social Support and Peer Counselling	Pokhrel et al; 2018 [54] Nepal	Depression Tool: CESD-20	Gender: M & F HIV:100% ART: 100%	RCT CSPC = 344 CONTROL = 338 Follow-up: six months	Sessions: 6 LHW and Specialist delivered C:IF Ratio = 114 Adherence: NS	Social Support Positive coping skills	Stakeholders: YES Community aware: YES Training IFs: YES Supervision IFs: YES Feasible: NS Acceptable: NS Fidelity: NS	The intervention was more effective in reducing depression symptoms than the control group
Structured Support Groups	Mundell et al; 2011 [51] South Africa	Depression Tool: CESD-20	Gender: F HIV:100% ART:0%	Quasi Experimental CSPC = 144 CONTROL = 217 Follow-up: eight months	Sessions: 10 Specialist delivered C:IF Ratio = 24 Adherence:50%	Social Support Positive coping skills	Stakeholders: YES Community aware: YES Training IFs: YES Supervision IFs: NA Feasible: NS Acceptable: NS Fidelity: NS	There was no significant difference in depressive symptoms between intervention and control groups
Accredited Social Health Activist	Nyamathi et al; 2012 [39]	Depression Tool: CESD-20	Gender: F HIV:100%	RCT ASHA = 34	Sessions: 6 LVW delivered	Positive coping skills Psych-education	Stakeholders: YES Community aware: YES	There was a greater reduction in the depression scores in the

Table 2. (*Continued*)

Intervention	Reference country	Mental disorder	Sample	Study design	Intervention characteristics	Active ingredients	Intervention strategies	Key findings
(ASHA-LIFE) Intervention	India		ART:100%	CONTROL = 34 Follow-up: six months	C:IF Ratio = 9 Adherence: NS		Training IFs: YES Supervision IFs: YES Feasible: NS Acceptable: NS Fidelity: NS	intervention group compared to the control group
Omega-3 Fatty acids	Ravi et al; 2016 [44] India	Depression Tool: BDI, PHQ, HADS	Gender: M & F HIV:100% ART:100%	RCT Omega-3 Fatty acids = 54 PLACEBO = 56 Follow-up: two months	Sessions: NA Deliverer = Specialist C:IF Ratio = NS Adherence: 93%	Complementary/ alternative treatment	Stakeholders: Not mentioned Community aware: Not mentioned Training IFs: YES Supervision IFs: YES Feasible: NS Acceptable: NS Fidelity: NS	Depression symptoms decreased significantly in the Omega-3 fatty acids group compared to the placebo group
Yoga Intervention	Kuloor et al; 2019 [37] India	Depression Tool: HADS	Gender: M & F HIV:100% ART:100%	RCT Yoga = 30 CONTROL(WL) = 30 Follow-up: Post-test	Sessions: 40 Delivered = NS C:IF Ratio = NS Adherence: 90%	Relaxation Meditation Behavioural activation Physical activity	Stakeholders: Not mentioned Community aware: Not mentioned Training IFs: NS Supervision IFs: NS Feasible: Assessed Acceptable: NS Fidelity: NS	There was significantly more reduction in depression scores among participants in the intervention than in the control group
Aerobic Exercise Physical Activity and Counselling	Aweto et al; 2016 [46] Nigeria	Depression Tool: BDI-II	Gender: M & F HIV:100% ART:100%	RCT AE = 20 CONTROL = 20 Follow-up: Post-test	Sessions: 18 Delivered : NS C:IF Ratio = NS Adherence: 90%	Physical activity Relaxation	Stakeholders: Not mentioned Community aware: Not mentioned Training IFs: NS Supervision IFs: NS Feasible: NS Acceptable: NS Fidelity: NS	There was a significantly more reduction in depression scores in the intervention than in the control group
Physical Activity	Daniels et al; 2018 [33] South Africa	Depression Tool: BDI-II	Gender: F HIV:100% ART: 100%	RCT PA = 30 CONTROL = 30 Follow-up: Post-test	Sessions: 6 Delivered : Specialist C:IF Ratio = NS Adherence: NS	Physical activity	Stakeholders: YES Community aware: YES Training IFs: NS Supervision IFs: YES Feasible: NS Acceptable: NS Fidelity: NS	There was no significant difference in the reduction of depression scores between the intervention and control groups
Medication (SSRI – Antidepressants Citalopram)	Moosa et al; 2012 [34] South Africa	Depression Tool: HAMD, SCID	Gender: M & F HIV:100% ART: 100%	RCT Citalopram = 19 IPT = 13 Follow-up: Post-test	Sessions: NA Delivered : Specialist C:IF Ratio = 19 Adherence: 98%	Medication	Stakeholders: Not mentioned Community aware: Not mentioned	There was no significant difference in the reduction of depression scores between the intervention and control groups

Table 2. (*Continued*)

Intervention	Reference country	Mental disorder	Sample	Study design	Intervention characteristics	Active ingredients	Intervention strategies	Key findings
							Training IFs: NA Supervision IFs: NA Feasible: NS Acceptable: NS Fidelity: NS	
Medication (Escitalopram)	Hoare et al; 2014 [36] South Africa	Depression Tool: MADRS, MINI	Gender: M & F HIV:100% ART: 100%	RCT Escitalopram = 51 PLACEBO = 51 Follow-up: Post-test	Sessions: NA Treatment duration: six Weeks Delivered : Specialist C:IF Ratio = NS Adherence: 100%	Medication	Stakeholders: Not mentioned Community aware: Not mentioned Training IFs: NA Supervision IFs: NA Feasible: NS Acceptable: NS Fidelity: NS	There was no significant effect recorded for Escitalopram over placebo on the Montgomery-Asberg Depression Rating Scale.
Medication SARI – Antidepressants (Trazodone)	Alikhani et al; 2020 [45] Iran	Depression, and anxiety Tool: BDI-II	Gender: M HIV:100% ART: 100%	RCT Trazodone = 25 PLACEBO = 50 Follow-up: three months	Sessions: NA Treatment duration: 12 Weeks Delivered : Specialist C:IF Ratio = NS Adherence: 100%	Medication	Stakeholders: Not mentioned Community aware: Not mentioned Training IFs: NA Supervision IFs: NA Feasible: NS Acceptable: NS Fidelity: NS	There was significantly more reduction in depression scores in the intervention than in the control group
Medication - Minocycline	Nakasujja et al; 2013 [63] Uganda	HIV Associated Neurocognitive Impairment Tool: Neuropsychological Test Battery	Gender: M & F HIV:100% ART: 0%	RCT Minocycline = 36 PLACEBO = 37 Follow-up: six months	Sessions: NA Treatment time: 24Weeks Delivered : Specialist C:IF Ratio = NS Adherence: 71%	Medication	Stakeholders: YES Community aware: Not mentioned Training IFs: YES Supervision IFs: YES Feasible: NS Acceptable: NS Fidelity: NS	Minocycline had no advantage for neurocognitive impairment over the placebo.
Medication - Minocycline	Emadi-Kouchak et al; 2016 [42] Iran	Depression Tool: HDRS	Gender: M & F HIV:100% ART: 100%	RCT Minocycline = 25 PLACEBO = 25 Follow-up: Post-test	Sessions: NA Treatment time: 6Weeks Delivered : Specialist C:IF Ratio = NS Adherence: 92%	Medication	Stakeholders: Not mentioned Community aware: Not mentioned Training IFs: NS Supervision IFs: NS	There was significantly more reduction in depression scores in the intervention than in the control group

Table 2. (*Continued*)

Intervention	Reference country	Mental disorder	Sample	Study design	Intervention characteristics	Active ingredients	Intervention strategies	Key findings
							Feasible: NS Acceptable: NS Fidelity: NS	
Medication -Lithium	Decloedt et al; 2016 [62] South Africa	HIV Associated Neurocognitive Impairment Tool: GDS	Gender: M & F HIV:100% ART: 100%	RCT Lithium = 32 PLACEBO = 34 Follow-up: six months	Sessions: NA Treatment time: 24Weeks Delivered : Specialist C:IF Ratio = NS Adherence: 45%	Medication	Stakeholders: YES Community aware: YES Training IFs: YES Supervision IFs: YES Feasible: NS Acceptable: NS Fidelity: NS	Lithium had no advantage for neurocognitive impairment over the placebo.
Nutrition Supplement-(Fish oil Omega fatty acids)	Opiyo et al; 2018 [49] Kenya	Depression Tool: BDI-II	Gender: F HIV:100% ART: 0%	RCT Omega3 Fatty acid = 109 CONTROL = 107 Follow-up: 2 months	Sessions: NA Treatment time: 8Weeks Delivered : Specialist C:IF Ratio = NS Adherence: 79%	Complementary/ alternative treatment	Stakeholders: Not mentioned Community aware: Not mentioned Training IFs: YES Supervision IFs: YES Feasible: NS Acceptable: NS Fidelity: NS	Omega-3 fatty acids had no advantage for depression over the placebo
Herbal supplement (Saffron Herbal Capsules)	Jalali et al; 2018 [38] Iran	Depression Tool: BDI-II	Gender: M HIV:29% ART: 28%	RCT SHC = 109 CONTROL = 107 Follow-up: Post-test	Sessions: NA Treatment time: 8Weeks Delivered : Specialist C:IF Ratio = NS Adherence: NS	Complementary/ alternative treatment	Stakeholders: Not mentioned Community aware: Not mentioned Training IFs: NS Supervision IFs: NS Feasible: NS Acceptable: NS Fidelity: NS	There was a significantly more reduction in depression scores in the intervention than in the control group

ADS, Addiction Severity Index; AE, Aerobic Exercise; AER, Aerobic and Resistance Exercise; AIBS, Alcohol-related Irrational Beliefs Scale; ART, Anti-retroviral Therapy; ASHA, Accredited Social Health Activist; AUDIT, The Alcohol Use Disorders Identification Test; AUDS, The Alcohol Use Disorder Scale; BDI-II, Beck Depression Inventory-II; C:IF, Client to Intervention Facilitator ratio; CBI, Cognitive Behavioural Intervention; CBSM, Cognitive Behavioural Stress Management; CBT, Cognitive Behavioural Therapy; CBT-AD, Cognitive Behavioural Therapy with Adherence and Depression; CESD-20, The Center for Epidemiologic Studies for Depression tool; CRCT, Cluster Randomized Controlled Trial; CSPC, Community Home-Based Social Support and Peer Counselling; DASS-2, Depression Anxiety Stress Scale; DST, Depression Screening Test; DST-15, Dexamethasone Suppression Test; EPDS, Edinburg Postnatal Depression tool; F, Female; FBPST, Friendship Bench-Problem Solving Therapy; GCBT, Group Cognitive Behavioural Therapy; GCEP, Group Coping Enhancement Programme; GDS, Global Deficit Score; GHE, Group HIV Education; GSMT, Group Stress Management Training; GSP, Group Support Psychotherapy; HADS, Hospital Anxiety and Depression Scale; HDRS, The Hamilton Depression Rating Scale; HIV, Human Immunodeficiency Virus; HSCL-15, Hopkins Symptom Checklist for Depression-15; IC, Individual counselling; IES – 15, The Impact of Event Scale-15; IPT, Interpersonal Psychotherapy; LHW, Lay Health Workers; M, Male; MBSR, Mindfulness-Based Stress Reduction; MINI, The Mini-International Neuropsychiatric Interview; NA, Not Applicable; NS, Not Assessed; PA, Physical Activity; PCL-5, The Post-traumatic Stress Disorder Checklist for DSM-5; PDA, Percent days abstinent from alcohol; PDA, Percent drinking-days Absent; PDD, Percent drinking days; PHQ-9, The Patient Health Questionnaire –9; PSS-10, The Perceived Stress Scale; PST, Problem-Solving Therapy; PST-AD, Problem Solving Therapy of Adherence and Depression; PTGI-21, The Post-traumatic Growth Inventory-21; RCT, Randomized Controlled Trial; REBT, Rational-Emotive-Behaviour-Based Therapy; SARI, Serotonin Antagonist and Reuptake Inhibitor; SBARI, Single Brief Alcohol Reduction Intervention; SCID, Severe combined immunodeficiency; SCL-90-R, Symptom Checklist-90-Revised; SFGT, Schema Focused Group Therapy; SHC, Saffron Herbal Capsules; SRQ-20, The Self-Reporting Questionnaire; SRQ-20, The Self-Reporting Questionnaire- 20; TCA, Tricyclic Antidepressants; TFSCI, Trauma-Focused Stress and Coping Intervention; TS, Telephone Support; WL, Wait list.

components included qualifications of intervention deliverer (mental health specialist vs. non-specialist vs. lay health worker), delivery approach (individual vs. group approach), case load per intervention deliverer, number of treatment sessions, adherence rate to treatment sessions and number of active ingredients per intervention. We found that studies of interventions with significant effects had significantly a higher number of active ingredients than those without significant effects [3.41 (2.24) vs. 1.84 (1.46) Mean (SD)] [Mean difference = −1.56, 95% CI = −3.03 to −0.09, $p = 0.037$]. Table S1 shows the relationship between specific active ingredients and intervention effectiveness of all reviewed studies.

Studies of interventions with significant effects had higher treatment adherence rates, lower case load per intervention deliverer than studies without significant effects; however, the differences did not attain statistical significance [85.47 (25.12) vs. 77.3 (24.88) Mean (SD)] [Mean difference = −8.16, 95% CI = −27.05 to 10.72, $p = 0.384$] and [23.29 (29.11) vs. 42.00 (46.62) Mean (SD)] [Mean difference = 18.71, 95% CI = −9.69 to 47.11, $p = 0.188$] respectively. Subgroup analyses indicate that among studies of psychological interventions, those where intervention deliverers had a low case load were more likely to have significant intervention effects than those where intervention deliverers had high case load [26.27 (35.23) vs. 70.14 (47.08) Mean (SD)] [Mean difference = 43.87, 95% CI = 2.77 to 84.96, $p = 0.038$]. The approach used to deliver interventions and qualifications of the intervention deliverer were not associated with intervention effectiveness. Table S2 in the supplementary file shows the detailed relationships between intervention components extracted and intervention effectiveness.

3.7 | Assessing the quality of the synthesis

Of the 30 studies reviewed, 13 (43.33%) received a global rating of "strong" and 13 (43.33%) other studies received a global rating of "moderate" on the EPHP quality assessment tool. The remaining four studies (13.33%) were rated as "weak." Overall, study quality was not associated with intervention effectiveness. However, subgroup analyses indicate that randomized controlled trials of strong quality were more likely to report non-significant effects than those of moderate quality [72.43% vs. 18.18%, $X^2 = 4.89$; $p = 0.08$]. Table S3 shows the quality assessment ratings of all reviewed studies.

4 | DISCUSSION

This review indicates that there have been advances in mental health treatments for PLWH in LMICs since the review by Collins and colleagues in 2006 [64] and the review by Sikkema and colleagues in 2015 [24]. Data presented indicate strong evidence that common mental health problems including depression, anxiety and PTSD are responsive to first-line psychological treatments in LMICs. All reviewed RCTs of antidepressants for depression treatment, however, did not have any advantage over placebo.

Prior research in LMICs indicates significant challenges in anti-depressant use. A large cluster randomized controlled trial of task-shifting delivery models of antidepressants in Uganda [65] found that perfect adherence to antidepressants was the sole predictor of treatment adherence, yet perfect adherence was achieved by only 56% of treated PLWH. In Malawi, integration of depression management using antidepressants did not improve depression and was hindered by a nationwide stock out of antidepressants [66]. These findings coupled with prior evidence [67] and recommendations [68], support first-line use of psychological interventions over pharmacological interventions in mental healthcare of PLWH in LMICs.

In this review, almost two-thirds of psychological interventions evaluated were found to be effective for major depression, depression symptoms and alcohol use problems. However, only group support psychotherapy in Uganda [35], and the mobile health intervention in China [47] demonstrated sustained remission of depression. The scarcity of reported long-term intervention effects calls for more large-scale conclusive trials providing long-term follow-up data.

There was a low yield of research activity focusing on how and for whom interventions work. A study from China [62] suggests that interventions delivered via mobile health may work better for young single individuals than older married ones. This should stimulate more research on how mobile technologies could be used to increase accessibility to mental health services among the younger population in LMICs. A study from Uganda [34] suggests that a culturally sensitive group supports psychotherapy intervention delivered to gender-specific groups leads to greater improvement among men than women 12-month post-treatment. In the reviewed studies, only 2664 men participated in the interventions compared to 3638 women. Interventions that attract men may make it possible to address issues like the perpetration of domestic violence and alcohol and drug use problems which are some of the drivers of the HIV epidemic [69,70]. Provision of psychological treatments to both men and women would ensure holistic care for communities in LMICs.

The findings from this review indicated that active ingredients of mental health intervention may be critical for intervention effectiveness. Effective mental health interventions were more likely to have three or more active ingredients. The active ingredients associated with intervention effectiveness were cognitive restructuring, positive coping skills, venting (sharing personal problems) social support and behaviour activation. Future studies of intervention development should find simple and culturally appropriate ways of incorporating these active ingredients.

The Lancet Psychiatry Commission on psychological treatments research recommends that psychological treatments can be simplified and shaped in line with local cultural norms and conditions [71]. For example if one of the major maintaining factors of depression concerns lack of behaviour activation in daily life, then treatment strategies to increase behaviour activation can be formed in many different ways depending on what is the most relevant, acceptable, and affordable in the specific context or culture in which the problem exists.

This review showed that intervention adherence rates may be important for intervention effectiveness. Interventions tailored to the cultural context of the target population are more likely enhance treatment adherence rates than western interventions brought into a LMIC setting.

Although the approach used to deliver interventions and qualifications of the intervention deliverers were not associated with intervention effectiveness, interventions delivered in a group format and by lay health workers are more likely to ensure accessibility and sustainability of mental health interventions in LMICs. Given that our review also found that case load per intervention deliverer is critical to intervention effectiveness, counselling training programmes for lay health workers will be important in narrowing the mental health treatment gap in LMICs.

Contextual influences may also affect intervention effects. Only half of the studies reviewed described some form of stakeholder involvement and public involvement and these were not associated with significant intervention effects. A lack of stakeholder buys-in may limit the extent to which the target population engages with activities required to deliver the intervention. The study integrating depression management with anti-depressants in Malawi reports how Government officials failed to provide antidepressants at health facilities participating in intervention evaluations. Furthermore, the stakeholders failed to nominate community health workers who had a keen interest and were ready to commit time to deliver the interventions. Thus, therapy sessions had to be delivered by only one study employed community health worker [66].

Creating awareness through community sensitization meetings may go a long way in ensuring that community members support affected individuals to get to their therapy meetings. Involving the target population in intervention design is crucial in ensuring that the target population adheres to the intervention sessions. Including content and formats desired by the target population increases community ownership of the intervention. Nakimuli-Mpungu *et al* [35] included gender-specific groups, cultural rituals, livelihood skills – all requested for by the target population – moved therapy sessions to villages and provided a small financial incentive to intervention deliverers, thereby eliminating financial and transport barriers reported frequently by other studies.

In other studies, spiritual activities have been included into therapy sessions to make the intervention more meaningful to the target population and thereby enhance adherence to the intervention [53]. Recent research indicates that accommodating patient preference in mental health services maximizes treatment uptake and reduces financial costs of premature dropout and disengagement [72].

Several limitations need to be acknowledged, which mostly arise from the inherent risk of bias at review (e.g. incomplete retrieval of identified research and reporting bias). This emphasizes a need for a thoughtful interpretation of our results. One major problem we found was inconsistent reporting of interventions, with some studies providing sufficient detail about the mental health intervention, whereas others offered limited descriptions. Thus, our analyses of the association between specific intervention components with intervention effectiveness were limited by the description of the interventions provided in the reviewed articles. There is a risk that some interventions included components that were not reported and that some of the reported components were not received by all patients in the study. For example descriptions of stake holder or public involvement, training and supervision of intervention deliverers were not forthcoming for many studies.

Going forward, there is a need for conclusive trials of mental health interventions for PLWH with severe mental disorders. None of the reviewed studies described a mental health intervention for PLWH with severe mental disorders, including psychotic disorders. Second, this review did not find any definitive trials of mental health interventions among PLWH in Latin America. Given that the region still grapples with the HIV epidemic, there is an urgent need to address the mental health needs of PLWH in this region. Third, more research focused on intervention components such as intervention deliverers and active ingredients in mental health interventions would shed more light on which components lead to symptom remission and ultimately improve intervention effectiveness. Future studies could pool datasets across LMICs and use patient-level to explore the mediating and moderating role of intervention components on the effects of mental health interventions in PLWH. Lastly, more evidence is needed for long-term outcomes of mental health interventions for PLWH which were limited in the studies reviewed.

5 | CONCLUSIONS

Sufficient evidence supports the presence of effective psychological treatments for common mental health problems in PLWH, including depression anxiety, and alcohol use disorders. Potential interventions using social media and mobile technologies should be explored given the COVID-19 pandemic. Culturally appropriate, feasible and acceptable interventions that have been successfully piloted and fully evaluated in LMICs should be scaled up.

Evaluative research should be integral to national HIV care programmes, including access to adequate funding to encourage and permit the necessary studies. Because mental health treatment is critical for the success of the Treat All Policy, the implementation of proven, evidence-based, and cost-effective strategies should be the duty and responsibility of public health policy makers and healthcare providers.

COMPETING INTEREST

All authors declare no competing interests.

AUTHOR'S CONTRIBUTIONS

EN-M, JJ, CMS, MVI, BA, MR and SM conceptualized the study. MVI, MR and AVW managed the literature searches. EN-M, BA and CMS conducted statistical analyses. EN-M, CMS, BA and MVI wrote the initial manuscript. SM, JJ, JB, EM, AS and DC revised the manuscript critically for important intellectual content. All authors contributed to the final manuscript.

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DISCLAIMER

The views expressed are the authors' own and do not necessarily represent the views the United States government or any of its agencies.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Association between active ingredients and intervention effectiveness

Table S2. Relationship between intervention components and intervention effectiveness

Table S3. Quality Assessment of Quantitative studies of Mental Health interventions for Persons Living with HIV in LMIC

Figure S1. Search strategy

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VIEWPOINT

Global mental health and HIV care: gaps and research priorities

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Keywords: mental health; HIV; biological factors; implementation science; health behaviour

Common mental disorders, including depression, anxiety and post-traumatic stress disorder (PTSD), occur at high rates among people living with HIV (PLWH) [1]. Mental disorders are associated with poorer HIV care continuum outcomes [2] and co-occur with other psychological and structural factors including violence, stigma and other social determinants of health, which are additional barriers to HIV treatment [3]. Furthermore, mental disorders may interact with and impact biological factors to worsen HIV outcomes.

This viewpoint highlights three research gaps in mental health among PLWH: (a) understanding complex interactions between biological, psychological and structural factors that influence mental disorders in PLWH; (b) developing and testing interventions to address mental health, as well as co-occurring psychological and structural factors, to improve HIV outcomes and (c) implementation science to understand how to best implement and scale up evidence-based interventions to improve mental health and HIV outcomes (see Figure 1).

Understanding the complex interactions between biological, psychological/behavioural, social and structural factors that influence mental disorders in PLWH

Biological, psychological, social and structural factors interact to influence the development of mental disorders among PLWH. Both HIV and Antiretroviral therapy (ART) (e.g. efavirenz, dolutegravir) [4] cause inflammatory immune-related changes in the Central nervous system (CNS) and the periphery, and these alterations may lead to disturbances in neurotransmitters and circuits modulating mood and behaviour [5]. The impact of HIV and ART on the peripheral immune system and neuroimmune milieu is well studied [6,7]; however, these changes have not yet been linked to mental health outcomes seen in PLWH.

In addition, co-occurring factors, such as stigma, access to education and living in the context of structural poverty and a fragile health system have an impact on the mental health of PLWH [8]. Few studies concurrently examine somatic mechanisms such as HIV- and ART-related immune activation, neuroimmune dysfunction, microbiome alterations and metabolome variations alongside non-somatic aetiologies such as violence, stigma and stress. Analyzing genetic, metabolomic, microbiome, neurobiological, imaging, behavioural, psychological, demographic and clinical data from long-standing cohorts, such as the Rakai Community Cohort in Uganda [9] or South Africa's National HIV Programme cohort [10], could lead to better understanding of the aetiologies underlying mental disorders in PLWH. In low-resource countries where such cohort data might not be readily available, methods to capture key parameters utilizing primary care and community-derived data should be developed.

A better understanding of complex interactions between factors at multiple levels will aid in identifying key modifiable targets to inform the development of targeted pharmacological and non-pharmacological interventions for PLWH with mental disorders. For example research has found that adverse childhood experiences are associated with less responsiveness to some antidepressants, suggesting that experience may impact biology in a way that subsequently impacts response to depression treatment [11]. This research can be expanded to include PLWH, incorporate other psychological and social stressors and identify the mechanisms underlying differential response to treatment, to inform novel and targeted interventions.

Developing and testing interventions to address mental health and other psychological and structural comorbidities, to improve hiv outcomes

Although studies have demonstrated the effectiveness of evidence-based mental health interventions on mental health outcomes, the extent to which they impact HIV outcomes is less clear [12]. Studies from the United States have shown that a combined approach integrating mental health treatment

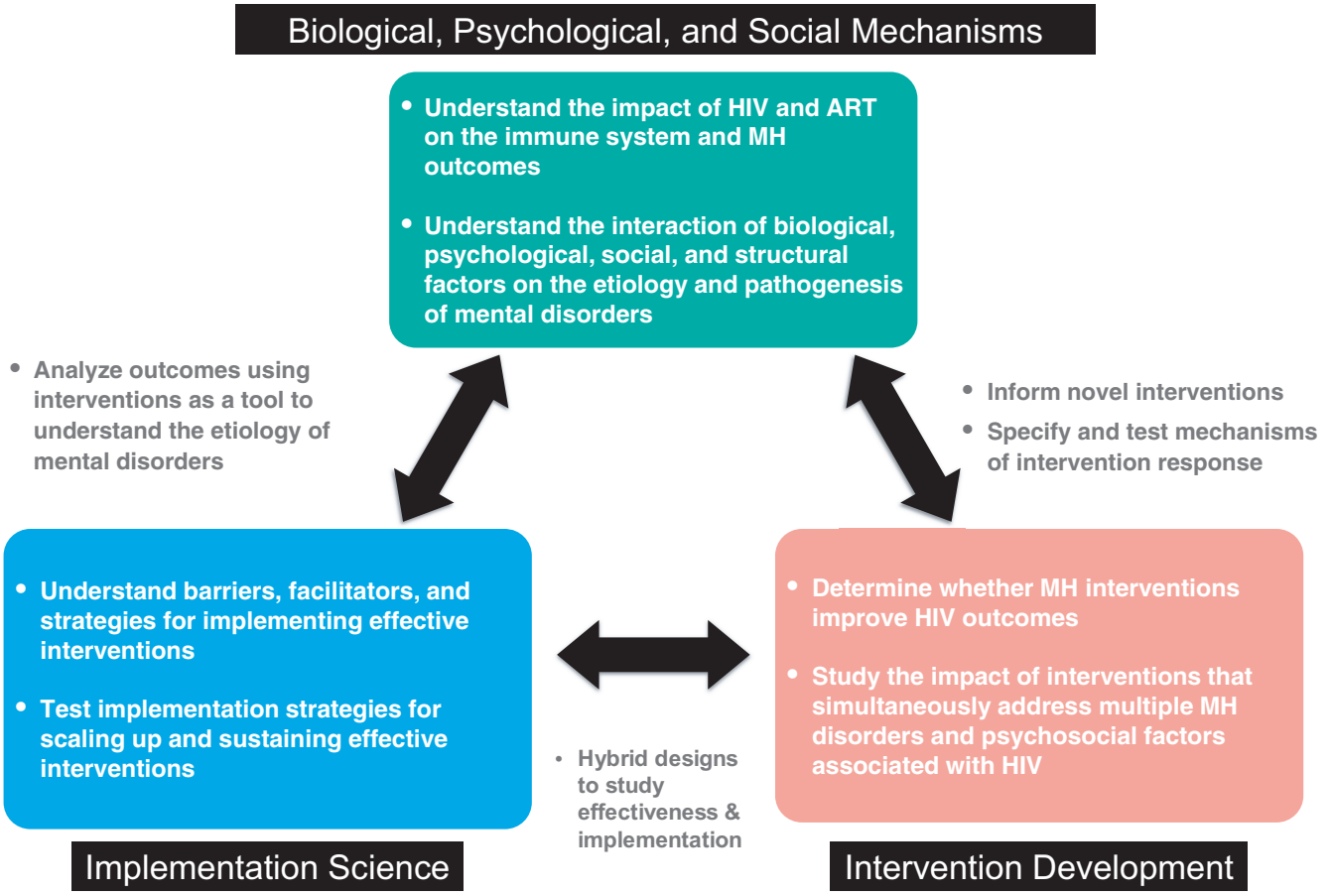

Figure 1. Research gaps in the study of mental health among people living with HIV. MH, mental health; PLWH, people living with HIV; ART, antiretroviral therapy.

with HIV care interventions (e.g. Problem Solving Therapy for depression and adherence) [13] can lead to improvements in both categories of health outcomes [14,15], but comparable data are not widely available across low-resource settings.

There are few empirically supported interventions that simultaneously address multiple common mental health disorders and social factors associated with HIV. One promising approach is the Common Elements Treatment Approach (CETA). This transdiagnostic intervention, consisting of common techniques underlying depression, anxiety and substance use treatment [16], improved mental health, substance use and intimate partner violence in a recent randomized controlled trial [16,17], but needs more investigation in terms of HIV outcomes [18]. Another cross-cutting, integrative approach in need of rigorous evaluation is the World Health Organization Mental Health Gap Action Programme (mhGAP) Intervention Guide (IG), that delivers evidence-based screening, treatment and referral to address common mental, neurological and substance use disorders [19]. Key interventions (e.g. accelerators) that simultaneously impact multiple targets, or combine to support individual targets, could promote a holistic approach to meet wide-ranging needs [20]. Targeting positive affect, coping and resilience is a growing area of research that could improve HIV outcomes [21]. Specifying and testing mechanisms of intervention action will be key to understanding why interventions do (or do not) work.

Implementation science to deliver and scale up mental health interventions

Evidence-based mental health interventions for PLWH must be implemented effectively and delivered across global contexts using scalable and cost-efficient approaches. Researchers have begun to examine key factors impacting the delivery of mental health interventions for PLWH, including barriers and facilitators to implementation, as well as feasibility, acceptability and costs. Implementation strategies are often elicited from patients, stakeholders and experts across contexts, and tested through rigorous designs. Strong implementation science research is guided by a theoretical framework, which may inform implementation planning, barriers and facilitators to implementation, and/or implementation evaluation [22]. Hybrid designs allow for simultaneous testing of intervention and implementation outcomes.

Additional research is needed to understand the mediators through which implementation strategies impact outcomes, to improve understanding of successful (and unsuccessful) approaches and help ensure strategies are appropriately used in new settings and populations [23]. Once successful approaches have been implemented, further research is needed to ensure these approaches are sustained. Implementation strategies to address mental health in PLWH that could be studied further include: task sharing, where interventions

are adapted for delivery by individuals with less advanced training [24]; mHealth approaches, to deliver interventions cost-efficiently or in settings where transportation is a barrier [25]; differentiated care approaches, where treatment intensity, frequency or type is matched to an individual's needs, reducing costs of providing excess or inappropriate treatment [26]; integration of mental health and HIV services [27]; and transdiagnostic interventions [16] which target a range of mental disorders. All these approaches hold promise for scaling up mental health interventions for PLWH globally. Finally, as many countries with high HIV burdens already have platforms for providing HIV treatment, these may be leveraged to share costs and more efficiently deliver mental health services to PLWH.

In conclusion, the substantial burden of mental health disorders among PLWH negatively impacts health and wellbeing. Research on the aetiology and pathogenesis of mental disorders in PLWH, intervention research that addresses both mental health and HIV care outcomes, and implementation science research to implement, scale up and sustain interventions is needed to improve physical and mental health in PLWH.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TES, GLG and VRR contributed to the conception of the manuscript, were involved in drafting the manuscript, and critically revised the manuscript. All authors have read and approved the final manuscript.

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DISCLAIMER

The views expressed in this paper are those of the authors, and these views do not necessarily represent the official views of the National Institute of Mental Health, the National Institutes of Health or the U.S. government.

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SHORT REPORT

Project Khanya: results from a pilot randomized type 1 hybrid effectiveness-implementation trial of a peer-delivered behavioural intervention for ART adherence and substance use in HIV care in South Africa

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Abstract

Introduction: South Africa (SA) has the highest number of people living with HIV (PLWH) globally, and a significant burden of alcohol and other drug use (AOD). Although integrating AOD treatment into HIV care may improve antiretroviral therapy (ART) adherence, this is not typically routine practice in SA or other low-resource settings. Identifying interventions that are feasible and acceptable for implementation is critical to improve HIV and AOD outcomes.

Methods: A pilot randomized hybrid type 1 effectiveness-implementation trial ($N = 61$) was conducted to evaluate the feasibility and acceptability of *Khanya*, a task-shared, peer-delivered behavioral intervention to improve ART adherence and reduce AOD in HIV care in SA. *Khanya* was compared to enhanced treatment as usual (ETAU), a facilitated referral to on-site AOD treatment. Implementation outcomes, defined by Proctor's model, included feasibility, acceptability, appropriateness and fidelity. Primary pilot effectiveness outcomes were ART adherence at post-treatment (three months) measured via real-time electronic adherence monitoring, and AOD measured using biomarker and self-report assessments over six months. Data collection was conducted from August 2018 to April 2020.

Results and discussion: Ninety-one percent of participants ($n = 56$) were retained at six months. The intervention was highly feasible, acceptable, appropriate and delivered with fidelity (>90% of components delivered as intended by the peer). There was a significant treatment-by-time interaction for ART adherence (estimate = −0.287 [95% CI = −0.507, −0.066]), revealing a 6.4 percentage point increase in ART adherence in *Khanya*, and a 22.3 percentage point decline in ETAU. Both groups evidenced significant reductions in alcohol use measured using phosphatidylethanol (PEth) ($F(2,101) = 4.16$, $p = 0.01$), significantly decreased likelihood of self-reported moderate or severe AOD ($F(2,104) = 7.02$, $p = 0.001$), and significant declines in alcohol use quantity on the timeline follow-back ($F(2,102) = 21.53$, $p < 0.001$). Among individuals using drugs and alcohol, there was a greater reduction in alcohol use quantity in *Khanya* compared to ETAU over six months ($F(2,31) = 3.28$, $p = 0.05$).

Conclusions: Results of this pilot trial provide initial evidence of the feasibility and acceptability of the *Khanya* intervention for improving adherence in an underserved group at high risk for ongoing ART non-adherence and HIV transmission. Implementation results suggest that peers may be a potential strategy to extend task-sharing models for behavioral health in resource-limited, global settings.

Keywords: HIV; substance use; antiretroviral therapy adherence; global mental health; implementation science; South Africa

Additional Supporting Information may be found online in the Supporting information tab for this article.

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1 | INTRODUCTION

South Africa (SA) is home to the largest number of people living with HIV (PLWH) globally [1]. Despite a large antiretroviral therapy (ART) programme, limited ART regimens are readily available in the public health sector [2]. ART non adherence increases the risk of developing drug resistance and treatment failure, contributing to ongoing viral transmission, morbidity and mortality [3,4].

Alongside the HIV epidemic, alcohol and other drug use (AOD) are highly prevalent among PLWH in SA [5,6]. Individuals with AOD are at greater risk for poor ART adherence, viral

non-suppression, and ongoing HIV transmission [7-14]. Integrating AOD treatment into HIV care can improve ART adherence, yet this is not typically routine practice in SA or other low-resource settings [15-17]. Furthermore, ART adherence interventions are rarely adapted for AOD – a missed opportunity for maximizing HIV treatment outcomes [18-23].

We conducted a hybrid type 1 effectiveness-implementation [24] pilot study to evaluate the feasibility, acceptability, appropriateness and fidelity of a peer-delivered intervention ("*Khanya*"), and preliminarily examine whether *Khanya* was associated with improvements in ART adherence over three months and AOD over six months versus enhanced treatment as usual (ETAU) [25,26].

2 | METHODS

2.1 | Recruitment and screening

Individuals were recruited between August 2018 and October 2019 from HIV care in Khayelitsha, a community with the highest HIV prevalence in the Western Cape [27]. Inclusion criteria were as follows: (1) HIV positive and on ART; (2) 18 to 65 years old; (3) at least moderate AOD on the WHO Alcohol, Smoking, and Substance Involvement Screening Test (WHO-ASSIST [28]); (4) ART non-adherence in the past three months, defined by either: (a) missing a pharmacy refill; (b) reinitiating first-line treatment or being on second-line treatment or (c) having unsuppressed viral load (≥400 copies/mL). Exclusion criteria were as follows: (1) high-risk opiate or alcohol use warranting medical management; (2) untreated major mental illness; (3) inability to provide informed consent or speak English or isiXhosa; (4) third-trimester pregnancy or (5) currently enrolled in AOD treatment. Eligible and interested participants completed informed consent and baseline assessments. Participants were given a Wisepill device [29] to monitor ART adherence over two weeks. At two-weeks post-baseline, participants were randomly assigned in parallel (1:1) to ETAU or *Khanya* using Research Electronic Data Capture (REDCap). Participants were assessed by a trained, blinded assessor at three- and six-month post-baseline. Participants received a 150ZAR (approximately $10 USD) grocery voucher for completing study assessments. All procedures were approved by the University of Cape Town Health Sciences Faculty Human Research Ethics Committee (HREC 187/2018). Magidson *et al.*[30] includes full protocol details.

2.2 | Allocation groups

2.2.1 | *Khanya*

Khanya is a six-session peer-delivered behavioral intervention that integrates several evidence-based intervention components [31-34] – behavioral activation, problem solving, motivational interviewing and mindfulness-based relapse prevention – adapted during formative work preceding this trial [35,36]. The intervention aims to support increased ART adherence and individualized goal setting for AOD reduction by teaching evidence-based behavioral skills (i.e. behavioral monitoring, activity scheduling, mindfulness practice, relapse prevention) to support the attainment of these goals. Home practice is assigned between sessions to reinforce skills. Real-time electronic adherence monitoring is discussed in session in relation to skill practice to address barriers to adherence and relapse prevention. Participants are offered up to six optional booster sessions to further reinforce skills. Participants were not compensated for intervention sessions but travel costs were reimbursed. Sessions lasted approximately 60 minutes. The interventionist was a peer – an individual with lived AOD experience – paid full-time as part of the research team, trained and supervised by clinical psychologists. Intervention, supervision and training details are provided elsewhere [30,37].

2.2.2 | *Enhanced treatment as usual*

TAU for individuals with AOD in this context is a referral letter to Matrix [38,39], an evidence-based, co-located 16-week AOD programme that includes an initial screening and brief intervention session [25,26]. We enhanced TAU by discussing the referral to Matrix, offering to accompany participants to the intake if they wished, and following up on referral uptake at subsequent visits.

2.3 | Measures

Implementation outcomes were guided by Proctor's model [40], including feasibility, acceptability, appropriateness and fidelity. *Feasibility* and *acceptability* were assessed based on uptake (percentage who initiated the intervention and session attendance respectively) and a validated quantitative measure was used for assessing implementation outcomes in Low-and-middle-income countries (LMICs) [41], including feasibility, acceptability and appropriateness (ratings on a four-point scale: 0 = "not at all"; 3 = "a lot"). *Fidelity*. A randomly selected 20% of *Khanya* sessions were rated by the interventionist and an independent coder (trained in fidelity monitoring and not involved in this study) following best practices and other studies examining fidelity of task-shared interventions [42]. A 15 to 19 item (depending on session) checklist of core session components was developed a priori. The independent coder also rated common factors (i.e. verbal communication, self-disclosure, normalization, empathy) using the ENhancing Assessment of Common Therapeutic factors (ENACT; 1 to 3 rating scale) [43].

ART adherence was assessed from baseline (past two weeks) through post-treatment (approximately three months) using Wisepill, a real-time adherence monitoring device [29]. Adherence was measured as the percentage of days' adherent from baseline to the week prior to post-treatment. Observations, where the device battery was dysfunctional, were excluded.

AOD was assessed using biomarker and self-report at baseline, three months and six months. *Phosphatidylethanol (PEth)* testing was conducted from dried blood spots (≥50 ng/mL reflects unhealthy drinking up to 21 days [44]). *Urinalysis* assessed cocaine, marijuana, amphetamines, opiates, phencyclidine and alcohol (<80 hours; 300 ng/mL; [45,46]), and methaqualone (Mandrax), a local sedative. The *WHO-ASSIST* assessed past three-month self-reported AOD [28] using defined risk categories (*alcohol*: ≥27 high risk; 11 to 26 moderate; 0 to 10 low; *drugs*: ≥27 high risk; 4 to 26 moderate; 0 to 3 low). The *Timeline Follow-Back (TLFB)* [47], a calendar-aided assessment of AOD, assessed the quantity of alcohol

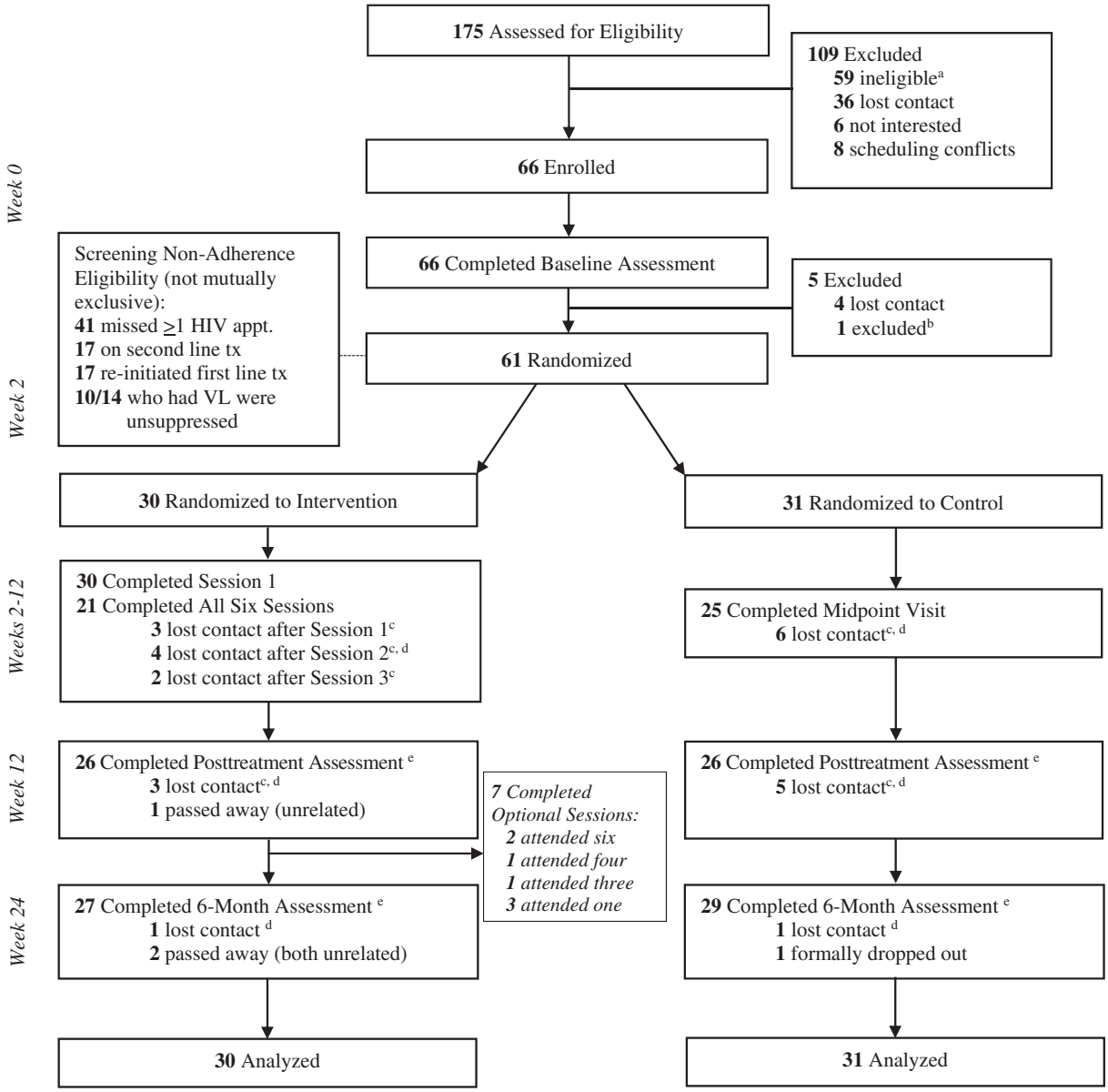

Figure 1. Consort diagram.[a]WHO-ASSIST too low only (n = 54); not struggling with adherence only (n = 1); WHO-ASSIST too low and not struggling with adherence (n = 1); undertreated major mental illness (n = 2); incomplete screening (n = 1). [b]1 participant excluded pre-randomization for severe alcohol dependence (medical management of withdrawal symptoms needed). [c]Participants uncontactable for specific event, but attended later events. [d]1 participant was uncontactable for remainder of study. [e]Due to staffing resource restraints, only 36/52 assessments were blinded at post-treatment (69%), and only 19/56 assessments were blinded at six-month follow-up (34%).

use in the past two weeks and the percentage of days used (any substance). Recall was aided by the use of empty, locally recognizable alcohol containers.

Viral load (exploratory) was extracted from medical records (within three months before baseline, 30 days of follow-ups) or drawn and tested by the National Health Laboratory Service when unavailable. Viral suppression was defined as <400 copies/mL per local clinic standards.

2.4 | Data analytic plan

This pilot study aimed to establish the feasibility and acceptability of *Khanya*, examined using descriptive statistics (means and standard deviations) of implementation outcomes. The study sample size followed recommendations for pilot studies [48,49]. Effectiveness outcomes were examined using multilevel modelling to account for repeated measurements [50]. Time was treated categorically to capture differing rates of change between time points, and all models included a random intercept. Analyses used an intent-to-treat framework [51], including all available data. Missing data were treated as missing at random. All analyses were run using SAS version 9.4 [52]. Presented models were adjusted for baseline age and gender, determined a priori [30], and observed baseline differences in theoretically relevant factors (relationship status, viral suppression and substance use severity). As

Table 1. Baseline demographic and clinical characteristics of sample by treatment group

Characteristic	Total sample (*N* = 61)	Khanya (*n* = 30)	ETAU (*n* = 31)
Age, *M* (SD)	37.00 (9.63)	39.80 (10.47)	34.29 (7.99)
% Female (n)	54.1 (33)	43.3 (13)	64.5 (20)
% Graduated high school or above (n)	23.0 (14)	26.7 (8)	19.4 (6)
% Casual or full-time employment (n)	21.3 (13)	13.3 (4)	29.0 (9)
% Married or common-law (n)	26.2 (16)	10.0 (3)	41.9 (13)
HIV characteristics			
Years since HIV diagnosis, *M* (SD)	6.27 (4.87)	7.14 (5.97)	5.43 (3.39)
% Suppressed viral load (<400 copies/mL) (n)	63.9 (39)	50.0 (15)	77.4 (24)
CD4 count	376 (253)	330 (210)	420 (285)
% Days adherent via Wisepill over two weeks, *M* (SD)[a]	51.4 (30.7)	53.6 (32.1)	49.3 (29.7)
% On second-line (n)[b]	26.7 (16)	24.1 (7)	29.0 (9)
Substance use characteristics			
% Positive alcohol urine test (n)	88.5 (54)	86.7 (26)	90.3 (28)
% PEth unhealthy drinking (n)	83.6 (51)	90.0 (27)	77.4 (24)
WHO-ASSIST alcohol score, *M* (SD)[c]	25.66 (6.88)	25.93 (6.70)	25.39 (7.16)
% Days consumed any substance on TLFB, *M* (SD)	34.1 (23.5)	38.8 (24.6)	29.5 (21.7)
% Days consumed alcohol on TLFB, *M* (SD)	30.3 (21.0)	37.1 (22.9)	23.7 (16.9)
Average number of drinks on days drinking on TLFB, *M* (SD)	7.60 (4.75)	7.17 (3.79)	8.03 (5.59)[d]
% Positive (any) drug urine test (n)	31.2 (19)	40.0 (12)	22.6 (7)
WHO-ASSIST (any) drug score, *M* (SD)[e]	13.10 (9.47)	9.25 (6.34)	15.67 (10.84)
% Days consumed other drugs on TLFB, *M* (SD)[f]	39.8 (26.0)	47.6 (35.9)	33.9 (19.7)

[a]Data from randomization visit; [b]n = 29 for Khanya arm; [c]data from screening visit; [d]n = 30; [e]score for those who reported using substance in past 3 months (N = 11 WHO ASSIST scores from 10 participants, n = 4 Khanya arm, n = 7 ETAU arm); [f]Cannabis was the only substance reported at this assessment; n = 3 for Khanya arm, n = 4 or ETAU arm. TFLB, Timeline Follow-Back; SD, Standard deviation

sensitivity analyses, models were re-run without covariates and with age and gender only. Models were also run with time treated continuously and a random slope. The pattern of results for sensitivity analyses did not differ. We also examined all results separately for a subsample who also used drugs in the past three months (*n* = 21). See supplemental materials for the more detailed data analytic plan.

3 | RESULTS AND DISCUSSION

3.1 | Participants

A total of *N* = 61 participants were enrolled and randomized; see Figure 1 for consort diagram. The sample was largely Black African and 54% female. Individuals were ART adherent 51.4% of days over two weeks at baseline, over 80% had unhealthy drinking, and approximately one-third had current drug use. Table 1 includes baseline characteristics, and Table 2 includes all outcomes by treatment group by time point.

3.2 | Outcomes

3.2.1 | Implementation outcomes

Although AOD treatment utilization is typically low in SA [53], treatment uptake was high in this sample. Of the participants randomized to *Khanya*, 100% initiated the intervention, and 70% attended all six sessions (*M* = 4.77; *SD* = 1.96); 88% of *Khanya* participants reported satisfaction with the number of treatment sessions. Feasibility, acceptability and appropriateness of *Khanya* were rated very highly (feasibility: *M* = 2.98; *SD* = 0.18; acceptability: *M* = 2.98; *SD* = 0.04; appropriateness: *M* = 2.94, *SD* = 0.09). For ETAU, 80.6% (*n* = 25) attended the Matrix referral, of whom 68% (*n* = 17) attended only one session (range 0 to 11). Interventionist self-reported fidelity was 96.5% (*SD* = 7.2) for *Khanya*; average independent rater fidelity was 91.7% (*SD* = 13.3). Peer therapeutic common factors, such as warmth and non-judgement, were rated highly using ENACT (*M* = 2.69; *SD* = 0.28).

3.2.2 | Effectiveness outcomes

Overall model results for all effectiveness outcomes are presented in Table 3. Drug subsample results for all outcomes are in Tables S1-S6.

ART adherence

There was a significant treatment-by-time interaction (estimate = −0.287 [95% CI = −0.507, −0.066]), such that ETAU's pre-post treatment change in days' adherent was 28 percentage points lower than *Khanya*. Average adherence increased 6.4 percentage points in *Khanya*, whereas adherence declined by 22.3 percentage points in ETAU (see Figure S1).

Although the study was focused on implementation, the fact that we saw large effects on behavioral adherence in this small sample is noteworthy. Improving ART adherence among individuals with AOD is a known challenge [15]. Interventions to enhance adherence are critical for improving individual HIV outcomes and supporting treatment as prevention.

Table 2. Sample means and percentages for primary outcomes at assessment time points by treatment group

	Khanya			ETAU		
Outcome measure	**Baseline (*N* = 30)**	**Three-month (*N* = 26)**	**Six-month (*N* = 27)**	**Baseline (*N* = 31)**	**Three-month (*N* = 26)**	**Six-month (*N* = 29)**
% Days adherent via Wisepill, *M (SD)*	53.6 (32.1)[a]	60.0 (37.1)[b]	–	49.3 (29.8)	28.2 (32.1)[c]	–
% (n) suppressed viral load, <400 copies/mL	50.0 (15)	65.4 (17)	59.3 (16)	77.4 (24)	73.1 (19)	75.9 (22)
PEth score, *M (SD)*	686.0 (639.9)	484.2 (398.7)	538.4 (554.4)[d]	456.1 (530.8)	414.7 (389.6)[d]	386.1 (392.6)
% Positive alcohol or drug urine test *(n)*	90.0 (27)	96.2 (25)	83.3 (20)	93.6 (29)	88.5 (23)	82.8 (24)
% Moderate or high risk on WHO-ASSIST	100 (30)	88.5 (23)	88.9 (24)	100 (31)	96.2 (25)	75.9 (22)
% Days consumed any substance on TLFB, *M (SD)*	38.8 (24.6)	29.1 (24.6)	30.7 (25.9)	29.5 (21.7)	24.5 (20.2)	25.1 (23.2)
Average number of drinks on days drinking on TLFB, *M (SD)*	7.17 (3.79)	5.36 (3.84)	4.61 (3.29)	8.03 (5.59)[e]	5.47 (3.77)[d]	4.96 (4.25)

[a]*n* = 29; [b]*n* = 28; [c]*n* = 27; [d]*n* = 25; [e]*n* = 30. SD, standard deviation; TLFB, Timeline Follow-Back

Table 3. Overview of all model results by time and time by treatment interaction

	Time only (effect of Khanya on outcome)				Time by Treatment (effect of ETAU on outcome)			
Effect	**Estimate (SE) or DF**	**95% CI**	***F* or *t***	***p***	**Estimate (SE) or DF**	**95% CI**	***F* or *t***	***p***
Wisepill adherence	–	–	–	–	–	–	–	–
PT	0.064 (0.078)	[−0.092, 0.220]	0.82	0.41	−0.287 (0.110)	[−0.507, −0.066]	−2.61	0.01
FU	–	–	–	–	–	–	–	–
PEth	2, 101	–	4.16	0.01	2, 101	–	0.97	0.38
PT	−227 (80)	[−385, −69]	−2.85	0.005	157 (113)	[−67, 382]	1.39	0.16
FU	−169 (81)	[−329, −9]	−2.09	0.03	84 (111)	[−136, 304]	0.76	0.44
Alcohol/drug urine test	2, 101	–	1.67	0.19	2, 101	–	0.59	0.55
PT	−1.14 (1.36)	[−3.85, 1.56]	−0.84	0.40	1.95 (1.79)	[−1.61, 5.50]	1.09	0.27
FU	0.80 (1.04)	[−1.26, 2.87]	0.77	0.44	0.71 (1.49)	[−2.24, 3.67]	0.48	0.63
Categorical ASSIST	2, 104	–	7.02	0.001	2, 104	–	0.10	0.90
PT	−1.35 (0.67)	[−2.67, −0.03]	−2.03	0.04	0.25 (0.89)	[−1.51, 2.00]	0.28	0.77
FU	−1.68 (0.66)	[−2.98, −0.37]	−2.55	0.01	−0.14 (0.87)	[−1.85, 1.58]	−0.16	0.87
TLFB average drinks	2, 102	–	21.53	<0.001	2, 102	–	0.05	0.94
PT	−0.32 (0.11)	[−0.54, −0.10]	−2.91	0.004	−0.05 (0.16)	[−0.36, 0.26]	−0.32	0.74
FU	−0.46 (0.11)	[−0.69, −0.24]	−4.07	<0.001	−0.03 (0.16)	[−0.34, 0.28]	−0.18	0.85
Viral suppression (<400)	2, 104	–	0.27	0.76	2, 104	–	0.72	0.49
PT	1.01 (0.77)	[−0.52, 2.53]	1.31	0.19	−1.31 (1.13)	[−3.56, 0.93]	−1.16	0.24
FU	0.81 (0.75)	[−0.69, 2.30]	1.07	0.28	−0.89 (1.10)	[−3.08, 1.29]	−0.81	0.41

Alcohol and other drug use

Biomarker There was a significant main effect of time in the model predicting PEth ($F(2,101) = 4.16$, $p = 0.01$) and a non-significant treatment-by-time interaction ($F(2,101) = 0.97$, $p = 0.38$), indicating both groups demonstrated reductions in PEth. In the model predicting negative urinalysis results for drug use or past three-day alcohol use, the time ($F(2,101) = 1.67$, $p = 0.19$) and treatment-by-time interaction were not significant ($F(2,101) = 0.59$, $p = 0.55$).

WHO alcohol, smoking, and substance involvement screening test There was a significant main effect of time in the model predicting the likelihood of moderate or high-risk WHO-ASSIST category ($F(2,104) = 7.02$, $p = 0.001$), but not the treatment-by-time interaction ($F(2,104) = 0.10$, $p = 0.90$). The probability of being in the high-risk category reduced 30 percentage points at three months and 40 percentage points at six months.

Timeline follow-back There was a significant effect of time in the model predicting the average number of drinks consumed for *Khanya* ($F(2,102) = 21.53$, $p < 0.001$). Participants in *Khanya* consumed on average 5.3 and 4.6 drinks at the subsequent time points, compared to 7.3 at baseline.

However, the treatment-by-time interaction was not significant, indicating similar changes across groups over time. For the subsample who also used drugs, there was a marginally significant treatment-by-time interaction ($F(2,31) = 3.28$, $p = 0.05$); *Khanya* had a greater reduction in the number of drinks at six months compared to ETAU (see Figure S2). Given the *Khanya* intervention did not require abstinence, it can be understood that individuals reduced amounts of alcohol consumed rather than abstinence.

Viral load (exploratory)

There was no treatment effect on viral load ($F(2,104) = 0.72$, $p = 0.49$). However, we were not adequately powered in this pilot study to detect changes in viral load over a relatively short follow-up period [54,55], especially since 63.9% of the sample was suppressed at baseline. However, there was a significant relationship between viral suppression and adherence; individuals with higher adherence at post-treatment were more likely to be virally suppressed ($t = 2.31$; $p = 0.02$). Results are consistent with other behavioral intervention trials with a primary focus on ART adherence that did not demonstrate treatment effects on viral load [56-58].

4 | CONCLUSIONS

This pilot trial provides initial evidence of the feasibility and acceptability of the peer-delivered *Khanya* intervention for improving adherence alongside AOD in South African HIV care. Peers offer a potential solution to known implementation barriers of task-sharing behavioral interventions with CHWs, including high caseloads and other clinical demands [35,59]. Peers bring with them lived experience, which can foster connection with patients and potentially reduce HIV and AOD stigma [60,61]. Initial results regarding the implementation success of *Khanya* and ART adherence improvements are promising. Results suggest that engagement in AOD treatment alone without integrated adherence support may not be sufficient to improve ART adherence; however, a larger trial is needed to evaluate longer term effectiveness outcomes, including viral suppression, and to consider a stepped care approach to efficiently allocate resources to support individuals most in need of intensive intervention.

Strengths of this trial included a rigorous comparison condition, prioritization of individuals most in need of intervention – with both AOD and ART non-adherence – use of a hybrid effectiveness-implementation design, and high retention rates. Primary limitations relate to this being a pilot trial, including small sample size and relatively short follow-up. As a pilot study, we were not powered to detect differences in viral load – an exploratory outcome. Furthermore, our urinalysis assessment of substance use included detection of alcohol use in the past three days; based on the alcohol use severity in this population and *Khanya*'s focus on reduction of use and harms rather than abstinence, we also had limited power to detect changes in urine-verified abstinence. Finally, although real-time electronic adherence monitoring is a strength, it has its limitations; Wisepill can act as an intervention in itself, and non-use of Wisepill may be conflated with ART non-adherence – although we limited our assessment to three months to minimize potential non-use over time [29]. Despite these limitations, this pilot study contributes new knowledge about incorporating peers as AOD interventionists within HIV care in SA. As SA Department of Health refines its strategy for integration of behavioral health services into primary care, findings may have important implications for the feasibility and acceptability of incorporating peers into task-shared services for improving ART adherence among PLWH with AOD.

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COMPETING INTERESTS

Dr. Safren receives royalties from Oxford University Press, Guilford Publications, and Springer/Humana Press for books related to cognitive behavioral therapy. All other authors declare no conflicts of interest.

AUTHORS' CONTRIBUTIONS

JFM conceptualized the idea and secured funding for the project with JAJ, BM and SAS. JM led all aspects of the study and wrote the first draft of the manuscript. JAJ, BM, COC and SAS provided guidance throughout the study and provided a critical review and edits of the manuscript. JMB conducted the analyses, oversaw data management and provided edits to the manuscript. LSA provided oversight of study operations, contributed to idea conceptualization and provided a critical review of the manuscript. KSR developed the protocol with JFM and SM and led all aspects of study start up, operations, data oversight and regulatory compliance, along with SM, and contributed to manuscript writing. ALR oversaw study operations, procedures for biomarker specimen testing and analysis along with SM, and contributed to manuscript writing. All authors approve of the final manuscript to be submitted for publication.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Model-implied Wisepill adherence at baseline and post-treatment (three-months) for ETAU and Khanya intervention groups

Figure S2. Model-implied alcohol use quantity at baseline, post-treatment, and follow-up time points for ETAU and intervention groups among the subsample who used both drugs and alcohol (n = 21)

Table S1. Linear model predicting wisepill adherence

Table S2. Linear model predicting continuous PEth and categorical model predicting dichotomous urine

Table S3. Cumulative logit model predicting moderate and high risk categories of WHO-ASSIST

Table S4. Count model predicting average number of drinks consumed on days drinking on the timeline followback

Table S5. Linear model predicting percentage days used any substance on the timeline followback

Table S6. Categorical model predicting binary viral load suppression

AUTHOR INDEX

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