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# Roll-out of HIV pre-exposure prophylaxis: a gateway to mental health promotion

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## ABSTRACT

HIV remains a pressing global health problem, with 1.5 million new infections reported globally in 2020. HIV pre-exposure prophylaxis (PrEP) can lower the likelihood of HIV acquisition among populations at elevated risk, yet its global roll-out has been discouragingly slow. Psychosocial factors, such as co-occurring mental illness and substance use, are highly prevalent among populations likely to benefit from PrEP, and have been shown to undermine persistence and adherence. In this analysis, we review the high burden of mental health problems among PrEP candidates and contend that inattention to mental health stands to undermine efforts to implement PrEP on a global scale. We conclude that integration of mental health screening and treatment within PrEP scale-up efforts represents an important strategy for maximising PrEP effectiveness while addressing the high burden of mental illness among at-risk populations. As implementers seek to integrate mental health services within PrEP services, efforts to keep access to PrEP as low-threshold as possible should be maintained. Moreover, programmes should seek to implement mental health interventions that are sensitive to local resource constraints and seek to reduce intersecting stigmas associated with HIV and mental illness.

## INTRODUCTION

HIV remains a significant global health problem. In 2020, an estimated 680 000 individuals died from HIV-related causes globally, while there were 1.5 million new infections.<sup>1</sup> Although HIV-related mortality has declined nearly 50% over the past decade, declines in new infections have been sluggish, particularly among key populations at elevated risk of infection (eg, men who have sex with men, transgender people, people who inject drugs and adolescent girls and young women).<sup>1</sup> To address the high burden of new infections among these populations, there exists a pressing need to rapidly expand access to high-quality HIV prevention programming.

The introduction of oral pre-exposure prophylaxis (PrEP) was a watershed moment

## Summary box

- ▶ HIV remains a global health problem, with millions of new infections each year. Pre-exposure prophylaxis (PrEP) can substantially reduce the risk of HIV infection; however, its scale up has been slower than hoped, reaching only a fraction of individuals likely to benefit from its use.
- ▶ Psychosocial factors, such as co-occurring mental illness and substance use, are highly prevalent among candidates for PrEP, with some studies reporting prevalence of mental illness as high as 20%.
- ▶ Findings from both qualitative and quantitative studies implicate poor mental health as a barrier to PrEP uptake and persistence, suggesting a need to address mental health as part of PrEP implementation.
- ▶ Integration of mental health screening and treatment within PrEP scale-up efforts represents an important strategy for maximising PrEP effectiveness while addressing the high burden of mental illness among at-risk populations. The feasibility of this strategy is supported by studies from both high-income and low-income and middle-income countries showing the potential population health benefits of integrating primary care services within existing HIV prevention and treatment programmes.

in the history of HIV prevention. When taken on a daily or on-demand basis, PrEP use can substantially lower the likelihood of HIV acquisition.<sup>2-3</sup> Yet despite PrEP's immense promise, its global scale up has been slow.<sup>4</sup> Like HIV treatment, high-quality PrEP services can be conceptualised according to a 'cascade' of necessary, sequential steps, extending from PrEP awareness and initiation through to PrEP adherence and retention.<sup>5</sup> Persistence (ie, ongoing use) and adequate adherence to recommended dosing in the setting of HIV risk are key components of the PrEP cascade that, if not effectively promoted and supported, have the potential to undermine PrEP's effectiveness.<sup>6</sup> To be maximally protective, PrEP use must consistently coincide with potential HIV exposure

events (ie, prevention-effective adherence),<sup>7</sup> but data suggest that PrEP discontinuation is common, with many individuals discontinuing PrEP within the first 6 months of initiation.<sup>8</sup> Although discontinuation of PrEP in the absence of anticipated HIV exposure may be ‘strategic, effective and efficient,’<sup>7</sup> people who discontinue PrEP in the setting of ongoing exposure events and inconsistent or absent condom use during sexual intercourse may be at risk for HIV acquisition.<sup>9</sup>

Psychosocial factors are a central concern in PrEP discontinuation. Empirical data about predictors of PrEP persistence are scant, but a recent qualitative study of people recruited through San Francisco safety-net clinics who acquired HIV despite initiating PrEP implicated substance use and poor mental health as contributors to discontinuation.<sup>10</sup> Mental disorders have long been shown to amplify the risk of HIV acquisition among men who have sex with men through diminished self-efficacy, increased compulsivity, and reduced engagement in HIV preventive behaviours.<sup>11 12</sup> High rates of mental disorders have also been reported among other at-risk populations, including adolescent girls and young women in sub-Saharan Africa.<sup>13</sup> Unfortunately, screening and treatment rates for these disorders remain low, particularly in low-income and middle-income countries (LMICs) with high burdens of HIV. Given the mutually causal link between mental disorders and HIV risk, an approach to PrEP scale up that focuses solely on HIV risk reduction without consideration of individuals’ mental health and psychosocial needs is untenable.<sup>4</sup>

In this analysis, we describe the burden of mental disorders among populations that are likely to benefit from PrEP. We review findings showing that mental disorders may undermine long-term persistence with PrEP and therefore warrant the attention of researchers and implementers seeking to maximise the effectiveness of PrEP at the population level. We conclude that the ambitious scale up of PrEP offers an opportunity to undertake concurrent scale up of screening and treatment for mental disorders, both as a strategy to improve PrEP effectiveness and as a pathway to expand access to mental healthcare among populations at elevated risk of HIV acquisition.

## MENTAL DISORDERS AMONG PREP USERS: A THREAT TO EFFECTIVE IMPLEMENTATION

Mental disorders are highly prevalent among populations likely to benefit from PrEP. Prevalence data are most robust for sexual-minority and gender-minority populations in high-income settings, where population-based surveys have reported rates of depression, anxiety and other mental disorders that consistently exceed those in the general population by a factor of two.<sup>14</sup> Because many key populations are marginalised, reaching them has been a challenge for researchers in LMICs. Other populations, such as adolescent girls and young women, may not be resourced or empowered to engage in sexual

health.<sup>15</sup> Data from LMICs and among key populations such as sex workers are often not routinely collected, but available studies have demonstrated mental health disparities of an equivalent—if not greater—magnitude compared with those observed in high-income settings.<sup>16</sup> Studies of PrEP users, in particular, document high rates of mental disorders and poor mental health. [Table 1](#) presents studies identified as part of a scoping review of electronic databases (ie, EMBASE, PubMed, Web of Science, PsycINFO) to examine the prevalence of mental disorders among PrEP candidates.

The prevalence of mental disorders in these populations has been associated with differential exposure to numerous structural causes, including stigma,<sup>17</sup> racism<sup>18</sup> and interpersonal violence.<sup>19</sup> In particular, stigma is highly prevalent among these populations, and has been labelled a ‘fundamental cause’ of health inequalities.<sup>20</sup> Stigma is defined as ‘labelling, stereotyping, separation, status loss and discrimination in a context in which power is exercised,’<sup>20</sup> and may be associated with multiple, simultaneously held statuses and identities, including race, gender expression, sexual orientation and presumed HIV status. Stigma has been linked to mental disorders through increased social isolation, maladaptive coping, and stress.<sup>21–23</sup> Moreover, stigma frequently interacts with other structural causes, such as racism and interpersonal violence, to further worsen mental health. Although stigma remains a worthwhile target of public health intervention, attention to its downstream consequences, such as poor mental health, is also warranted.

Across all settings, mental disorders remain underdiagnosed and undertreated, contributing to significant morbidity.<sup>24</sup> Mental disorders have also been linked to poorer physical health, in part due to their association with self-harm, substance use disorders and disability, but also due to reduced care seeking and limited engagement in longitudinal care. While evidence of the association between mental disorders and physical health is strongest for chronic conditions that typically require intensive self-management such as diabetes, heart failure and HIV, emerging data suggest that mental disorders may also undermine PrEP persistence. For example, a study by Krakower *et al* of 663 people who initiated PrEP through a Boston community health centre specialising in healthcare for sexual and gender minorities found that those with a mental health diagnosis were 1.2 times more likely to discontinue PrEP compared with those without a mental health diagnosis.<sup>9</sup> The study also showed a compounding risk of discontinuation with increasing burden of mental illness, a concerning finding given the phenomenon of syndemic disease burden within some key populations.<sup>11 25–27</sup> A study of PrEP service users in Wales (UK) similarly found a 29% prevalence of mental health problems among people who were either poorly engaged in PrEP care or who were lost to follow-up.<sup>28</sup> Qualitative studies conducted in high-income countries<sup>29 30</sup> and low-income countries<sup>31</sup> have also implicated

**Table 1** Prevalence of mental disorders and poor mental health among people initiating PrEP

Publication	Location	Sample size	Population studied	Prevalence of mental disorders
Cochrane and Knapper <sup>28</sup>	Wales	n=176	Individuals commencing PrEP across a network of sexual and reproductive health clinics	Electronic health record documentation of 'mental health issues,' 24%
Doblecki-Lewis et al <sup>64</sup>	USA	n=554	Participants in a multicity PrEP demonstration project	Positive screen for depression (PHQ-2), 23.8%
Haberer et al <sup>65</sup>	Kenya and Uganda	n=985	HIV-negative partners in serodiscordant relationships as part of a PrEP demonstration project	Positive screen for depression (Hopkins Checklist>1.75), 10%
Krakower et al <sup>9</sup>	USA	n=663	Individuals prescribed PrEP at an urban community health centre	Electronic health record documentation of anxiety disorders, 37.3%; depressive disorders, 36.2%; attention-deficit/hyperactivity disorder, 16.0%; post-traumatic stress disorder, 5%; and bipolar disorder or schizophrenia, 3.6%
Rusie et al <sup>66</sup>	USA	n=3451	Individuals starting PrEP in an urban network of community health centres	One or more mental health conditions, 20.6%; >2 mental health conditions, 5.2%
Scott et al <sup>67</sup>	USA	n=348	Individuals initiating PrEP across primary care clinics in an urban municipal health network	Electronic medical record documentation of anxiety disorders, 9%; depressive disorders, 22%; post-traumatic stress disorder, 7%; and bipolar disorder or schizophrenia, 10%
Serota et al <sup>68</sup>	USA	n=131	A longitudinal cohort of young, black men who have sex with men in an urban area	Moderate to severe symptoms of anxiety (GAD-7), 22%; moderate to severe symptoms of depression (PHQ-8), 17%
Spinelli et al <sup>69</sup>	USA	n=364	Individuals prescribed PrEP across primary care clinics in an urban municipal health system	Electronic medical record documentation of anxiety or depressive disorder, 31%; and bipolar disorder or schizophrenia, 9%
van Epps et al <sup>70</sup>	USA	n=1086	Individuals initiating PrEP in the Veteran Health Affairs health system	Electronic medical record documentation of depression, 53.4%
Zucker et al <sup>71</sup>	USA	n=696	Individuals assessed for HIV prevention services in an urban hospital network	Mild to severe symptoms of depression (PHQ-9), 17.6%

GAD-7, 7-item Generalised Anxiety Disorder scale; PHQ-2, 2-item Patient Health Questionnaire; PHQ-8, 8-item Patient Health Questionnaire; PHQ-9, 9-item Patient Health Questionnaire; PrEP, pre-exposure prophylaxis.

substance use and mental health problems in PrEP non-adherence and/or discontinuation.

Despite the observed association between mental disorders and PrEP discontinuation, current studies are limited by the lack of consensus about how PrEP discontinuation is defined, the poorly understood reasons for why people discontinue PrEP, and whether discontinuation coincides with potential HIV exposure.<sup>32</sup> There are also few studies from LMICs, and few studies of mental health and PrEP engagement in certain populations such as at-risk cisgender women.<sup>33</sup> Despite these shortcomings, the high burden of mental disorders among first-time initiators of PrEP is cause for concern, and represents a potential roadblock in efforts to maximise PrEP's long-term effectiveness at the population level.

### PREP AS A GATEWAY TO ENGAGEMENT IN LONGITUDINAL HEALTHCARE AND COMMUNITY MENTAL HEALTH

International guidelines recommend that PrEP users attend clinical visits every 3 months to screen for HIV seroconversion, address barriers to prevention-effective adherence and provide ongoing sexual health services.<sup>8</sup> These guidelines have led some researchers to question whether quarterly visits are too burdensome for patients, and have spurred the development of alternative models.<sup>34</sup> These ongoing discussions notwithstanding, the movement of HIV prevention into the clinic presents a unique opportunity to embed PrEP within primary care, which could engage key populations in care for chronic health and mental health conditions.

PrEP may serve as a gateway to primary care and preventive services. In a cohort of PrEP-eligible individuals in the USA, investigators found that those subsequently prescribed PrEP were also more likely to receive preventive health screening, including influenza vaccination, tobacco screening, glucose testing and depression screening.<sup>35</sup> A similar phenomenon has been reported in LMIC settings,<sup>36</sup> where recent work from South Africa has documented a so-called 'antiretroviral therapy (ART) advantage.'<sup>37</sup> As part of this 'advantage,' this work has shown that individuals engaged in ART programmes are more likely to receive screening for hypertension and diabetes, and are also more likely to achieve adequate control of these conditions relative to others in the general population.<sup>37</sup>

Findings from these studies bolster a consensus that integrated care delivery is both feasible and necessary to support the health needs of populations affected by HIV across the life course.<sup>38</sup> Unfortunately, limited attention is being paid to mental disorders by implementers within these integration efforts, particularly in LMICs, where efforts to expand access to mental healthcare have focused primarily on small-scale efficacy and effectiveness studies rather than implementation strategies for population-wide scale up.<sup>39</sup> Moreover, with HIV in particular, efforts to integrate mental healthcare into primary care settings have largely occurred in the

context of treatment programmes, with little consideration of how prevention programmes—and HIV testing programmes—might benefit from these efforts.<sup>40</sup> Across all settings, the high burden of mental disorders in key populations—coupled with findings that PrEP initiation can spur engagement in primary healthcare—points to the high likelihood that offering routine screening and treatment for mental disorders as part of HIV prevention programming will yield benefits for both HIV prevention and mental health.

### PREP AND MENTAL HEALTHCARE: PROMISES OF BENEFIT

As the global scale up of PrEP continues, there is a growing appreciation of the many barriers that influence an individual's choice to initiate and remain engaged with PrEP. Although PrEP only reduces the risk of HIV acquisition, encounters with the health system for PrEP initiation offer an ideal opportunity to address a number of these other barriers, including undiagnosed or undertreated mental illness, that can undermine long-term engagement in HIV prevention behaviours. PrEP use may also be beneficial for emotional well-being through empowerment and reduced anxiety about contracting HIV,<sup>41</sup> further underscoring the potential benefits to be gained from addressing mental disorders and HIV prevention as part of an integrated approach to care delivery.

Although the goals of care integration are the same across contexts, what integration looks like in practice may vary, and will require programmes to implement models that can be embedded within the local health system. Possible models include incorporating screening for mental disorders within PrEP programming, situating HIV risk screening within mental healthcare, or embedding both PrEP and mental health screening within primary care.<sup>42</sup> Regardless of the model that is selected, we believe that any implementation effort should be driven by three principles that affirm the importance of patient choice and enable delivery of care that is sensitive to the context-specific barriers individuals may face in accessing PrEP.

1. Low-threshold care: While PrEP initiation is an opportunity for engagement in longitudinal care, access to PrEP should be as low-threshold as possible.<sup>43</sup> Screening and subsequent treatment for mental disorders at PrEP initiation may improve the long-term effectiveness of PrEP but should not be used as a condition for initiating PrEP. Ideally, screening for common mental disorders could occur during initial prescription, with periodic reassessment and an offer of treatment initiation or referral if clinically indicated. Collaborative care or stepped-care approaches may serve as useful models in this regard.<sup>44–46</sup> Instruments used to screen for common mental disorders have been validated across diverse contexts, take only minutes to administer, and can be readily adapted to populations with low levels of literacy.<sup>47</sup> Yet, each additional instrument poses a real burden in the workflow of a

healthcare worker. Wherever possible, efforts to minimise the burdens of PrEP care on patients, providers, and health systems should be pursued.<sup>48</sup> Ultrashort screening instruments are also available.<sup>49–51</sup> Finally, strategies such as mHealth solutions, provider-facing alerts and task sharing may be helpful in streamlining inclusion of mental health screening as part of this process.

2. Access to mental healthcare: Screening in the absence of effective treatment raises important ethical and logistical concerns.<sup>52</sup> Non-pharmacological approaches to mental health treatment—cognitive-behavioural therapy, mindfulness, stress management, peer counselling and motivational interviewing—have been studied among people living with HIV across multiple contexts.<sup>53</sup> These may be of particular importance in LMICs where there is limited access to pharmacotherapies, although due to chronic underfunding the capacity of many LMIC mental health systems to deliver non-pharmacological treatments is also limited.<sup>54</sup> However, questions of how these interventions ought to be delivered in the context of PrEP care remain largely unanswered, including which cadres of healthcare workers can participate in task sharing, how care might be escalated in patients with severe or worsening mental disorders, and whether medication management or abbreviated interventions might feasibly be completed as part of quarterly PrEP visits in primary care. Importantly, answers to these questions may vary according to geography, cultural context, regulatory context, target population, and other factors.<sup>55</sup> New PrEP agents will raise new questions about delivery.<sup>56</sup> Addressing these and related questions will be crucial to the success of integration efforts and would benefit from a rigorous implementation science approach that considers how evidence-based treatment interventions might be adapted to local contexts.<sup>57</sup>
3. Stigma reduction: Stigma is one of the most potent barriers to accessing PrEP,<sup>58</sup> mental healthcare<sup>59</sup> and substance use treatment<sup>60</sup> and may imperil integration efforts if not adequately addressed. Individuals with mental disorders and an indication for PrEP face multiple, potentially layered stigmas including those associated with HIV, mental illness and identification with marginalised groups such as sex workers and men who have sex with men.<sup>61</sup> These stigmas often reinforce one another, and can be abetted by healthcare settings that are unsupportive or unprepared to respond to individuals' unique care needs.<sup>62</sup> Evidence-based approaches for addressing health-related stigma in healthcare settings exist<sup>62–63</sup> but are often underused in practice. As integration of PrEP and mental healthcare is considered, stigma-reduction efforts will be crucial to ensuring that patients' encounters with the health system lead to long-term engagement rather than to further distancing from needed care.

## CONCLUSION

If successful, the global roll-out of PrEP has the potential to transform how millions of at-risk individuals achieve HIV prevention. To maximise PrEP's effectiveness, however, attention must be paid to the cascade of PrEP care beyond awareness, acceptability, and dispensing, in order to ensure that PrEP users experience adequate and persisting protection from HIV acquisition. As HIV prevention programmes seek to secure the engagement of key populations in the long term, integration of PrEP and mental healthcare offers an opportunity both to address the high burden of mental disorders in these populations and to maximise PrEP adherence and persistence. Implementation efforts must be low threshold, recognise differential access to mental healthcare, and emphasise stigma reduction. However, limitations will include overburdened human resources of healthcare; geographical, cultural and systems-related barriers to implementation; and unrecognised and unaddressed dimensions of stigma.

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