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ORIGINAL PAPER

Depression Among Pregnant and Breastfeeding Persons Participating in Two Randomized Trials of the Dapivirine Vaginal Ring and Oral Pre-Exposure Prophylaxis (PrEP) in Malawi, South Africa, Uganda, and Zimbabwe

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Abstract

Depression is associated with lower adherence to oral pre-exposure prophylaxis (PrEP) to prevent HIV, but data are not currently available on how depression may affect use of other HIV prevention methods including the dapivirine vaginal ring (DVR). We conducted a mixed methods study using data from the Microbicide Trials Network (MTN) 042/DELIVER ($n = 558$) and MTN-043/B-PROTECTED ($n = 197$) studies to describe the prevalence of depressive symptoms and explore how depressive symptoms may have influenced attitudes about use of the monthly DVR and once-daily oral PrEP tablet among pregnant and breastfeeding persons, respectively, in Malawi, South Africa, Uganda, and Zimbabwe. Eleven participants had high Edinburgh Postnatal Depression scores ≥ 10 in MTN-042/DELIVER (2%) and four participants (2%) in MTN-043/B-PROTECTED. In interviews with 9 participants who had high scores (6 DVR, 3 oral PrEP), those with depressive symptoms described overlapping stressors which were magnified by job loss and economic instability during the COVID-19 pandemic, and by experiences of pregnancy/postpartum. These participants experienced a lack of support from partners or family members, and conflict with partners related to trust, and infidelity. While we did not find evidence of a change in product adherence, there was a strong sense of commitment and motivation to use the study products for protection from HIV for participants themselves and their baby. Although lack of social support is usually an obstacle to adherence, in this study, the participants' lives and relationships seemed to have reinforced the need for HIV prevention and motivated women to protect themselves and their babies from HIV.

Keywords HIV prevention · Depression · Pregnant persons · Breastfeeding persons · Dapivirine vaginal ring · Oral PrEP

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Introduction

Pregnant and breastfeeding persons have a high risk of HIV and mental health comorbidities including depression. Risk of HIV acquisition is higher during the perinatal and postnatal periods due to both biological and behavioral changes, such as increased intimate partner violence, and reduced condom use [1–6]. Concurrently, pregnant and breastfeeding persons have a high risk of depression [7]. A systematic review of studies in low and middle income countries (LMICs) found a mean prevalence of depression of 15.6% antenatally (95% confidence interval, CI: 15.4-15.9%) and slightly higher at 19.8% postnatally (19.5-20.0%) [7]. In studies using the Edinburgh Postnatal Depression Scale (EPDS) to screen for depression in pregnant and postpartum persons in Eastern and Southern Africa, the prevalence has ranged widely from 30 to 50% for a score over 13 which typically corresponds with a high possibility of depression [8–15]. Given the large number of pregnant and breastfeeding persons with depression concomitantly with heightened risk of HIV, it is critical to consider how depression might affect use of HIV prevention products.

Depression has been shown to affect use of daily oral pre-exposure prophylaxis (PrEP; "pills",) to prevent HIV and antiretroviral therapy (ART) for HIV treatment. Elevated depressive symptoms are associated with lower adherence to ART among people living with HIV and specifically among pregnant and breastfeeding persons [16–20]. A review of 51 studies found that the pooled proportion of persons with adequate ART adherence levels was higher during the antepartum period compared to the postpartum period (75.7% vs. 53.0%; $P=0.005$) and that nonadherence was associated with depression [21]. Depressive symptoms have also been associated with lower PrEP adherence to prevent HIV, but evidence is lacking among pregnant and breastfeeding persons [22, 23]. Data are not currently available on how depressive symptoms may affect use of other HIV prevention methods such as the dapivirine vaginal ring ("ring"), which will soon become available for widespread use in countries in Africa [24, 25]. More data are needed to understand how depressive symptoms in pregnant and breastfeeding persons may affect use of new and existing HIV prevention products with different delivery platforms and dosage durations.

We used data from the Microbicide Trials Network (MTN) 042/DELIVER and MTN-043/B-PROTECTED studies among pregnant and breastfeeding persons in South Africa, Malawi, Zimbabwe, and Uganda, to describe the prevalence of depressive symptoms, describe experiences of women with depressive symptoms, and explore how depressive symptoms may have influenced use of the ring and pills in pregnant and breastfeeding participants. We used a mixed methods approach combining quantitative data to describe depressive symptoms with qualitative data to explore how depressive symptoms influenced product use in both studies.

Methods

Study Population

We used data from MTN-042/DELIVER and MTN-043/B-PROTECTED Phase 3B, open-label trials, among pregnant and breastfeeding persons, respectively, in South Africa, Malawi, Uganda, and Zimbabwe. These studies evaluated the safety, drug detection, adherence, and acceptability of the monthly vaginal ring ("ring"; 25 mg dapivirine), and once-daily oral PrEP ("pills", 200 mg emtricitabine (FTC)/300 mg tenofovir disoproxil fumarate (TDF)). In both studies, participants were screened for depressive symptoms at enrollment and follow up visits. Those with high scores were referred for counseling but were still enrolled in the study. The MTN-042/DELIVER study was designed to enroll approximately 558 pregnant persons in three cohorts defined by gestational age from January 9, 2020 with follow up on-going at the time of this study and interim safety reviews between each cohort. Enrolled participants were on study product (ring or pill) for 2 to 30 weeks and followed up for up to 36 weeks, depending on their gestational age at enrollment and timing of pregnancy outcome. The MTN 043/B-PROTECTED study enrolled 197 healthy, HIV-uninfected breastfeeding persons and their healthy infants between 6 and 12 weeks old (inclusive) at the time of enrollment from August 2020 to November 2021. Each enrolled mother-infant pair was followed up for 14 weeks. Mothers were instructed to use the product (ring or pill) for 12 weeks.

Qualitative Subsample

Both studies included a nested qualitative study to characterize acceptability of study products. In cohort 1 of the DELIVER study, a subsample of 48 participants were randomly selected to complete an in-depth interview (IDI) before exiting from the trial [26]. Participants were interviewed at 38 weeks gestation or a minimum of two weeks after study product dispensation, and before exiting the trial. The qualitative sample was proportionally aligned with the number of enrollments at each site. In DELIVER cohorts 2 and 3, participants were purposively sampled according to site, randomization assignment, and parity. A total of 35 participants were interviewed in cohort 2 and 42 in cohort

3. Participants were interviewed at their 4-week visit closest to 36 weeks gestation, and prior to study exit.

In B-PROTECTED, a subsample of 51 participants were purposively sampled to complete an IDI according to site, randomization assignment and EPDS score at enrollment (high versus low) [27]. An EPDS score of 10 or higher was considered high [28, 29]. Participants were interviewed at their final month-3 study visit. Additionally, participants across sites in both studies were selected to complete a special case interview reserved for those who were selected by the site because they had interesting circumstances that could affect study product acceptability or use (e.g., high EPDS score, frequent reported removal of the ring or social harm). The IDIs that were selected for analysis in this study were from participants who were identified as meeting the high probability of depressive symptoms criteria (EPDS $\geq$ 10).

IDIs in both trials were conducted in English or the local language (i.e., Zulu, Shona, Sesotho Chichewa, Luganda) using a semi-structured interview guide by local, trained interviewers. Topics assessed included: personal context (e.g., COVID-19), product acceptability, experiences, disclosure, and satisfaction. The MTN-043/B-PROTECTED guide asked about depression and how breastfeeding and study product use were impacted by mental health. All IDIs were audio recorded, transcribed, and translated into English (if required). Transcripts went through a quality control process before coding and analysis.

Quantitative Data Collection

The EPDS is a 10-item screening measure with values for each item ranging from 0 to 3 [28–31]. Response options are based on frequency and vary by question but for most questions are "Yes, most of the time" (score of 3), "Yes, sometimes" (score of 2), "No, not very often" (score of 1) and "No, not at all" (score of 0). Items are summed for a score from 0 to 30, with an EPDS score of 10 or higher generally considered high probability of depression [28–31]. High scores identify persons who should be formally evaluated for depression by a trained professional. The EPDS was developed to identify symptoms of depression in the postnatal period but can also identify depressive symptoms antenatally [31]. The EPDS scale has been used and validated in Africa [30, 32]. We asked about use of mental health services, including depression diagnoses, access to therapy, treatment or other mental health services, or desire to access services.

Mixed Methods Approach

We used convergent mixed methods where we analyzed quantitative data to describe depression in the sample and qualitative data to understand how symptoms of depression may have impacted HIV prevention behaviors [33]. Analysis of quantitative and qualitative data was done concurrently from both studies.

Quantitative Analysis

We described participant characteristics, access to mental health services, and EPDS scores across both studies. Demographic characteristics and EPDS information were available for all three cohorts of MTN 042 whereas data on behavioral characteristics were only available for MTN-042 cohort 2 due to the stage of data collection at the time of this manuscript.

Qualitative Sample and Analysis

A qualitative interview guide was developed using the Theoretical Framework of Acceptability and was informed by codebooks used in prior MTN studies [26]. Additional details are published in the qualitative results paper from this study [26]. For the purposes of this study, the aim of the qualitative analysis was to assess whether there were differences in the lives of women with depressive symptoms versus not. Two qualitative analysts read five randomly selected transcripts from women with high EPDS scores, and the same number from women with low scores in the same countries and using the same products. In reading these transcripts these women did not report obstacles to adherence that we had not heard from the full sample, but this comparison highlighted marked differences in the life situations of participants. Based on that initial finding, we proceeded to explore the experiences of the depressed women to highlight their experiences. A team of analysts including eight members across sites read the transcripts from persons with high scores, agreed on key themes, and identified how having a high EPDS score may have influenced product use. Concurrently, five qualitative analysts in the United States coded the transcripts using Dedoose software. As described previously, the codebook for analysis included descriptive codes that directly corresponded to topical areas relevant to the study (e.g., ring, tablet, pregnancy, study product attributes, side effects), and analytical codes that corresponded to Theoretical Framework of Acceptability [26]. The analysis team used content analysis to examine the results of the coding process across participants. Coded excerpt reports were exported weekly to test intercoder reliability and come to consensus on discrepancies, refine the codebook as

needed, and discuss emergent themes. For the purposes of this analysis, we restricted the sample to only those who had high EPDS scores, and exported codes related to the themes that were identified in the team meeting with those who had read the full transcripts. While the coding team coded all transcripts with a larger number of codes, the codes that were exported and analyzed in this study corresponded to the themes identified by analysts across sites. Code reports were summarized to capture key quotes and topics within each theme. Pseudonyms are used in results to protect the identity of participants.

Results

Quantitative Results

The median age was 25 among breastfeeding participants in B-PROTECTED (and similar among pregnant participants in DELIVER (cohort 1 median 25; cohort 2 median 26; cohort 3 median 24; Table 1). Across both studies, participants were split approximately evenly across sites and almost all (96–97%) had a primary partner. Demographic characteristics were similar when comparing the qualitative samples with the overall sample from each study.

Overall, 2–3% had high EPDS scores but more participants with high EPDS scores were in the qualitative sample (2–9%) given purposive sampling (Table 1). In B-PROTECTED, few (4/160) women had a high EPDS score; and similarly, in DELIVER cohort 1 (4/150), cohort 2 (4/157) and cohort 3(3/251). In MTN 043, most participants with a high EPDS score were ring users ($n=3$, 75%). In MTN 042, 3 participants (27%) with a high EPDS score were pill users and 8 (73%) were ring users. When examining the distribution of EPDS scores across studies (Fig. 1), it was skewed to the left towards lower scores; although, the scores did range from 10 to 19 with no clear pattern by study.

Roughly 5% ($n=11$) were ever referred for counseling in B-PROTECTED and 4% ($n=7$) in DELIVER cohort 2 (Table 2). A larger percentage of breastfeeding persons (20%, $n=40$) had ever talked to a doctor or nurse about mental health or depression compared to pregnant persons (6%, $n=10$), and this most often occurred prior to breastfeeding (8%, $n=16$), during pregnancy (8%, $n=15$) or since having the baby (7%, $n=14$). Few persons in both studies had ever wanted to talk to a health professional about mental health or depression and couldn't (B-PROTECTED 7%, $n=13$; DELIVER 3%, $n=4$) or were diagnosed with depression by a healthcare provider (B-PROTECTED 3%, DELIVER $n=6$; 3% $n=4$) and almost all of those who were diagnosed received some form of counselling or other treatment. The most common reasons that participants said they would

Table 1 Demographic characteristics and EPDS scores of participants enrolled in MTN 043 and each MTN 042 cohort at enrollment

	MTN 043			MTN 042 Cohort 1			MTN 042 Cohort 2			MTN 042 cohort 3		
	All ($N=197$)	High EPDS ($N=4$)	Qualitative Sample ($N=52$)	All ($N=150$)	High EPDS ($N=4$)	Qualitative Sample ($N=48$)	All ($N=157$)	High EPDS ($n=4$)	Qualitative Sample ($N=35$)	All ($N=251$)	High EPDS ($n=3$)	Qualitative Sample ($N=42$)
Age, median (interquartile range (IQR))	25 (23, 30)	29 (25.4, 33.5)	25 (21, 32)	25 (21, 28)	30.5 (25.5, 33.0)	23.5 (21, 26.5)	26 (22, 30)	25 (23.5, 30.5)	24 (21, 29)	24 (22,29)	24.0 (20.0, 37.0)	24 (21, 28)
Product Assignment, n(%)												
Oral PrEP	49 (24.9)	3 (75)	12 (23.15)	49 (32.7)	2 (50)	15 (31.3)	51 (32.5)	1 (25)	8 (22.9)	49 (19.5)	0 (0)	8 (19.0)
Vaginal Ring	148 (75.1)	1 (25)	40 (76.9)	101 (67.3)	2 (50)	33 (68.8)	106 (67.5)	3 (75)	27 (77.1)	202 (80.5)	3 (100)	34 (81.0)
Site, n (%)												
Blantyre, Malawi	39 (19.8)	0 (0)	12 (23.1)	27 (18.0)	0 (0)	8 (16.7)	40 (25.5)	1 (25)	9 (25.7)	66 (26.3)	0 (0)	10 (23.8)
Johannesburg, South Africa	36 (18.3)	1 (25)	12 (23.1)	42 (28.0)	4 (100)	16 (33.3)	28 (17.8)	2 (50)	10 (28.6)	44 (17.5)	1 (33.3)	11 (26.2)
Chitungwiza, Zimbabwe	67 (34.0)	2 (50)	15 (28.9)	37 (24.7)	0 (0)	11 (22.9)	47 (29.9)	0 (0)	8 (22.9)	73 (29.1)	2 (66.6)	11 (26.2)
Kampala, Uganda	55 (27.9)	1 (25)	13 (25.0)	44 (29.3)	0 ()	13 (27.1)	42 (26.8)	1 (25)	8 (22.9)	68 (27.1)	0 (0)	10 (23.8)
Has primary partner	192 (97.5)	3 (75)	51 (98.1)	146 (97.3)	4 (100)	47 (97.9)	153 (97.4)	4 (100)	35 (100)	242 (96.4)	3 (100)	37 (88.1)
EPDS Score, median (IQR)	0 (0,1)	0 (0,1)	0 (0,1.5)	1 (0,3)	1 (0,3)	1, (0,3)	0 (0,2)	0 (0,2)	1 (0,4)	0 (0, 1)	0 (0, 1)	1 (0,2)
High EPDS Score (> = 10), n (%)	4 (2.0)	4 (2.0)	3 (5.8)	4 (2.7)	4 (2.7)	1(2.1)	4 (2.5)	4 (2.5)	3 (8.6)	3 (1.2)	3 (1.2)	2 (4.7)

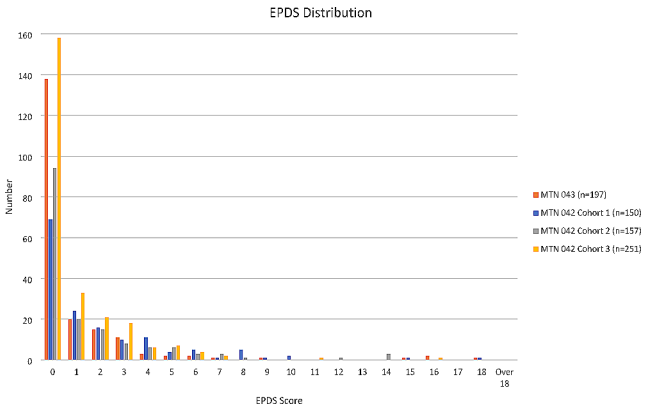


Fig. 1 Distribution of EPDS scores at enrollment for MTN 043 and each MTN 042 cohort

not ask for help when it was needed were cost of transport (B-PROTECTED 13%, $n=25$, DELIVER 9%, $n=14$), a fear of what others may think (B-PROTECTED 10%, $n=21$; DELIVER 7%, $n=11$), family may not approve (B-PROTECTED 9%, $n=17$), DELIVER 7%, $n=10$) and being embarrassed to talk about personal matters with others (B-PROTECTED 8%, $n=16$; DELIVER 7%, $n=10$).

Qualitative Results

Four main themes emerged across interviews with nine persons who had high EPDS scores: (1) overlapping stressors magnified by the COVID-19 pandemic and by pregnancy/postpartum; (2) conflictual relationships and lack of support from sexual partners and other family members; (3) life stressors motivating prevention method use; and (4) psychosocial support from study staff helping to address life challenges. These factors were mentioned overall and not specifically in reference to product adherence. When asked directly, participants were not able to identify ways in which their depression interfered with their use of either study product.

Overlapping Stressors Magnified by the COVID-19 Pandemic and Pregnancy/Postpartum

All participants with high EPDS scores described stressful life circumstances such as job loss, financial instability, and housing instability. Stressful life circumstances were raised as a host of events that overlapped and intersected with one another. For example, one pill user from South Africa ["Nandi"] described her life by saying *"Right now, uhm, I am a 24-year-old, I am pregnant, unemployed, stay with a boyfriend who is also unemployed, and with two kids… I am currently struggling financially, mostly that is my problem."* Another pill user in Zimbabwe ["Maida"] said *"They evicted me in a way of saying they don't want me there anymore as they were saying my husband is a thief… So, they, they removed the roof while it was raining. And I walked a lot with the baby going to the police and all. And also, when looking for a house."*

Table 2 Access to mental health services among participants in MTN 043 and MTN 042 cohort 2 at enrollment

	MTN 043	MTN 042 Cohort 2
	All ($N=197$)	All ($N=157$)
Participant ever referred for high EPDS at enrollment, n (%)	5 (2.5)	5 (3.1)
Participant with high EPDS score at enrollment or during study, n (%) ever referred for additional support?	11 (5.6)	7 (4.4)
Doctor or nurse ever talked about mental health or depression, n (%)	40 (20.3)	10 (6.3)
When did the health professional talk to you about depression/mental health, n (%)		
During pregnancy	15 (7.6)	7 (4.4)
Since having baby	14 (7.1)	NA
In prior pregnancy	7 (3.6)	1 (0.6)
Prior breastfeeding	16 (8.1)	NA
When not pregnant	8 (4.1)	2 (1.3)
Ever wanted to talk to a health professional about depression and couldn't, n (%)	13 (6.6)	4 (2.5)
Ever diagnosed with depression, n (%)	6 (3.1)	4 (2.5)
When Diagnosed, n (%)		
Since having baby (043)/ while pregnant (042)	1 (0.5)	1 (0.6)
During a previous pregnancy	4 (2.0)	1 (0.6)
Breastfeeding after prior pregnancy	0 (0)	
When not pregnant	1 (0.5)	2 (1.3)
Did you get counseling or any other treatment for your depression (among diagnosed), n (%)	6 (100)	3 (75)
Would any of the following keep you from asking for help with depression if you thought you needed it, asked at study exit, n (%)		
Embarrassed to talk about personal matters	16 (8.3)	10 (6.6)
Afraid of what others may think	21 (10.9)	11 (7.2)
Family members may not approve	17 (8.8)	10 (6.6)
Cost of transport	25 (13.0)	14 (9.3)
Had no time	9 (4.6)	8 (4.0)
Other, distance from hospital	1 (0.5)	0 (0)

All participants noted that their stressful circumstances were related to or magnified by the COVID-19 pandemic. Some participants worried about COVID-19 illness or had trouble following practices and policies related to COVID-19. Yet more common than worries about sickness and policy restrictions was stress associated with financial instability and job loss related to. For example, one breastfeeding pill user from Uganda ["Amahle"] described:

R: COVID-19 affected me so much because my marriage broke up, male partner left and abandoned us in the house. So, I have not had peace.
I: What was the Cause of the Break Up?
R: It was because he had failed to provide for the family and then he decided to run away from us. He had lost his job because of COVID-19 and had no other way of getting money. Things had become difficult. He got up one morning, picked everything that was his and then he went away.

Pregnancy and breastfeeding made already stressful situations more difficult. Many participants noted pregnancy symptoms like nausea and vomiting. Participants also said that becoming pregnant was challenging, as ["Kaya"], one pregnant ring user in South Africa described: *"Because I never expected, and I was not ready to be a mother…. Because financially I wanted to be stable first since things are difficult these days and a lot of money is required when you are raising a child….But I tried to accept the situation, but it was hard for me, and it was even hard to tell my family that I am pregnant and also the symptoms."*

Several participants described that being pregnant had caused them to lose jobs, which caused financial instability and more conflict with sexual partners. Job loss due to pregnancy frequently occurred in combination with other stressors. ["Anele"], a pregnant participant from South Africa stated:

"When I got pregnant, that's when things changed. My boss said "No", when they found out that I was pregnant then they [former employer] said "It is fine you can no longer come to work." And I said, "It is fine I will start looking for another job," but it was hard for me to find another job. I started getting sick too much. Then I ended up not going to work when I found out that I am pregnant. Then he [participant's partner] lost his job. …So, I was alone, and it was my first time to get [become] pregnant. I did not know some of the things, what to do if I am not feeling well. And then I had to run up and down going to the police station, and to court. And I was stressed that he went to prison for something that he did not do.

Some participants mentioned that their stress caused physical symptoms including headaches, weight loss, and reduction in the flow of breastmilk. For example, ["Maida "] described "*It [stress] had a bit of an effect because I could no longer eat, so I was now producing less milk. I noticed that the milk supply was now low."* ["Maida"] later said that she also had headaches: "*I was thinking about COVID, and also thinking about my husband who had been imprisoned. The day I gave birth to my child is the same day my husband was arrested… So, I think it was just too much on me and in my mind, and that caused the headache."*

Disagreements and Lack of Support in Relationships

In addition to general life stressors, most participants had disagreements with their sexual partners and a lack of support from their partners financially, emotionally and in the care of their baby. These disagreements often caused emotional distress for the participants. A few participants suspected that relationship conflicts and changes were due to the pressure of having a child together. One pregnant participant in South Africa ["Thandiwe"] said, "*it is not the pregnancy, it is just someone who is running away from his responsibilities, that is all*." She later said "*I think he was disappointed that I got pregnant, he was not expecting that, he always says it is a mistake.*" On the other hand, a pregnant participant from South Africa ["Kaya"] explained "*He has been supportive, he has been with me, it is just that as for him he is happy, but on my side, I was not ready, that's what makes me worry sometimes that I am… A lot of things about me they are going to change, my lifestyle and all that."*

Often disagreements and conflicts with sexual partners were around infidelity, mistrust of a partner and alcohol use. One pregnant participant in Zimbabwe ["Tinashe"] explained *"Yeah, emotional traumas you know. You know how men are at times, he would cheat on and cheated me and all. So, sometimes I would have an emotional breakdown*."

["Anele"] mentioned that her mood had also been affecting her relationship with her male partner: "*Yes, I am in a relationship but sometimes we fight [argue], because sometimes I am just not in a mood. Sometimes I feel like not talking to him [participant's partner] while he did not do anything. Sometimes I feel mostly when we fight, sometimes I do not feel like he should be next to me or touch me or do sex with me because I would just be out of the mood*."

Several participants noted other problems in relationships with in-laws, family, and friends, that were occasionally related to their relationships with their partners. One breastfeeding pill user in Zimbabwe ["Maida"] explained how she had felt lonely after her partner was arrested saying "*During that time, it was caused by the fact that I was always alone. I did not have time to meet with friends or stay with others….I would always be depressed. Right now, I can associate with others, talking etc., so I no longer have time to think a lot.*"

Life Stressors Add Motivations For Prevention Method Use

Despite disagreements and lack of support from sexual partners, most participants stated that issues with their partners did not affect their ring or pill use. One pregnant ring user in South Africa ["Thandiwe"] said "*I do not even listen, I*

do not want to lie, because using it [the ring] is for my own benefit not his own benefit….I am the one who is going to be protected and the baby, not him." Many of the participants disclosed study product use to their partners and several had supportive partners. A minority of participants did not disclose because they did not think their partners would be supportive. As exemplified by [“Amahle”], a breastfeeding pill user in Uganda: ="*He would not allow me to participate, he would have the same fears I had…. He would not allow his son to be involved in the study*." Another pill user in South Africa [“Nandi”] said that she misled her partner about the reason for her study product use, she said, "*the way I spoke to him about this preventing HIV I did not put in a way that I do not trust him, you might bring me HIV, I spoke to him about getting infected in a way other than sexual activities, so I believe he is about protecting."* One participant had disclosed to her mother so that someone knew about her product use, but that she was very worried about others finding out.

A majority of participants described that life complexities and difficult relationships with their partners were a source of motivation for product use. Several mentioned that they had heightened insecurities due to partner infidelity and diagnoses of other sexually transmitted infections (STIs) that caused them to want to protect themselves and their babies from HIV. A pregnant ring user from South Africa [“Kaya”] said "*I was scared for my baby that maybe she might be infected with HIV because at this moment sometimes I don't feel like having sex with my partner, so he might think that I am cheating or something and goes out and do it [have sex]with other people not knowing whether they are okay or what [HIV positive or not]…So, I wanted it for my health and also for the baby*." All participants empathized the importance of feeling like both them and their child are protected. One pregnant ring user in Malawi [“Grace”] stated *"Yeah, since you know we are human beings, I do not know what he [her partner] is doing wherever he is right now, so I thought it would be best to be safe especially for the baby."*

In addition to fear of infidelity from male partners, some participants mentioned that other considerations motivated their product use. One pregnant pill user in South Africa [“Nandi”] said "*I see HIV prevention as a good thing for me because you know seeing the way [her stepchild] had suffered because she does not have a mother even though she [stepchild's mother] did not die of HIV, but I feel like I want to be there for my kids do you understand… I want to live for my kids until they are big enough."* In general, protection of the baby offered peace of mind and was a big motivation to product use. [“Amahle”] described: *"I have liked it [study product] because it has given me the peace I did not have before [I joined the study]. I didn't have peace and would even find it difficult to sit and converse with people. But the product gave me peace, I would be happy and be able to do my work."*

Psychosocial Support From Study Staff Helped Address Life Challenges

Many participants said that being in the study was a source of support for them financially and emotionally. This came up in the form of increased knowledge, reimbursement from the study and psychosocial or emotional support. Several participants explicitly mentioned getting emotional support from study counsellors and how they helped them deal with stressful life circumstances. Several also mentioned that they had not spoken with anyone about their problems, including counselors or other mental health professionals, before being in the study. A breastfeeding pill user in Uganda [“Amahle”] explained:

> *R: When I had just given birth, I had a lot of stress, I had many thoughts and I was worried of how we were to survive. At that time, my male partner had just left and I didn't know how I was to get the basics for the home, how to feed the children and I didn't know how we were to be.*
> *I: Hmm*
> *R: But when I came here in the study, I talked to some counsellors who comforted me and gave me the hope and they told me that I am not the only person who is going through such a situation, that there are some others who are going through a situation that is worse than mine. The counsellors played a very big role to comfort me during that time and they made me feel better as I feel now.*

Discussion

In the sample of persons who joined two randomized trials of HIV prevention products during pregnancy and breastfeeding, we found that the measured prevalence of depressive symptoms was low compared to other settings. Few participants had ever talked to a doctor or nurse about mental health or depression, or ever had a prior diagnosis of depression. Persons with depressive symptoms had extreme and overlapping stressors in their lives like job loss, and financial and housing instability that were made harder with the COVID-19 pandemic and with pregnancy and becoming a mother. They also commonly experienced disagreements in relationships and a lack of support from partners and other family members. While participants did not describe these

factors as direct barriers to product adherence, they have been associated with adherence in prior studies [34–38]. Whereas depression is often seen as an obstacle to adherence, this sample described their complicated situations and relationships as a motivator for product use. Almost all participants described that fear of infidelity or STIs caused them to want to protect themselves and their babies from getting HIV. Many persons expressed concerns about study product side effects, and labor and delivery with the ring inserted (not shown in results), as has been reported among the full sample of participants [26, 27] but did not experience side effects themselves and were reassured by study staff about any potential issues. Study staff also provided valuable mental health and emotional support for participants that eased stressful circumstances.

Prior evidence shows that HIV prevention product use is highly dependent on positive influencers such as having social support (e.g., family members, friends, sexual partners), and to other negative external social such as stigma [34–38]. In particular, partner support and disclosure has been shown to strongly affect women's use of HIV prevention products including oral PrEP and the ring [39–43]. In quantitative data (not shown), most participants in both studies had disclosed product use to a partner who was supportive, but very few knew for sure that their partners did not have other partners. In qualitative results, we found that participants with symptoms of depression who were using the ring and oral PrEP said that conflict or lack of support from partners for product use did not change their motivation to use the products. In fact, almost all noted that fears of infidelity, STIs, or having their partner leave had increased their motivation to use the products to prevent HIV for themselves and their babies. Protection of their babies through use of the study products was an important consideration across the board and is similar to our prior findings which show that protecting their child from HIV exposure is a motivating factor for PrEP use among pregnant and postpartum individuals [26, 27].

The prevalence of depressive symptoms in our study was much lower than what has been reported in other studies in Eastern and Southern Africa that use the same scale [8–15]. A study summarizing the evidence on the validity of screening tools for common mental illness in low and middle income countries (LMICs) found very strong validity of the EDPS for screening for postnatal depression and moderate validity for screening for antenatal depression [44]. The EPDS has typically performed well in LMICs because it is short (10 items) and avoids using the word 'depression' so can more easily be integrated into clinical settings [45]. However, one study in Nigeria did find that a lower cut off score for a diagnosis of postnatal depression (≥ 10) using the EPDS compared to what is used in the United States (≥ 13) [46]. It is possible that the low prevalence of depression symptoms in our study is because of selection bias whereby those who chose to enroll in a clinical trial were less likely to have depression. Additionally, evidence has shown that idioms of distress or the experience of an illness can be distinct across cultures [47–49]. Lastly, stigma around mental health is common and may have caused participants in the study to be less likely to answer questions honestly about their mental health. Stigma also can impact the presentation of distress and cause more physical rather than psychological symptoms, whether this is conscious or unconscious [50].

Participants with a high EPDS score valued having access to study counsellors for support. In our prior work, we also found that support from staff helped to address participants concerns about side effects and impacts of the ring and the pill on the baby's health [26]. In quantitative findings, few participants had ever talked to a counsellor about mental health or had a diagnosis of depression from a healthcare provider. While very few also said that they ever wanted to talk to a counsellor about mental health and couldn't, the limited prior access to services suggests that there is little awareness about symptoms of depression and available services. In addition, many participants cited embarrassment and stigma from others, including family members, as reasons not to seek mental health care. These findings highlight the importance of education and awareness around mental illness, availability of services, as well as increased access to psychosocial support and counselling specifically for persons who are experiencing difficult life events and transitions, including pregnant and breastfeeding persons. The prevalence of perinatal depression is likely to be much higher in non-research settings where agencies are providing the ring or oral PrEP, than was reported in our sample with persons in clinical trials. Agencies that provide HIV prevention services should be prepared for persons with depressive symptoms and build capacity for inhouse or referral networks, or supportive lay interventions [15, 51, 52].

This study provides novel information about how depressive symptoms may affect vaginal and oral PrEP in two studies with pregnant and breastfeeding persons. There were some limitations to our study. First, the prevalence of depressive symptoms was low in our sample leading to qualitative interviews with only a small number of participants and those who likely had more severe cases of depression. Not all participants with a high EPDS score were interviewed as several exited the study before they could be asked to participate in an IDI. However, the number who were not interviewed was small (1 in MTN 043 and 5 in MTN 042) and is not likely to affect findings. The small number of persons who reported symptoms of depression in the overall sample

also limits our ability to examine quantitative relationships between depression and product use. Second, participants in this study described mild to moderate reactive depression in the face of difficult situations. However, the experiences of individuals with more severe depression, endogenous depression, and post-partum depression may differ from our findings, including how their depression may affect adherence to HIV prevention products. Third, participation in a trial may have led to some social desirability bias in participant responses about sexual behavior and about mental health due to perceived stigma. Lastly, the time frame for the two studies differed and occurred during different stages of the COVID-19 pandemic. Other circumstances around the timeframe and the pandemic may have influenced behaviors and depression among the study participants.

Conclusions

We found that the measured prevalence of depressive symptoms was low compared to other settings but that women with depressive symptoms expressed the value of having access to study counsellors who they could talk to about their difficult life circumstance. Given that the prevalence of perinatal depression is likely to be much higher in non-research settings where agencies will be providing the ring or oral PrEP, increased capacity is needed within these agencies to support persons with depressive symptoms. Additionally, all persons with depressive symptoms noted extreme and overlapping stressors, and ongoing conflict and lack of support from their sexual partners. Notwithstanding these challenges, these persons were engaged in the study, and the challenges that they experienced were described as an added motivation to protect themselves and their babies from HIV. These findings highlight the importance of ensuring that pregnant and breastfeeding persons, including those with mental health challenges, receive access and support for use of a range of HIV prevention products.

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Data Availability Data are available through the Microbicide Trials Network.

Declarations

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the following Institutional Review Boards/Ethics Committees and Drug Regulatory Authorities: Prevention Sciences Research Committee of the US National Institute of Allergy and Infectious Diseases; US Food and Drug Administration; College of Medicine Research and Ethics Committee; Johns Hopkins School of Public Health Institutional Review Board; Pharmacy, Medicines and Poisons Board of Malawi; Human Research Ethics Committee: (Medical), University of Witwatersrand, Johannesburg; South African Health Products Regulatory Authority; Joint Clinical Research Centre Institutional Review Board; Uganda National Council for Science and Technology; Johns Hopkins Medicine Office of Human Subjects Research Institutional Review Board; National Drug Authority of Uganda; Medical Research Council of Zimbabwe; Joint Research Ethics Committee for the University of Zimbabwe Faculty of Medicine and Health Sciences and Parirenyatwa Group of Hospitals; Research

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