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The importance of assessing and addressing mental health barriers to PrEP use during pregnancy ...

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COMMENTARY

The importance of assessing and addressing mental health barriers to PrEP use during pregnancy and postpartum in sub-Saharan Africa: state of the science and research priorities

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Abstract

Introduction: Pregnant and postpartum women (PPW) in sub-Saharan Africa are at disproportionately high risk of HIV infection compared to non-pregnant women. When used consistently, pre-exposure prophylaxis (PrEP) can prevent HIV acquisition and transmission to the foetus or infant during these critical periods. Recent studies have demonstrated associations between mental health challenges (e.g. depression and traumatic stress associated with intimate partner violence) and decreased PrEP adherence and persistence, particularly among adolescents, younger women and women in the postpartum period. However, mental health is not currently a major focus of PrEP implementation research and programme planning for PPW.

Discussion: PrEP implementation programmes for PPW need to assess and address mental health barriers to consistent PrEP use to ensure effectiveness and sustainability in routine care. We highlight three key research priorities that will support PrEP adherence and persistence: (1) include mental health screening tools in PrEP implementation research with PPW, both to assess the feasibility of integrating these tools into routine antenatal and postpartum care and to ensure that limited resources are directed towards women whose symptoms may interfere most with PrEP use; (2) identify cross-cutting, transdiagnostic psychological mechanisms that affect consistent PrEP use during these periods and can realistically be targeted with intervention in resource-limited settings; and (3) develop/adapt and test interventions that target those underlying mechanisms, leveraging strategies from existing interventions that have successfully mitigated mental health barriers to antiretroviral therapy use among people with HIV.

Conclusions: For PPW, implementation of PrEP should be guided by a robust understanding of the unique psychological difficulties that may act as barriers to uptake, adherence and persistence (i.e. sustained adherence over time). We strongly encourage PrEP implementation research in PPW to incorporate validated mental health screening tools and ultimately treatment in routine antenatal and postnatal care, and we stress the potential public health benefits of identifying women who face mental health barriers to PrEP use.

Keywords: barriers; mental health; postpartum; pregnancy; PrEP; sub-Saharan

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1 | INTRODUCTION

Women remain at high risk of HIV acquisition and are the most affected by the global HIV epidemic. In sub-Saharan Africa (SSA), 59% of new adult infections occur among cisgender women [1]. This risk is compounded during pregnancy and postpartum, when the probability of HIV acquisition increases. In serodiscordant couples, women in late pregnancy and in the early postpartum period are three to four times more likely to acquire HIV per condomless sex act than women who are not pregnant [2].

Interaction of biological and behavioural factors exacerbates risk during these periods [2–7]. Couples may be more likely to engage in condomless vaginal and anal sex during pregnancy, as contraception may drive condom use [8–11], and men may seek out other sexual partners during extended periods of pregnancy- or breastfeeding-related abstinence, increasing the risk for HIV transmission when sexual activity with the pregnancy partner resumes [10]. Moreover, biological changes, such as high levels of oestrogen and progesterone, induce changes in the genital tract, increasing susceptibility to HIV and sexually transmitted infections (STI) infection [4, 12].

In areas of high HIV prevalence, cisgender women across the lifespan are at elevated HIV risk, unless they are in a mutually monogamous relationship with a known HIV-uninfected partner. Women who are not in relationships that fit this description are in an important target group for pre-exposure prophylaxis (PrEP), especially if they have the potential for pregnancy. In SSA, women do not always have full agency to use condoms and/or engage in other HIV prevention behaviours [13]; PrEP offers the ability to prevent HIV if sexual activity with a non-monogamous or serostatus unknown partner cannot be avoided.

Once daily oral tenofovir disoproxil fumarate co-formulated with emtricitabine as PrEP is safe when taken during pregnancy [14–20], recommended by the World Health Organization [21], and has extensive public health benefits. Prioritizing oral PrEP for women in the general population, as opposed to focusing PrEP rollout on women at highest risk (e.g. sex workers), could avert substantially more infections [22]. Models predict that PrEP use in pregnant and postpartum women (PPW) will reduce new HIV infections in South Africa alone by up to 7.2% by 2030 [23]. With global breastfeeding targets of 24 months and beyond [24–28], postnatal transmission is a growing percentage of all HIV transmission [2, 7, 29], accounting for 75% of all perinatal transmission in 2018, up from 40% in 2005 [30, 31]. Accordingly, strengthening the uptake of and adherence to effective prevention strategies like PrEP during the postpartum transition is of high importance.

2 | DISCUSSION

2.1 | PrEP uptake, adherence and persistence challenges during pregnancy and the postpartum period

When PrEP is offered to PPW in research studies, rates of uptake range but are relatively high. In two ongoing South Africa-based cohorts, one that enrolled participants in antenatal care (ANC) [32] and one that recruited women planning for pregnancy [20, 33], PrEP initiation rates were approximately 90% and 60%, respectively (though initiation rates appear to be lower in Kenya at 21.7% [34]). With the high utilization of ANC across SSA (78.9%) [35], these services are an opportune time to introduce PrEP and expand implementation.

PrEP adherence rates are low in African women of reproductive age. In a recent study, only one in five participants had high adherence (defined as tenofovir diphosphate concentrations [TFV-DP] $\geq$ 700 fmol/punch) over the first 6 months [36]. Importantly, differences in TFV-DP concentrations in vaginal versus rectal tissue [37, 38] suggest that women need to be *more* adherent to maintain the same level of protection as men who have sex with men [39]. This is especially true during late pregnancy when TFV-DP concentrations are one-third lower than in the postpartum period [40, 41], indicating that daily PrEP use is necessary for prevention-effective adherence during pregnancy [42, 43].

PrEP persistence, or sustained PrEP adherence over time, is crucial during pregnancy and the postpartum transition. Recent studies among PPW have reported persistence rates of 75% and 62% at 1 and 3 months post-initiation [32]. Rates in adolescent girls and younger women who become pregnant are likely lower; only a third of adolescents and younger women in Kenya who initiated PrEP continued use after 1 month [34, 44]. The likelihood of PrEP persistence is also demonstrably lower among postpartum women at 3-month post-initiation (aOR = 0.31; 95% CI = 0.16–0.61) [45]. Persistence can be especially difficult post-delivery, when the routine is disrupted and concealing PrEP use from partners is complicated by fears of perceived infidelity or promiscuousness (unlike during pregnancy, when pill-taking is expected) [46]. Noted barriers to PrEP adherence among pregnant and non-pregnant African women likely also have negative impacts on persistence through the postpartum transition. These barriers include structural factors, low familial or social support, anticipated HIV-related stigma, side effects, fears of negative health consequences for the infant and mental health challenges [46–58]. Relative to other barriers, mental health has received little attention and has high relevance for PPW.

Notably, new biomedical HIV prevention products, including long-acting injectables and the dapivirine ring, may benefit PPW with mental health barriers to oral PrEP use. Both injectable cabotegravir and the dapivirine ring appear to be safe for use during pregnancy [59, 60]. In addition to ensuring adequate representation of cisgender women and PPW in research on PrEP modalities that are in the pipeline and/or already in clinical trials [61], we must assess the degree to which the absence of daily dosing may mitigate or potentiate mental health-related adherence challenges. Though the focus of the discussion below is on oral PrEP, the mental health considerations that we highlight are likely relevant to other PrEP formulations.

2.2 | Mental health, pregnancy and consistent PrEP use

Many PPW in SSA face unique psychological and psychosocial challenges to PrEP adherence and persistence. Intimate partner violence (IPV), associated post-traumatic stress and depression are related to reduced PrEP adherence during this high-risk period [47–51]. Reported by up to 57% of pregnant women in SSA [62], IPV is a strong predictor of both post-traumatic stress and depression [63, 64]. Women who report IPV or depression have an increased risk of low PrEP adherence [47–51], and IPV-related stress contributes to adherence challenges [47]. In an analysis of depression symptom trajectories among young women initiating PrEP, 48.5% had persistent elevated depression symptoms; these women were more likely to report IPV and less likely to have detectable TFV-DP throughout follow-up than participants with mild or no depression symptoms [65]. Although only IPV, post-traumatic stress and depression have been linked to low PrEP adherence and persistence in the published literature, PPW with other mental health disorders and concerns—anxiety, suicidality and alcohol use disorder are common [66–68]—likely also face challenges to consistent PrEP use. PPW with approach-oriented coping skills, social support and high levels of resilience may be able to effectively navigate the complex barriers to PrEP adherence and persistence, but these relationships have not yet been assessed.

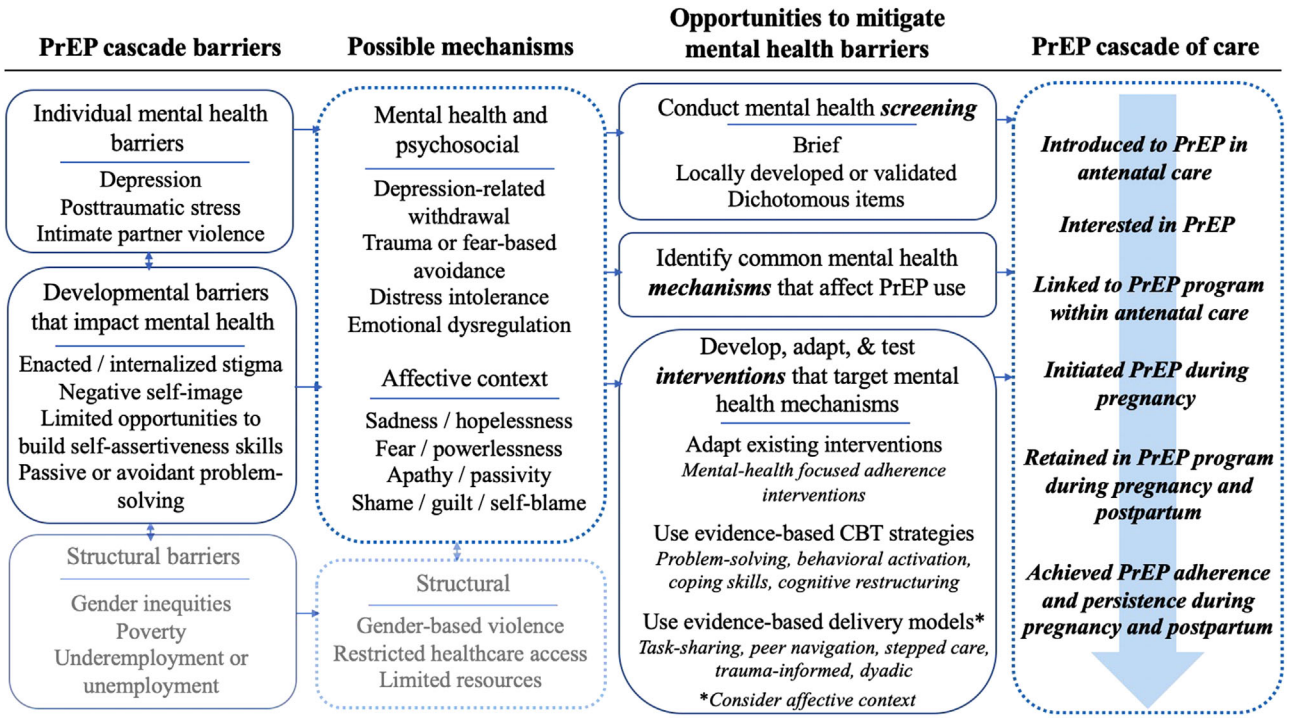

Figure 1. PrEP cascade of care in antenatal/postpartum care and opportunities to address mental health barriers to PrEP use.

Mental health barriers to PrEP adherence and persistence may be particularly important to address among adolescents and young adults (AYAs), who are more likely to have unplanned pregnancies than older women [69]. Unplanned pregnancies are common in SSA (29%) and can have severe consequences [70, 71], including depression and suicide, stigma, sexual/romantic relationship challenges, violence and abuse, and lack of emotional support [72]. Any one of these factors may significantly compromise consistent PrEP use. In AYAs, the relationship among poor mental health, early and unplanned pregnancy, and risk for HIV acquisition has been conceptualized as a "syndemic," or clustering of risk factors that together increase vulnerability to negative health outcomes above and beyond the effect of any one risk factor alone [73, 74]. With these intersecting challenges, it may be particularly difficult for AYAs with unplanned pregnancies to maintain PrEP adherence and persistence.

The integration of mental health screening and treatment into ANC has been a priority in SSA for at least a decade, with the understanding that addressing mental health in this context would ensure that gains in maternal and child health as well as the expansion of HIV services are maintained [75]. A multilevel approach to managing mental health concerns in antenatal and postpartum care is likely required [76]; this might include health promotion and primary/secondary prevention efforts in community and healthcare settings, identification and management of mental health concerns integrated into routine maternal and child healthcare by supervised non-specialist workers, and access to specialist mental health services if needed. As implementation research identifies the most efficient and effective strategies to achieve these goals, the importance of aligning mental health integration with HIV prevention cannot be understated.

2.3 | Research priorities and opportunities

To facilitate PrEP implementation for perinatal populations [77], we highlight three key research priorities for assessing and addressing mental health barriers to PrEP. Figure 1 presents these priorities as opportunities, documents individual mental health and associated developmental barriers (as well as structural barriers, which we do not address), offers relevant psychosocial mechanisms (with consideration for the affective context) and maps these categories onto the PrEP cascade for PPW.

2.3.1 | Include mental health screening tools in PrEP implementation research with PPW

Although screening guidelines for depression, for example, have been established for PPW in high-income countries [78, 79], there are limited evidence-based screening models for depression and other mental health disorders among PPW in SSA. Providers cite concerns about the acceptability and benefits of routine screening, the limitations of screening tools, the lack of access to follow-up services and the added cost of both screening and treatment [80–82]. Given these concerns, it is important to extend the assessment of perinatal mental health screening tools beyond diagnostic validity to include characteristics that streamline implementation and ensure sustainability (e.g. cultural appropriateness, acceptability, question structure and length). These characteristics can

be measured and compared across tools to facilitate informed screening choices that make the best use of limited resources.

Tools like the Edinburgh Postnatal Depression Scale [83] and the Patient Health Questionnaire-9 [84] have technically been validated among PPW across SSA [83, 85, 86], but they may not be feasible for routine care. Their length (9–10 items) and reliance on Likert-style scoring may cause confusion, negatively affect the accuracy of responses and compromise implementation by non-specialist health workers [87, 88]. These concerns have led to an increased focus on (1) ease of implementation [89], prioritizing brevity (e.g. four items) and binary response options [90, 91], and (2) high specificity [92] to minimize costs spent on "false positives" (i.e. PPW for whom mental health is not negatively impacting PrEP use). Locally developed and validated screening tools that meet these criteria will both identify women with psychological vulnerabilities for low adherence and persistence, allowing for limited resources to be directed to those who need them most, and facilitate the integration of screening into perinatal care. There are already several tools that fit this description but may need to be adjusted for ease of use. Both the 14-item Shona Symptom Questionnaire [93], developed to screen for depression and anxiety in Zimbabwe [94, 95], and the 16-item South African Depression Scale [96] could be shortened and tested among PPW, as can tools that have been developed for patients with low literacy levels [97]. As SSA continues to cope with the spread of COVID-19, with corresponding challenges to community mental health, advancing our understanding of mental health barriers to PrEP use via appropriate screening among PPW is particularly timely.

2.3.2 Identify cross-cutting, transdiagnostic psychological mechanisms that affect PrEP use and can realistically be targeted with intervention in resource-limited settings

There has been little to no attention paid to the specific ways in which underlying psychological mechanisms may impact PrEP use among PPW. Behavioural scientists should work to identify the mechanisms that are linked to low PrEP adherence. For example, from a behavioural perspective, both post-traumatic stress and depression are maintained by withdrawal and avoidance [98]. Individuals with post-traumatic stress avoid experiences that elicit painful memories [98], and individuals with depression withdraw from life activities due to unremitting sadness and loss of pleasure [99]. In both cases, avoidance and withdrawal interfere with proactive self-care behaviours [100], including taking PrEP.

Other mechanisms that may be driving the associations among depression, post-traumatic stress and low PrEP adherence include distress tolerance [101] and emotion regulation. PPW with low distress tolerance may not be able to manage the negative affect states (e.g. sadness and fear) that accompany depression or post-traumatic stress, and/or they may not be able to navigate the distressing, intersecting barriers associated with refilling their prescriptions and continuing to take PrEP time. Similarly, women who lack emotion regulation skills and are experiencing negative self-conscious emotions (e.g. shame and guilt) that are associated with post-traumatic stress and depression may also struggle to take PrEP.

2.3.3. Develop/adapt and test interventions that target those underlying mechanisms

Targeting multiple, cross-cutting psychological mechanisms—including withdrawal, avoidance, distress tolerance and emotion regulation [102–107]—in PrEP use interventions for PPW will streamline implementation. Transdiagnostic mental health interventions (e.g. the Unified Protocol [108], the Common Elements Treatment Approach [109]) capitalize on the similarities of symptoms across disorders and components of evidence-based programmes; reduce the number of models in which non-specialist providers need to be trained; and reduce the cost of that training [110–113]. These benefits are highly relevant to SSA.

Existing interventions and evidence-based intervention strategies that target post-traumatic stress and depression as pathways to improved antiretroviral therapy (ART) adherence among people with HIV can be adapted for PrEP use among PPW. For example, elements of a trauma-focused ART adherence intervention developed for South African women with histories of sexual violence can be leveraged; promising pilot data showed decreases in post-traumatic stress and increases in ART adherence motivation in the intervention [114], and a larger randomized controlled trial (RCT) is currently underway (NCT04793217). Similarly, a pilot study of cognitive behaviour therapy (CBT)-based intervention for ART adherence and depression led to decreased depression among postpartum women with HIV [115], and a separate RCT demonstrated that a CBT-based intervention targeting depression improved ART adherence and increased odds of having an undetectable viral load relative to control [116]. Specific treatment components of these interventions include CBT strategies like problem-solving [117], behavioural activation [116], approach-oriented coping skills training [118] and cognitive restructuring [116]. These components can then be packaged and assessed for feasibility, acceptability and signals of preliminary efficacy, both for mental health symptom reduction and increased PrEP adherence/persistence.

The designs of HIV care engagement interventions that target mental health could also be utilized. Task-sharing to lay counsellors, or peer mothers, may help manage the challenges posed by the limited availability of specialized mental health personnel [119]. Training lay counsellors to address the mental health barriers to PrEP use will build capacity and increase the sustainability of these programmes in ANC, providing critical support for women as they transition to postpartum care, where the focus shifts to the infant. It may be particularly meaningful for PPW to engage with other women who have successfully navigated mental health barriers to PrEP use; this approach was successful in a peer-run substance use reduction programme that increased engagement in HIV care. Stepped care designs may also prove viable. With the limited availability of psychopharmacology, stepped-care approaches may begin with brief counselling that targets underlying vulnerabilities across disorders and then escalates to additional treatment and/or a prescription only if symptom reductions and increases in PrEP adherence are not observed. Trauma-informed HIV care interventions [120] could be adapted to support adherence to PrEP, and dyadic designs could engage both partners while emphasizing the joint benefits of

continued PrEP use (e.g. increased intimacy and improved communication) [121]. Finally, integrating brief mental health counselling with PrEP counselling—as has been proposed for HIV primary care [122–124]—may be feasible in ANC, especially for women who initiate PrEP during pregnancy.

3 | CONCLUSIONS

We advocate that a comprehensive programme to optimize PrEP implementation in PPW should: (1) include mental health screening tools; (2) identify underlying mechanisms of mental health challenges that are associated with PrEP non-adherence; and (3) test efficient interventions that target those mechanisms, leveraging existing treatments, empirically-based strategies and delivery approaches. Although we focus primarily on oral, daily PrEP, mental health challenges will likely also compromise the consistent use of other PrEP agents; as such, we encourage all PrEP implementation research to assess and address mental health, regardless of PrEP formulation. Given the constellation of intersectional and structural challenges that increase the risk for HIV among PPW, interventions to optimize the PrEP cascade during pregnancy and postpartum may not be fully effective or sustainable until they address mental health.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

AMS developed the idea and initiated the collaboration for this manuscript. AMS drafted the paper with critical feedback and guidance from CO, LK, DLJD, LM, JAJ, KHM, LGB and CP. All authors read and approved this article.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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