EDITORIAL REVIEW

Mental health and HIV/AIDS: the need for an integrated response

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Tremendous biomedical advancements in HIV prevention and treatment have led to aspirational efforts to end the HIV epidemic. However, this goal will not be achieved without addressing the significant mental health and substance use problems among people living with HIV (PLWH) and people vulnerable to acquiring HIV. These problems exacerbate the many social and economic barriers to accessing adequate and sustained healthcare, and are among the most challenging barriers to achieving the end of the HIV epidemic. Rates of mental health problems are higher among both people vulnerable to acquiring HIV and PLWH, compared with the general population. Mental health impairments increase risk for HIV acquisition and for negative health outcomes among PLWH at each step in the HIV care continuum. We have the necessary screening tools and efficacious treatments to treat mental health problems among people living with and at risk for HIV. However, we need to prioritize mental health treatment with appropriate resources to address the current mental health screening and treatment gaps. Integration of mental health screening and care into all HIV testing and treatment settings would not only strengthen HIV prevention and care outcomes, but it would additionally improve global access to mental healthcare.

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Introduction

Tremendous advances have been made in HIV prevention and treatment since the discovery of the virus that causes AIDS. Today, most people newly diagnosed with HIV can expect a near normal lifespan with steady access and adherence to combination antiretroviral therapy (cART). Moreover, in recent years there is great optimism about the potential to end the HIV epidemic – or at least substantially 'bend the curve' of the epidemic – with current biological and behavioral tools. Preexposure prophylaxis (PrEP) is highly effective at protecting individuals from acquiring HIV when taken consistently [1]. Further, people living with HIV (PLWH) who maintain durable viral suppression do not transmit the virus to sexual partners, and in the case of pregnant women, to infants via pregnancy and delivery [2–4].

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Given these advances, many jurisdictions are making concerted efforts to turn the tide of the epidemic through PrEP scale-up for individuals vulnerable to acquiring HIV, and improved HIV diagnoses and rapid provision of cART for PLWH. The Joint United Nations Programme on HIV/AIDS (UNAIDS) goals of '90–90–90' call for 90% of PLWH to be diagnosed, with 90% of them initiating cART, and 90% of people initiating cART to achieve and sustain viral suppression through adherence to the treatment [5]. Some localities are moving toward even more ambitious goals of '95–95–95' and ultimately 'getting to zero' new HIV infections [6]. Although these goals are aspirational, many believe they are achievable with focused resources and concerted efforts.

However, these gains will not be achieved without addressing the significant mental and substance use problems among people vulnerable to acquiring or living with HIV, which exacerbate the many social and economic barriers to accessing adequate and sustained healthcare [7–12], and are among the most significant barriers to achieving the 90–90–90 targets [7–12]. We posit that it will be impossible to significantly 'bend the curve' and approximate an ending of the HIV epidemic without dramatically altering our approach to diagnosing and addressing comorbid mental health (including substance-use) problems among people most vulnerable to HIV.

Global burden of mental and substance use problems

In the general population, mental and substance use disorders are the number one contributors to number of years lived with disability, with greater impact than other communicable, maternal, neonatal, nutritional, and noncommunicable diseases, including HIV, and injuries [13]. Excess mortality among persons with mental, neurological, and substance use disorders is evident, with a shortened life span of approximately 15–20 years. The global burden of these disorders rises in late adolescence and peaks in young adulthood, which emulates the global HIV burden.

Mental health and HIV acquisition

Mental health disorders play a critical role in HIV acquisition across populations, increasing the risk of HIV acquisition by 4–10-fold [14,15]. In the United States, the prevalence of HIV is substantially higher among adults with serious mental illness (SMI; e.g. psychotic disorder, bipolar disorder, recurrent major depressive disorder, comorbid mood, and substance use disorder) – ranging from 2 to 6% – compared with the general population (0.5%) [16–18]. In Africa, where the HIV burden is even greater, the prevalence of HIV among adults with SMI ranges from 11 to 27% [19–22].

Mental health problems can increase risk of HIV acquisition through both direct and indirect pathways. Although people with SMI tend to be less sexually active compared with the general population, sexually active adolescents and adults with SMI evidence higher risk sexual behavior, including inconsistent condom use, having multiple sexual partners, trading sex, and drinking alcohol before sex [23–29]. The risk of HIV infection may also increase with severity of psychiatric illness. In a multisite study in the United States, the prevalence of HIV among persons with SMI rose from 3.9% in community mental health centers, to 5.1% in intensive outpatient case management programs, to 5.9% in psychiatric inpatient units [16]. HIV risk may be further compounded when there are multiple co-occurring conditions, such as a mood disorder, substance use disorder, and posttraumatic stress symptomatology from (for example) physical, sexual, or emotional abuse. A large multisite study of US MSM found a significant positive dose-response relationship between the number of co-occurring conditions and risk of HIV acquisition: men with four to five co-occurring conditions had more than eight times the hazard of HIV infection compared with those with no such conditions [30]. Mental health problems can also interfere with efforts to prevent HIV infection, including regular HIV testing and adherence to PrEP [31–33]. In the iPrEx and iPrEx-OLE trials, which studied PrEP efficacy and open-label use among MSM and transgender women, participants with higher depression scores had lower levels detectable PrEP medication (emtricitabine and tenofovir disoproxil fumarate) and higher levels of condomless receptive anal intercourse [34,35]. Screening and treatment for mental health problems and disorders will be essential to preventing vulnerable populations from acquiring HIV.

Prevalence of mental health disorders among people living with HIV

Many studies have shown that PLWH experience higher rates of mental health disorders than the general population. This includes research conducted with diverse groups of PLWH such as youth with perinatal or behaviorally acquired HIV, adult MSM of color, racial and ethnic minority women, people who inject drugs (PWID), and older adults [36–42]. In a US multisite study with over 2800 PLWH, 36% had major depression and 15.8% had generalized anxiety disorder [36], compared with only 6.7 and 2.1%, respectively, in the general population [43]. Other studies from North America have shown similarly higher rates of mental

health disorders among PLWH. PLWH presenting at an academic medical center in the Southeastern US showed high levels of mood disorder in the past year (32%) and past month (21%), as well as anxiety disorder in the past year (21%) and the past month (17%) [44]. In Ontario, Canada, available electronic medical records indicated that 41% of PLWH had a mental health condition compared with 22% among non-HIV infected adults [38]. A study by Blank *et al.*, conducted HIV tests with over 1000 people who were seeking mental healthcare at university-based psychiatric inpatient units, intensive case-management programs, and community mental health centers. They found that 4.8% had confirmed positive HIV tests – much higher than the HIV prevalence rate in the general US population [16]. Data from across the globe also indicates elevated rates of mental health disorders among PLWH compared with the general population. For example, a study among PLWH in India showed that 59% had signs of major depression [45]. In China, a recent review found prevalence of depressive symptoms in 61% of PLWH [46]. In Uganda, major depression was found in 14% of 1099 cART-naïve PLWH [47]. In South Africa, 26–38% of PLWH are estimated to have a mental disorder compared with 13% in the general population [48]. Although major depression is one of the most commonly seen mental health disorders in PLWH, rates of posttraumatic stress disorder (PTSD) are also much higher among PLWH than in the general population, ranging from 10 to 74% [49–52] compared with only 8% in the US general population [49–53]. Prevalence of substance use disorders also tend to be higher among PLWH than in the general population ranging from 21 to 71% [44,54], as do rates of neurocognitive impairment – about 50% of PLWH, even those who are virally suppressed [55].

Intersecting vulnerabilities

Many factors contribute to the high comorbidity of HIV and mental health conditions. People who have (or are at risk for) HIV and who are vulnerable to mental health conditions often face other significant individual, structural, social, and biological challenges to accessing and adhering to HIV prevention and treatment modalities. These factors fall into the domains of sociodemographics, neighborhood and local environmental factors, social structures, individual biology, and intersecting societal stigmas. Structural factors, including poverty, low education, unstable housing, and food insecurity, contribute to increased vulnerability to HIV infection and poor HIV health outcomes [56,57]. Neighborhood and environmental factors, including violence and lack of safety, lack of adequate safe and steady water supply, wars, and natural disasters, cause psychological trauma, disrupt the delivery of medical supplies, and present barriers to healthcare access [58–60]. Biological factors, including comorbid communicable diseases (e.g. tuberculosis, hepatitis) and noncommunicable diseases (e.g. diabetes, heart, and bone disease), as well as chronic immune activation, contribute to poorer physical and mental health outcomes [61,62]. Intersecting social stigmas, and criminalization in some contexts (e.g. sex work, drug use, and same-gender sex) present additional challenges to key populations that are highly affected by HIV, including MSM, transgender women, sex-workers, people who use drugs (including PWID), and racial and ethnic minorities. These groups experience perceived and internalized stigma as well as enacted stigma (e.g. discrimination) that negatively affect mental health, and this relationship is further compounded by the unfortunate stigma of mental illness in society and among patients and providers [63–65].

Mental health impairment and outcomes along the HIV care cascade

There is substantial evidence that impairment in mental health leads to negative health outcomes at each step in the HIV care continuum, starting with being diagnosed with HIV, all the way to achieving viral suppression. Lack of HIV diagnosis jeopardizes the health of PLWH by impeding access to the significant health benefits that cART confers. Lack of HIV diagnosis presents a further public health challenge because a substantive proportion of new HIV infections are attributable to persons who are not aware of their HIV status [66–72]. Mental health impairment that results from having a mental health disorder (e.g. major depression, alcohol or other substance use abuse or dependence) or significant levels of psychiatric distress (e.g. elevated depressive, anxiety, or PTSD symptoms) can interfere with regular HIV testing and learning one's HIV status, as well as successfully linking to HIV healthcare, staying in care, initiating cART, and remaining adherent to cART to achieve HIV viral suppression [66–72].

Mental disorders can present a substantial barrier to adequate engagement and retention in HIV primary care. Research has established links between the presence of psychiatric illness and poor rates of HIV care linkage and retention. In one Alabama study, missed HIV primary care visits during the first year of care were more common among patients who had substance abuse disorders, as well as those who were younger, female, black, and lacking private health insurance [73]. A large cohort study of PWIDs found that only 30.5% were continuously retained in HIV care over nearly 9 years of follow-up, and that active drug use was associated with lower care retention [74]. The preponderance of research therefore indicates that substance use disorders represent a frequent impediment to timely HIV care linkage as well as sustained retention in care [75].

The aspect of the HIV care continuum which has been most studied in relationship to mental health is cART adherence. Research has clearly identified depression as one of the strongest predictors of poor cART medication adherence [68]. A large meta-analysis found a significant association between depression and cART nonadherence across 95 independent samples [68], and determined that the likelihood of achieving good (80%) cART adherence was 42% lower among those with depressive symptoms than those without depressive symptoms across 111 independent samples. This robust finding was consistent across low, middle, and high-income countries [72]. Another large review and meta-analysis that synthesized 125 studies with a total of 19 016 patients across 38 countries found that self-reported depression and alcohol and other substance misuse were among the top 15 barriers to adherence, along with other reasons such as forgetting, being busy, a change in routine, and the experience of medication side effects [76]. In perinatally infected youth, for whom nonadherence to treatment across health conditions is a significant issue [77], a range of psychiatric disorders, not just mood disorders, have been associated with nonadherence to HIV treatment and elevated viremia [78].

Mental health impairment clearly contributes to poorer healthcare behaviors across the HIV care continuum, leading to negative HIV health outcomes (i.e. elevated viral load, decreased $CD4^+$ levels, and increased opportunistic illnesses). There is also evidence, however, that suggests a direct biological pathway from mental health impairment to poorer HIV health outcomes, especially in the context of depression.

Depression, HIV, and the immune system

There is evidence suggesting a bi-directional relationship between depression and the immune system [79–81]. Depression is known to negatively affect the immune system (e.g. $CD4^+$ cell decline) although the underlying mechanisms remain poorly understood. Chronic immune activation and hypothalamic–pituitary–adrenal axis dysregulation [82,83], which HIV infection can exacerbate [84–86], are established factors contributing to developing depression and likely contribute to high rates of depression among PLWH [62]. HIV crosses the blood brain barrier causing immune activation in the brain and the central nervous system [87]. Inflammatory proteins (e.g. C-reactive protein, cytokines) lead to oxidative stress and neuronal injury [88], specifically, the chronic inflammatory response to HIV infection leads to elevated cytokine levels, including IL-6 and TNF-α, which can trigger a chain reaction involving Tryptophan depletion through the activation of Indoleamine 2,3-dioxygenase enzyme [82,89,90]. Tryptophan depletion leads to reduced serotonin levels and increased Kynurenine and its metabolites, which are neurotoxic and associated with depression, suicide, anxiety, and physical health conditions, such as cancer, cardiovascular diseases and premature death [91–94]. Therefore, it is possible that chronic inflammation and tryptophan depletion contribute to the deleterious effects of depression on physical health outcomes.

Depression and mortality in the HIV context

Depression has been shown to increase the risk of mortality among PLWH [41,95]. For example, among 1487 women followed for 24 months in Tanzania, mortality was 6.6% among women with depressive symptoms versus 3.7% among women without depressive symptoms [66]. And among 765 HIV+ women at four US sites followed for up to 7 years, women with chronic depressive symptoms were twice as likely to die as women with limited or no depressive symptoms, even after adjusting for predictors of mortality (i.e., $CD4^+$ cell count, cART duration, age) [41]. In the Women's Interagency HIV Study prospective cohort ($N = 848$), chronic depressive symptoms were associated with over three times the hazard of mortality, among women on cART, and over seven times the hazard of mortality, among women not on cART, compared with women on cART with no depression [96]. Examining medical records of close to 6000 ($N = 5927$) PLWH, a dose–response relationship was found between depression length and HIV outcomes. For every 25% increase in days experiencing depression, there was a 19% increase in the risk of mortality [95].

Screening and treatment for mental health problems

Given the strong evidence for the contribution of mental health and behavioral problems to poor HIV health outcomes, there is an obvious need for universal mental health screening and the provision of mental health treatment integrated into ongoing HIV care. There is a wide array of mental health screening tools that are being used in clinical care as well as in research, and they have been validated across many regions of the world, including in low-income and middle-income countries [97]. Screening for mental and behavioral problems is insufficient and arguably unethical to conduct, if follow-up treatment is not made available for those who screen positive and are in need. To advance the provision of mental healthcare, there exists a wide-range of effective mental health treatments including psychopharmacological treatment, and various psychotherapies

(e.g. psychodynamic, cognitive-behavioral therapy, motivational enhancing therapy, and interpersonal therapy), stress reduction and mindfulness treatments, and harm reduction and abstinence treatments. Many of these approaches have been manualized and tailored across languages and cultures [51,98–101].

The broader challenge is that most people (70–85%) with mental disorders, across all country settings, do not receive the needed mental healthcare, in part because they are not even identified as having a mental health disorder [102–107]. Many factors contribute to this gap in mental health screening and provision of treatment, including human resource shortages, fragmented service delivery models, and lack of capacity for implementation and policy change. A central challenge is the stigma of mental illness that exists at all levels: patients, healthcare workers, and policy makers. According to the WHO, worldwide mental health budgets are significantly underfunded, with expenditure on mental healthcare being approximately one percentage of total expenditure on all of healthcare [108,109]. Further, looking at the availability of mental health professionals for the population, there are significant disparities between low-income and middle-income countries and high-income countries, with inadequacy across all settings. This is particularly true in low-income countries, where there is a dramatic paucity of providers, such as one psychiatrist/psychologist per 1.5 million people in South Africa, and 12 psychiatrists/16 psychologists per 13 million people in Zimbabwe [108,110,111].

Mental and behavioral health treatments for people living with HIV

Large systematic reviews and meta-analyses demonstrate that PLWH can benefit from a broad range of mental and behavioral health interventions [98–100]. Mental health research conducted with PLWH in low-income, middle-income, or high-income countries has tested pharmacological interventions and various psychological and psychosocial interventions (e.g. cognitive behavioral therapy, interpersonal therapy, group therapy, motivational interviewing, stress management, meditation, and psycho-educational family interventions). The duration of the tested interventions varies considerably, ranging from 1 to 30 hours, 1 to 54 weeks, and 1 to 48 sessions. The research syntheses report small to moderate positive effects of these interventions on mental health among PLWH, with demonstrated reductions in depression and anxiety, and improved quality of life and psychological well being. Some of the largest and most consistently positive effects have been seen among interventions delivered by mental healthcare professionals over lengthier intervals, and which primarily focus on mental health. Psychological interventions with cognitive-behavioral components were consistently effective. Psychotropic and HIV-specific health psychology interventions were generally effective, with some mixed findings. Within low-income and middle-income countries, multilevel interventions that were integrated into community-based healthcare and which included family interactions or peer support were among the most effective.

Although the evidence base for mental health interventions among PLWH is encouraging, several limitations are also evident. The preponderance of research on mental health interventions for PLWH has been conducted in high-income countries (and particularly in the United States) rather than low-income and middle-income countries, which is a mismatch to the global burden of HIV [98–100]. This gap could be addressed by drawing upon lessons learned from the large evidence base for delivering mental health interventions with fidelity and effectiveness in general populations using nonskilled personnel (i.e. task-sharing or task-shifting) in low-income and middle-income countries [112]. Mental health intervention trials with PLWH have also generally focused on short-term over long-term outcomes [98,99], and the research could benefit from improved quality and rigor [100]. There is also a paucity of studies that examine mental health interventions in relationship to HIV care outcomes, relative to studies that focus on mental health outcomes alone. Finally, few evidence-based mental health interventions have been tested with youth. One exception is the CHAMP+ program, based on the Collaborative HIV/AIDS Mental health Program [113], a family-based intervention originally developed in the United States to prevent HIV risk behaviors and promote mental health in vulnerable communities of adolescents, and that has been successfully adapted for South Africa [114] as well as Asia [115–117]. However, given the staggering numbers of children and adolescents with HIV globally [118,119], particularly in sub-Saharan Africa, there is a substantive need for development of more evidence-based mental health interventions focused on this particularly challenging developmental stage [40,120].

Scale-up of interventions: challenges and solutions

There are substantial challenges to the provision and scale-up of mental health screening and treatment for those in need, particularly within resource-constrained settings where HIV is endemic and the availability of mental health professionals and services is rare. The following four models offer promising approaches to efficient and effective mental healthcare delivery in resource-constrained settings: task shifting, stepped care, trans-diagnostic approaches, and technology.

Task shifting is a method of strengthening and expanding the health workforce by shifting responsibilities from highly qualified health workers to health workers with less training and fewer qualifications [121]. In the context of mental health screening and treatment, this represents a shift from mental health professionals to healthcare workers who lack formalized training in mental health. There are a few examples of this occurring with some success in HIV care settings. For example, a cluster randomized controlled trial conducted at ten clinics in Uganda studied two task-shifting approaches to integrating depression treatment into HIV care: delivery of depression screening and treatment by trained nurses using a structured protocol, or by trained primary care providers (PCP) using their own 'clinical acumen' rather than a structured protocol [122]. Successful screening occurred in 76% (nurses) and 80% (PCP) of cases, with clinically depressed patients being prescribed antidepressants in 69% (nurses) and 56% (PCP) of cases, and with treated patients achieving full remission of their depression being 65% (nurses) and 69% (PCP). The authors concluded that existing clinic staff (nurses, doctors) can provide quality depression care with limited training and supervision by available mental health specialists.

Stepped care approaches find efficiency by triaging intervention intensity based upon observed need [123]. Patients who do not benefit from initial, lower intensity interventions graduate to higher intensity or more resource-intensive interventions. Stepped care approaches have been used by several HIV-related mental health projects in sub-Saharan Africa. For example, a project in Zimbabwe piloted a stepped-care and task-shifted intervention for HIV patients with depression and low antiretroviral adherence [124]. Lay community health workers were trained to deliver a first-level intervention to patients (six sessions of problem-solving cognitive behavioral therapy for depression and medication adherence). Patients who did not benefit from the first-level intervention were triaged to more intensive treatment (an assessment by a trained clinician for potential provision of antidepressants and/or further counseling). A small pilot trial found reduced depression and improved viral load suppression among intervention recipients compared with enhanced standard care [124].

Transdiagnostic approaches represent another route to advance delivery of HIV-related mental healthcare in resource-constrained settings. Transdiagnostic approaches recognize that different mental disorders (e.g. depression, anxiety) frequently co-occur and may share-related symptomatology, so uniform treatment strategies might be employed to effectively address multiple mental health problems [125]. Applications of transdiagnostic approaches to HIV include cognitive-behavioral counseling to concurrently address depression, anxiety, and HIV risk related to minority stress among young gay and bisexual men in the United States [126]. Outside of HIV, randomized trials found that a transdiagnostic psychotherapy toolkit delivered by lay counselors successfully treated symptomatology from multiple trauma-related disorders among Burmese refugees [127] as well as survivors of violence in Iraq [128].

Finally, technology-based approaches like telephone-delivered and computer-delivered interventions can help scale mental healthcare and support lay-counselor interventions with PLWH who are in need [129,130]. Internet-based mental health interventions, such as internet-based cognitive behavioral therapies [131] are growing in popularity globally to improve access in low resource contexts, as well as among youth and young adults who are at high risk for nonadherence or nonaccess of mental health resources [132].

Community and public health messaging to reduce HIV-related psychological distress

Since the stigma of HIV can lead to significant psychological distress, community and public health campaigns to reduce stigma may have a substantive mental health effect. Improved access to and understanding of HIV treatment and prevention could particularly reduce HIV stigma and benefit mental health. Findings from the HPTN 052 trial and PARTNER studies have definitively demonstrated that HIV treatment is prevention [3,4]. Community advocates have built on this science by advancing a messaging campaign regarding 'U = U' (undetectable = untransmittable), which states that PLWH with sustained HIV viral suppression cannot transmit HIV through sex [133,134]. The campaign holds that the optimistic messaging of U = U will build hope in the community and contribute to a lessening of HIV-related stigma, which in turn can reduce psychological distress among PLWH and their sex partners. Community advocates and anecdotal reports indicate that the U = U message helps many PLWH feel unburdened by the shame and stigma that accompanies HIV infection [133]. There is a need for systematic research on patient understanding of U = U and its potential benefits for mental health and well being among PLWH.

Increased availability and use of effective HIV primary prevention tools could importantly benefit mental health, as well. The high efficacy of PrEP in nearly eliminating the risk of HIV acquisition among HIV-negative individuals adhering to PrEP has been shown to significantly reduce symptoms of anxiety and depression among young people vulnerable to acquiring HIV [135–137]. There is also emerging evidence that engagement in PrEP care can simultaneously promote greater engagement in screening and treatment for mental and behavioral health challenges, as well as screening and treatment for other health conditions, such as diabetes,

hypertension, and tobacco use [138]. With this understanding, expanded PrEP care delivery and use could benefit both HIV prevention and mental health.

Conclusion

Our review has identified the following understandings about the intersection of mental health and HIV/AIDS:

(1) Mental health problems (ranging from distress to SMI) are elevated among people at-risk for HIV and those living with HIV. This risk is true across populations most affected by the epidemic in different regions of the world.
(2) Mental health problems contribute to HIV acquisition and poor outcomes along the HIV treatment continuum.
(3) HIV and the resulting chronic immune activation increase the risk to develop mental health problems.
(4) We have the necessary assessment (screening) tools and efficacious treatments to treat mental health problems among people living with and at risk for HIV. However, we need to prioritize mental health treatment, especially mental health treatment integrated into HIV care, with appropriate resources to address the current screening and treatment gap.
(5) Promising advances have been made integrating mental healthcare into HIV primary care (via task-shifting, stepped-care interventions, and other strategies).
(6) Some community and public health driven campaigns regarding HIV treatment and prevention may help reduce stigma and psychological distress.

Despite the significant challenges that mental health presents to HIV prevention and treatment, there are many important and unmet opportunities to integrate mental healthcare with HIV care. Initiatives like PEPFAR have helped countries around the world dramatically expand HIV care, and the concomitant strengthening of their healthcare systems has offered substantial benefits to wider healthcare delivery. Further integration of mental health screening and care into this infrastructure would not only strengthen HIV prevention and care outcomes, but it would additionally improve global access to mental healthcare. Seizing these opportunities will be crucial if we are to further 'bend the curve' of the HIV epidemic and eventually find an end to AIDS. On a very fundamental and basic level, there can be no health, without mental health.

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Conflicts of interest

There are no conflicts of interest.

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