

© Copyright 2019

Jennifer Velloza

Depression and HIV Pre-Exposure Prophylaxis Use among sub-Saharan African Women

Jennifer Velloza

A dissertation

submitted in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy

University of Washington

2019

Reading Committee:

Renee Heffron, Chair

Connie Celum

Jane Simoni

Ali Rowhani-Rahbar

Program Authorized to Offer Degree:

Public Health – Epidemiology

University of Washington

Abstract

Depression and HIV Pre-Exposure Prophylaxis Use among sub-Saharan African Women

Jennifer Velloza

Chair of the Supervisory Committee:
Renee Heffron, Associate Professor
Departments of Global Health and Epidemiology

Daily, oral pre-exposure prophylaxis (PrEP) with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) is a highly efficacious HIV prevention strategy for key populations at high risk of HIV, including women, in sub-Saharan Africa. However, open-label studies and demonstration projects have reported that young women have difficulty adhering to PrEP over time, which limits its effectiveness as a prevention option. PrEP projects are now exploring modifiable barriers to adherence among women to maximize its public health benefit as it is being rapidly rolled out worldwide.

Mental health factors, including depression, traumatic stress symptoms, and stigma, are highly prevalent among women at high risk of HIV acquisition and are barriers to medication use and health promotion behaviors. However, there has been little consideration until now of how such factors might also influence PrEP adherence among women in sub-Saharan Africa. The aims in this dissertation attempt to fill this research gap by: 1) exploring the impact of depressive symptoms on PrEP adherence among women; 2) examining the mechanisms by which depressive symptoms influence PrEP adherence; 3) describing the broader context of HIV-

related stigma and empowerment on PrEP use; and 4) integrating depression screening into HIV care delivery to improve mental health and HIV outcomes.

Two studies have examined the influence of depression on PrEP adherence and found that depressive symptoms have a negative effect on daily PrEP use for transgender women and men who have sex with men. Ours is the first study to examine links between depression and PrEP adherence among cisgender women in sub-Saharan Africa. We used marginal structural models to estimate the association between depressive symptoms and PrEP adherence while adjusting for time-varying confounding by sexual behavior, stigma, and social support. We found that probable depression was significantly associated with poor PrEP adherence among women, but not men, suggesting that mental health and depression experiences have differential impact on HIV prevention behaviors by gender.

This work also led to questions about the mechanism of this association and whether there were important mediators of the relationship between depression and PrEP adherence that could explain at least some of this total effect. We conducted a mediation analysis using marginal structural models to estimate the controlled direct effect of depression on PrEP adherence, after accounting for the potentially mediating influence of HIV-related stigma, social support, and optimism about PrEP effectiveness. We found a significant negative direct influence of depression on PrEP adherence but this relationship was not strongly mediated by other psychosocial factors. Future research is needed to explore additional potential mediators of this relationship and identify areas for intervention.

Qualitative research methods allow us to explore narratives around PrEP use, experiences of stigma, and concerns about mental health that are not captured by quantitative data. We analyzed serial in-depth interview data from a cohort of young women using PrEP to understand

the broader context around their pill-taking, mental health, and relationships. In this study, we found that women described experiences of HIV-related stigma when they began taking PrEP which influenced their ability to take PrEP and their feelings about themselves. However, over time, women became more empowered to use PrEP and combat HIV-related stigma by becoming “ambassadors” of PrEP in their communities. This work highlights the potential for empowerment-based interventions to improve PrEP adherence and reduce community stigma and the richness of serially collected qualitative data.

In Aims 1-3, we found evidence of a strong negative impact of depression on PrEP adherence and high rates of depression among women at risk of HIV. This work suggests that integrated depression screening and treatment with HIV prevention service delivery could improve mental health outcomes and PrEP effectiveness for women. To support the design of future integrated interventions, we conducted cognitive interviews assessing comprehensibility and acceptability of a widely used depression screening tool in the context of a PrEP delivery intervention among pregnant and postpartum women in Thika, Kenya. We found that the tool was largely acceptable and well-understood, but several minor changes to item wording and instructions would improve symptom screening and linkage to mental health care. These changes are part of our recommendations for the future use of this tool.

The collective results presented in this dissertation illustrate the negative influence of depression and related psychosocial factors on consistent PrEP use for women, opportunities for stigma-reduction and empowerment-based intervention approaches to improve mental health symptoms and PrEP use in this population, and the potential to administer depression screening within the context of HIV prevention service delivery. This work contributes to a better understanding of the links between mental health and HIV risk for women and highlights the importance of integrating mental health and empowerment-based interventions with PrEP

delivery to improve mental health screening and treatment and PrEP effectiveness for women in sub-Saharan Africa.

TABLE OF CONTENTS

List of Figures.....	ii
List of Tables.....	iii
Chapter 1. Introduction.....	1
Chapter 2. Effect of Depression on Adherence to Oral PrEP among Men and Women in East Africa.....	12
Chapter 3. The Effect of Depression on Adherence to HIV Pre-Exposure Prophylaxis Adherence among High-Risk South African Women in HPTN 067/ADAPT	35
Chapter 4. The Influence of HIV-Related Stigma on PrEP Disclosure and Adherence among Adolescent Girls and Young Women in HPTN 082: A Qualitative Study.....	57
Chapter 5. Cognitive Testing of the PHQ-9 for Depression Screening among Pregnant and Postpartum Women in Kenya.....	82
Chapter 6. Discussion	108
References.....	123

LIST OF FIGURES

Figure 1. Conceptual model of the pathways between depression and PrEP use, adapted from the Information-Motivation-Behavioral Skills (IMB) model.....	6
Figure 2. Hypothesized relationships between depression, PrEP adherence, and time-varying confounding variables during study follow-up	30
Figure 3. Directed acyclic graph of the relationships between depressive symptoms, mediators, and PrEP adherence over follow-up.....	53
Figure 4. Key qualitative themes on the relationship between stigma, disclosure, and PrEP adherence in the HPTN 082 sample.....	78
Figure 5. Changes in stigma, disclosure, and PrEP experiences over time attributed to HPTN 082 intervention and national activities.....	81
Figure 6. Suggested English and Kiswahili PHQ-9 revisions.....	104
Figure 7. Suggested instructional tool to aid participants in selecting a PHQ-9 response option.....	105

LIST OF TABLES

Table 1. Characteristics of the study sample at enrollment (N=1013 unless otherwise indicated).....	31
Table 2. Associations between participant characteristics and probable depression during study follow-up (n=1013).....	32
Table 3. Associations between depression and low PrEP adherence ¹ during study follow-up (n=903 participants).....	34
Table 4. Characteristics of the study sample, by study arm (N= 174 unless otherwise indicated).....	54
Table 5. Total effect estimates for the association between depression and PrEP adherence (N=164 participants with PrEP adherence data available at Week 24) ¹	55
Table 6. Controlled direct effect estimates for the association between depression and PrEP adherence ¹ for each mediator (N=164 participants with PrEP adherence data available at Week 24).....	56
Table 7. Characteristics of the HPTN 082 study sample at enrollment ¹	77
Table 8. Representative quotations from IDI transcripts.....	78
Table 9. Participant characteristics for Phases 2 and 3.....	102
Table 10. Summary of findings by PHQ-9 item and types of cognitive process problems discussed.....	103
Table 11. Summary of key themes related to conceptualization of mood and factors related to depressive symptoms.....	106

ACKNOWLEDGEMENTS

This dissertation is a reflection of the expertise, support, and guidance of so many individuals.

First and foremost, I am deeply grateful to the members of my dissertation committee: Renee Heffron, Connie Celum, Jane Simoni, Ali Rowhani-Rahbar, and Barbra Richardson. They have each shaped my growth as an epidemiologist and have generously shared their time and knowledge with me over the past four years. I am especially thankful for my chair, Renee Heffron, who first took me on as a Research Assistant on her K99/R00 study, has delved into the weeds of global mental health and mediation analysis with me, and has been a tireless mentor and advocate. Regardless of which time zone we were both in, she has always made time to meet weekly, review countless pages of my writing, and brainstorm new avenues for me to grow and develop as a scientist. I am so fortunate to have worked with her during my time as a student.

Through this dissertation on four different research studies, I have had the incredible opportunity to receive mentorship from other leaders in the field of HIV prevention and global health research including (but not limited to): Jared Baeten, Nelly Mugo, Kenneth Ngunjiri, Sinead Delany-Moretlwe, Sybil Hosek, Linda-Gail Bekker, and Monica Gandhi. This research would not have been possible without the teams who implemented the Partners Demonstration Project, HPTN 067 and 082, and the Safer Conception Intervention for Partners Study and the thousands of research participants who participated in these studies. In particular, I am so thankful for our collaborators at the Thika Partners in Health and Research Development in Thika, Kenya and the Wits Reproductive Health Institute in Johannesburg, South Africa who welcomed me into their teams and taught me so much about conducting HIV prevention and mental health research with young women.

The University of Washington Epidemiology Department and the International Clinical Research Center (ICRC) have both been incredible places to work and learn for the past four years. At the ICRC, Kathy Thomas and Lara Kidoguchi were both patient and thoughtful mentors in the ways of data management, database design, and advanced statistical analyses. I have also appreciated learning about the operational side of research studies from Jenn Morton, Caitlin Scoville, and Justice Quame-Amaglo over the years. The Simoni lab (Jane Simoni, Frances Aunon, Megan Ramaiya, and Christopher Kemp) took me in during my second year here and I have learned so much from our weekly meetings and projects together.

This dissertation would not have been possible without the generous support of my funders, including the National Institute of Mental Health, the University of Washington Epidemiology and Global Health Departments, and the Remak and Magnuson families.

Finally, I am so grateful to my mentors, friends, and family who have supported me on this journey. Drs. Kathy Sikkema, Kelly L'Engle, and Ward Cates recognized my potential as a scientist before I did myself and inspired me tremendously in my work on mental health and HIV prevention among women. Darcy Rao, Erica Lokken, Kathryn Peebles, and Rachel Kubiak have been such thoughtful and compassionate friends and adventure buddies these past four years and I'm so glad we have been able to lean on each other during our time in the PhD program. Carl, Diane, and Kristen Velloza, Heather Howard, and Rod Cameron have been my biggest cheerleaders and support system through so many years of school. Lastly, my husband, Colin Cameron, has earned this dissertation as much as I have through his unconditional love, support, and understanding. He has listened to hours of mock presentations and has done more than his fair share of laundry and cooking. He celebrates every victory of mine as joyously as if it was his own, holds me up during the tougher times, and always reminds me to savor the sunny and snowy days.

DEDICATION

To my parents, Carl and Diane Velloza, who taught me the importance of passion and compassion

– AND –

For young women everywhere who deserve good health and a chance to pursue their dreams

Chapter 1. Introduction

Daily oral pre-exposure prophylaxis (PrEP) has demonstrated efficacy to prevent HIV transmission and is being scaled up throughout sub-Saharan Africa. Randomized trials of PrEP efficacy conducted in high-risk populations from 2010-2012 reported relative reductions in HIV incidence between 44-86% for intervention groups.¹⁻⁶ Following efficacy trials, demonstration projects and program evaluations continued to show success from 2012-2016, resulting in a rapid scale-up of PrEP delivery programs in some countries in sub-Saharan Africa. The PrEP regimen of once daily oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF, brand name Truvada®) and lamivudine (3TC)/TDF was approved with an HIV prevention indication in South Africa and Kenya in 2015, following WHO guidelines about PrEP that were published that same year. Ministries of Health in Kenya and South Africa followed quickly thereafter to release broad guidelines on the use of PrEP among high-risk individuals.^{7,8} PrEP scale-up projects must now focus on improving PrEP uptake and adherence in order to maximize its effectiveness among high-risk populations.^{9,10}

High-risk African women have shown difficulty adhering to a daily, oral PrEP regimen which represents a critical missed opportunity for HIV prevention. In contrast to randomized trials with men who have sex with men and HIV serodiscordant couples, the FEM-PrEP and VOICE trials were conducted among young African women and failed to demonstrate PrEP's efficacy in this group.^{11,12} Trial participants had less than 30% adherence to their drug regimens and the intervention groups had HIV incidence rates of 5-6% which were extremely high and not statistically different from women randomized to placebo medication.^{11,12} Open-label and demonstration projects since have shown that high risk women are generally able to adhere to daily oral PrEP

regimens when product efficacy is known and they are receiving active PrEP medication, but these studies still report waning adherence over follow-up.^{13,14} Poor drug adherence among women is associated with lower social and family support and perceptions of stigma related to PrEP use.^{15–17} Current PrEP studies are continuing to investigate barriers to PrEP use and strategies to overcome them in order to improve individual-level adherence and maximize the public health impact of PrEP programs for women.^{18–20}

Mental illness, in particular depression, is also highly prevalent among young women in sub-Saharan Africa and is related to HIV risk, daily pill-taking behavior, and poor health outcomes. An epidemiologic study conducted in South Africa showed that the prevalence of major depressive disorder was 10% among all adults, but women were nearly twice as likely to experience lifetime depression than men.²¹ Pregnant and postpartum women have even greater risk of depression and it is estimated that 35-50% of African women meet the criteria for major depressive disorder during these periods.^{22,23} In the general population of women, depression is linked with lower adherence to daily oral contraceptive pills, higher rates of contraceptive discontinuation, attendance at fewer prenatal visits, and poorer reproductive health outcomes.^{24–28} Depression has also been associated with a variety of HIV risk behaviors (i.e. multiple sexual partners, condomless sex) and sub-optimal use of antiretroviral therapy (ART) resulting in overlapping epidemics of HIV and mental health conditions among women living in many African locations.^{29–38}

Given that mental health conditions are so prevalent among African women and are strongly associated with medication adherence and health-seeking behaviors, it can

be hypothesized that there is also a relationship between depression and PrEP use among HIV-uninfected women in this setting. However, this association has not yet been comprehensively studied and represents a critical gap in HIV prevention research. To contribute to closing this gap, we have leveraged four NIH-funded studies led by highly experienced research teams to conduct quantitative and qualitative analyses investigating links between depressive symptoms, other psychosocial factors, and PrEP adherence among women in Kenya, South Africa, Uganda, and Zimbabwe. We also evaluated the comprehension and acceptability of a widely used depressive symptom screening tool among pregnant and postpartum Kenyan women to work toward the development of mental health screening as a component of PrEP delivery. Through these studies, we have contributed to the understanding of the pathways between depression, psychosocial factors, and PrEP use among high-risk young women and explored the most appropriate ways to measure depression among pregnant and postpartum women in order to identify opportunities to integrate mental health services with HIV prevention interventions in sub-Saharan Africa.

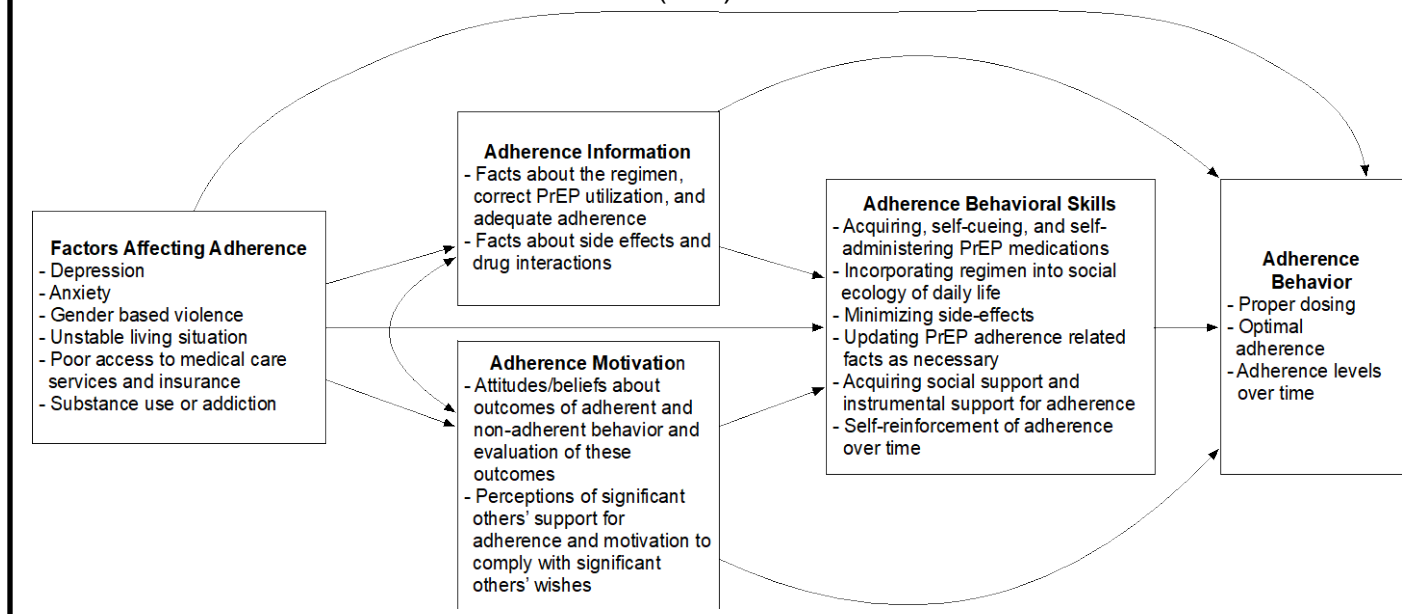
Chapter 2: Effect of Depression on Adherence to Oral PrEP among Men and Women in East Africa

Do depressive symptoms reduce PrEP adherence among women?

The psychosocial and behavioral pathways by which depression may influence PrEP adherence are illustrated in Figure 1, adapted from the Information-Motivation-Behavioral Skills (IMB) model.^{16,18,35,39,40} Depressive symptoms are associated with

behavioral and social factors creating a context of high HIV risk.^{22,41–44} Depression also has the potential to directly influence receipt of information about PrEP efficacy, motivations to use PrEP (i.e., HIV risk perception, normative beliefs about others' PrEP use, perceptions of PrEP-related stigma, perceptions of facilitators and barriers to PrEP use), and PrEP behavioral skills.^{35,39,45–48} While prior studies have explored these downstream information, motivation, and behavioral factors related to PrEP use, only one analysis to date has examined the direct associations between depressive symptoms and PrEP adherence.^{16,18,49,50} This analysis was conducted with men who have sex with men (MSM) and transgender women (TGW) in six countries, including South Africa, and found that while depression modestly reduced PrEP adherence, the impact of depression on adherence differed by population.⁴⁹ Specifically, modest depressive symptoms (Center for Epidemiologic Studies scale, or CES-D, score >16) were significantly associated with lower odds of protective PrEP drug levels among TGW.⁴⁹ However, among MSM, depression was only a barrier for PrEP use in the group with the highest severity of depressive symptoms (CES-D scores >26).⁴⁹ Causal analyses found that treating depression would have a lower impact on improving PrEP adherence among MSM than TGW in this study population.⁴⁹ Similar research has yet to be conducted among cisgender female populations and in other African settings and the IMB model may fail to capture the nuances of psychosocial factors or the influence of these important contextual factors or the on PrEP adherence for young women. It is imperative to develop a clear understanding of relationship between depression and PrEP adherence among high-risk, African women to identify future PrEP intervention targets.

Figure 1. Conceptual model of the pathways between depression and PrEP use, adapted from the Information-Motivation-Behavioral Skills (IMB) model



In Chapter 2, we examine the total association between depressive symptoms and PrEP adherence using longitudinal data collected through the Partners Demonstration Project. Our results provide evidence that women with depressive symptoms have significantly lower PrEP adherence than women without depressive symptoms, even after adjusting for confounding by sexual behavior over time. Moreover, this relationship between depression and PrEP adherence was statistically significant for women but not men in the sample, suggesting that the influence of depression on PrEP use differs importantly by gender.

Chapter 3: The Effect of Depression on HIV Pre-Exposure Prophylaxis Adherence among High-Risk South African Women in HPTN 067/ADAPT

What is the mechanism by which depressive symptoms reduce PrEP adherence among African women?

Depressive symptoms can impact self-care behaviors like daily adherence to ART and oral contraceptive pills directly or through their influence on psychosocial and behavioral factors like social support, perceived or experienced stigma related to HIV and mental health conditions, and optimism or hope around product effectiveness.^{35,51} Mediation analyses conducted among populations of individuals living with HIV have shown that there is both a direct effect of psychosocial factors (e.g., depressive symptoms, stigma) on ART adherence and an indirect of these factors on adherence through their impact on and interactions with one another.^{35,39} However, no analysis to date has examined the mechanisms by which depressive symptoms may influence PrEP adherence and these pathways may differ when considering medication taken for prevention (PrEP) rather than treatment (ART). Mediation analyses among HIV-uninfected individuals are also particularly important for identifying future intervention targets to improve PrEP efficacy in high-risk populations.

In order to answer questions about potential mediators of the pathway between depression and PrEP adherence, we utilize a counterfactual approach to mediation analysis and causal modeling techniques.^{52,53} These approaches allow us to answer questions of direct relevance to public health by estimating the controlled direct effect of depression on PrEP adherence after hypothetically intervening on mediating variables such as PrEP-related stigma, social support, and optimism about PrEP efficacy.⁵⁴ They are particularly useful in allowing us to control for confounding variables (e.g., HIV risk perceptions, sexual behaviors) and the presence of interaction between depression and our potential mediating variables.^{53,55}

While Chapter 2 shows that depression does have a significant influence on PrEP adherence for women, in Chapter 3 we use causal mediation analysis techniques to understand the mechanism of impact. Using longitudinal data from the HPTN 067/ADAPT open-label, randomized controlled trial, we confirmed our findings from Chapter 2, observing a robust, negative direct effect of depression on PrEP adherence among South African women and found that this relationship was not mediated by HIV-related stigma, social support, and PrEP optimism. These results suggest that interventions on stigma, social support, and PrEP optimism may not mitigate the relationship between depression and PrEP adherence, although future research is needed to explore other potential mediators of this relationship. This work points to a need to integrate depression screening and treatment into PrEP delivery approaches to improve PrEP effectiveness among high-risk women.

Chapter 4. The Influence of HIV-Related Stigma on PrEP Disclosure and Adherence among Adolescent Girls and Young Women in HPTN 082: A Qualitative Study

What are other important psychosocial facilitators and barriers to PrEP adherence for young women and how do they change over time?

Although our results from Chapter 3 did not point to a strong mediated effect of the relationship between depression and PrEP adherence by HIV-related stigma, social support, or feelings of optimism about PrEP, we know from prior research that these psychosocial and behavioral variables are important barriers to consistent PrEP use for

some women.^{18,19,56} Qualitative research techniques allow us to explore narratives around PrEP use and experiences of HIV-related stigma, social support, and feelings about PrEP without categorizing women into groups based on scale scores or focusing on p-values of effect measures.^{57,58} For example, the VOICE-C qualitative study showed that women were hesitant to use PrEP or disclose their PrEP use to others because they did not want to be mistakenly identified as having HIV.¹⁶ Qualitative work from the HPTN 067/ADAPT study found that belief in PrEP effectiveness and social support from peers were important facilitators of PrEP adherence but fears of stigma and unintentional product disclosure prevented women from being able to take PrEP every day.¹⁸ This body of qualitative research has also allowed us to contextualize quantitative findings from larger randomized controlled trials and identify new hypotheses for future interventions and statistical analyses.

In Chapter 4, we analyzed qualitative data from serial in-depth interviews and relationship timelines to understand the influence of HIV-related stigma, concerns around disclosing use of oral PrEP, and social support on PrEP use among adolescent girls and young women participating in the HPTN 082 open-label randomized clinical trial in Johannesburg and Cape Town, South Africa and Harare, Zimbabwe. We also utilized the unique longitudinal nature of the qualitative data to explore changes in stigma, disclosure, and PrEP adherence over time. This research showed that HIV-related stigma is a barrier to PrEP disclosure and adherence but may be mitigated by increasing community-level knowledge about PrEP, supporting women in their concerns around product disclosure, and providing empowerment-based adherence support to young women as part of the counseling that accompanies PrEP delivery.

Chapter 5. Cognitive Testing of the PHQ-9 for Depression Screening among Pregnant and Postpartum Women in Kenya

How can we improve the comprehensibility and acceptability of a depression screening tool for women in the context of PrEP delivery?

Results from Chapters 2-4 highlight the importance of depression and related psychosocial factors on PrEP adherence for African women, pointing to the need for integrated mental health and PrEP delivery services. To address this gap, in Chapter 5 we used cognitive interviewing techniques to evaluate the comprehension and acceptability of a widely used depressive symptom screening tool, the Patient Health Questionnaire-9 (PHQ-9), within the context of a larger PrEP delivery intervention conducted in Thika, Kenya among pregnant and postpartum women.⁵⁹ The PHQ-9 is convenient for evaluating depressive symptom severity in resource-limited settings where clinicians lack the resources to conduct diagnostic interviews; however, its ability to accurately measure culturally relevant depressive symptoms has not yet been established among high risk, HIV-uninfected Kenyan women and it recently has been shown to perform poorly among clinic populations with low average education levels.^{38,60–64}

Findings from our work have provided insight into the optimal way to administer depression screening tools to high-risk women eligible for PrEP. While we found that the PHQ-9 was well-understood, minor changes to the instructional language and English and Kiswahili item wording, and an additional visual aid for selecting response

options, could improve its accuracy and acceptability in this population. Future research is needed to validate the revised PHQ-9 with a larger sample of participants, but this work is an important first step toward successful integration of depression screening into PrEP delivery for high-risk African women.

Summary

This dissertation addresses links between depression, related psychosocial factors, and PrEP adherence among high-risk women in Kenya, Uganda, South Africa, and Zimbabwe. Our work provides robust evidence of the negative total and direct effects of depressive symptoms on PrEP adherence, describes related issues of PrEP-related stigma and fears around unintentional product disclosure as barriers to PrEP use, and highlights opportunities to incorporate depression screening into PrEP delivery for women. Together, these results highlight the need for integrated mental health and HIV prevention intervention approaches which have the potential to improve PrEP effectiveness, reduce the burden of HIV among African women, and normalize care-seeking behavior for mental health disorders.

Chapter 2. Effect of Depression on Adherence to Oral PrEP among Men and Women in East Africa

Published citation: Velloza J, Baeten JM, Haberer J, Ngure K, Irungu E, Mugo NR, Celum C, Heffron R, for the Partners Demonstration Project Team. Effect of Depression on Adherence to Oral PrEP among Men and Women in East Africa. *J Acquir Immune Defic Syndr.* 2018; 79(3): 330-338. doi: 10.1097/QAI.0000000000001821.

The effect of depression on adherence to oral PrEP among men and women in East Africa

Jennifer Velloza, MPH^{1,2}, Jared M. Baeten, MD, PhD^{1,2,3}, Jessica Haberer, MD, MS⁴, Kenneth Ngunjiri, MPH, PhD^{5,6}, Elizabeth Irungu, MBChB, MPH⁶, Nelly Mugo, MBChB, MMed, MPH⁷, Connie Celum, MD, MPH^{1,2,3}, Renee Heffron, MPH, PhD^{1,2}, for the Partners Demonstration Project Team

Affiliations:

¹University of Washington, Department of Global Health, Seattle, USA

²University of Washington, Department of Epidemiology, Seattle, USA

³University of Washington, Department of Medicine, Seattle, USA

⁴Massachusetts General Hospital, Boston, USA

⁵Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya

⁶Partners in Health and Research Development, Nairobi, Kenya

⁷Kenya Medical Research Institute, Nairobi, Kenya

Corresponding Author:

Renee Heffron, PhD, MPH

International Clinical Research Center

University of Washington

Box 359927

325 Ninth Avenue

Seattle, WA 98104

Phone: 206-520-3800

Fax: 206-520-3831

Email: rheffron@uw.edu

A portion of these data on depression and PrEP adherence among women were presented as a poster at the Conference on Retroviruses and Opportunistic Infections 2018 (CROI), Boston, MA, March 4-7, 2018.

Conflicts of Interest and Source of Funding: The authors declare that they have no conflicts of interest. The Partners Demonstration Project was funded by the National Institute of Mental Health of the US National Institutes of Health (grant R01 MH095507), the Bill & Melinda Gates Foundation (grant OPP1056051), and through the US Agency for International Development (cooperative agreement AID-OAA-A-12-00023). JV was supported by the National Institute of Mental Health of the US National Institutes of Health (grant F31 MH113420). Gilead Sciences donated the PrEP medication but had no role in data collection or analysis. The results and interpretation presented here do not necessarily reflect the views of the study funders.

Running Head: Depression and oral PrEP adherence

ABSTRACT

Background: Low adherence can undermine the efficacy of daily oral pre-exposure prophylaxis (PrEP). Mental health conditions, particularly depression, could be associated with low PrEP adherence, especially for women.

Setting: We analyzed data from 1013 Kenyan and Ugandan HIV-uninfected participants in the Partners Demonstration Project, an open-label study of PrEP delivered to HIV-uninfected members of serodiscordant couples.

Methods: Participants completed quarterly visits over two years and were encouraged to use PrEP until their partners living with HIV had ≥ 6 months of ART use (when viral suppression was expected). PrEP adherence was measured daily with electronic MEMS caps and dichotomized into low ($< 80\%$ of expected bottle openings) and high adherence. Depression was assessed annually using the 16-item Hopkins Symptom Checklist (HSCL-D) screening tool; scores > 1.75 indicate “probable depression”. The association between probable depression and PrEP adherence was assessed separately for men and women using generalized estimating equations and marginal structural models.

Results: At enrollment, 39 (11.7% of 334) women and 64 (9.4% of 679) men reported symptoms indicating probable depression, and these proportions decreased during follow-up ($p < 0.001$ for women and men). Probable depression was significantly associated with low PrEP adherence among women (adjusted risk ratio=1.77; 95% CI=1.14-2.77; $p=0.01$); there was no association between depression and adherence among men ($p=0.50$). Marginal structural models and sensitivity analyses confirmed these findings.

Conclusion: Depression was relatively uncommon in this population and was an independent risk factor for low PrEP adherence among women. For PrEP programs targeting African women, integration of depression screening may improve PrEP effectiveness.

Keywords: Depression; HIV; Pre-exposure prophylaxis; Africa; Women

INTRODUCTION

Oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) pre-exposure prophylaxis (PrEP) has demonstrated efficacy to prevent HIV transmission, with reductions in HIV incidence estimated to be >90% when daily adherence is high.¹⁻⁶ A recent open-label study conducted in South Africa (HPTN 067/ADAPT) found that high-risk women are generally able to adhere to daily oral PrEP regimens, providing reassurance about the usability of daily PrEP among women when efficacy is known and medication is accessible.¹¹⁻¹³ However, there remains a need to more fully understand factors influencing adherence as PrEP availability continues to expand throughout sub-Saharan Africa.^{15,65} While PrEP use could fluctuate appropriately to align with sexual behavior and HIV exposure, qualitative work suggests that salience of HIV (whether information about HIV comes to mind at times of HIV risk), perceived risk of HIV infection, stigma, social support, and fears about disclosure are important barriers to PrEP use among African women during periods of heightened HIV risk.^{15,16,18,65,66} Further research is needed to identify psychosocial factors related to PrEP use in the context of open-label PrEP delivery, explore gender-based differences in associations, and understand whether interventions targeting these constructs can improve PrEP adherence.

Mental health conditions, including depression, are also known barriers to healthcare engagement and daily medication adherence, but their relationship to PrEP adherence has not been well studied. Depression is highly prevalent worldwide, particularly among women who are 1.5-3 times more likely to experience lifetime depression than men, and depressive symptoms are related to increased HIV risk

behaviors (e.g., multiple sexual partners, condomless sex), poor social support, and substance abuse.^{15,16,17,18} Among adults living with HIV, those with depressive symptoms are approximately 55% less likely to achieve optimal daily ART adherence.^{36,37} Depression also has an impact on adherence to preventative behaviors, including daily contraceptive use and engagement in prenatal healthcare services, although the mechanisms underlying these associations likely differ from the relationship between depression and ART adherence. Among general populations of reproductive age women in sub-Saharan Africa and the United States, depression has been significantly associated with interruptions and cessation in effective contraception use over a six month period and failure to use dual protection methods, after accounting for fertility desires and sexual behavior.^{24,25,68}

Given the considerable burden of depression among individuals at high risk of HIV and associations between depression, health-seeking behavior, and daily medication, depression may also be linked with PrEP adherence. One recent study examined the influence of depressive symptoms on PrEP adherence, and concluded that depression modestly reduced PrEP adherence in men who have sex with men and transgender women (TGW).⁴⁹ Similar research has yet to be conducted among cisgender women in African settings. To contribute information to this gap, we evaluated the association between depression and PrEP adherence among a cohort of 1013 HIV-uninfected individuals participating in a PrEP demonstration project in Kenya and Uganda. We hypothesized that depression would be associated with low PrEP adherence and that there may be important gender-based differences in this relationship.

METHODS

Study population

The Partners Demonstration Project was a prospective, open-label implementation study to evaluate delivery of PrEP integrated into existing ART services among high-risk, heterosexual HIV serodiscordant couples in Kenya and Uganda.⁶⁹ The study was implemented between November 2012 and June 2016 at four clinical care research sites in Thika and Kisumu, Kenya and Kampala and Kabwohe, Uganda. Eligible couples were ≥ 18 years old, sexually active, and planned to remain a couple for at least one year. PrEP, prescribed as daily co-formulated FTC/TDF, was offered to HIV-uninfected participants and PrEP discontinuation was encouraged if their partners initiated and used ART for ≥ 6 months (when viral suppression would be expected) and if there were no concerns about their partner's ART adherence, or other considerations such as plans to become pregnant.⁶⁹

Data collection

HIV-uninfected participants attended quarterly study visits for up to 24 months and received HIV testing, PrEP refills (as needed), and HIV prevention counseling at each visit. Information on sexual behavior (e.g., condomless sex acts in the prior month), fertility intentions (e.g., intending to become pregnant in the next year), and contraceptive use were collected with standardized questionnaires, administered by interviewers in the participant's preferred language. Their partners living with HIV received ART on-site or were given referrals to a public health clinic of their choice, based on national ART eligibility guidelines.

At baseline and annual follow-up visits, sociodemographic data were collected and participants were assessed for depression, internalized stigma, heavy alcohol use,

perceived social support, and relationship satisfaction with validated questionnaires. Depression was assessed using the 16-item version of the Hopkins Symptoms Checklist for Depression (HSCL-D) screening tool.⁷⁰ Overall scores were calculated as a mean value (range 0-4), and a score >1.75 was indicative of “probable depression”.⁷⁰ This cutoff value has been previously validated in sub-Saharan Africa and corresponds well to depression diagnosis based on other screening tools and local informant interviews.^{71,72} Depression was analyzed as a time-dependent exposure; we used linear interpolation methods to estimate participants’ HSCL-D scores throughout the study period by fitting linear regression equations for the change in scores between annual visits and then calculating HSCL-D scores at intervening quarterly visits using the model coefficients.^{73,74} As part of routine counseling procedures, participants who screened positive for depression were referred to local specialists for mental healthcare.

Internalized stigma was measured by summing scores from a four-item scale (adapted from the validated Internalized AIDS-Related Stigma Scale), with a value closer to 16 indicating greater stigma.⁷⁵ Heavy alcohol use was defined as a response of “yes” to any of four items from the Rapid Alcohol Problems Screen.⁷⁶ Social support was measured as a continuous mean score from the 10-item Functional Social Support Questionnaire (range 1-4), with a higher score indicating greater perceived social support.⁷⁷ Relationship satisfaction was based on the sum score from an eight-item dyadic adjustment scale (range 8-48) and a higher sum score indicated greater satisfaction.⁷⁸ Stigma, alcohol use, social support, and relationship satisfaction were also analyzed as time-dependent covariates with scores carried forward between annual visits.

PrEP adherence

The primary outcome was PrEP adherence among participants choosing to take PrEP, measured using medication event monitoring system (MEMS) caps data which electronically captured a date-and-time stamp with each bottle opening. These data were downloaded at each study visit following PrEP initiation. MEMS data were collected as a research procedure and were not used in adherence counseling. Adherence was calculated as the number of pill bottle openings divided by the number of expected bottle openings during the period between visits and is reported as a percentage. Openings by the study staff during visits were excluded from the numerator. The number of expected bottle openings excluded days for which PrEP was not dispensed due to missed visits, protocol-defined PrEP stops (e.g., related to adverse events or sustained ART use by a partner living with HIV), or PrEP refill refusals. We also excluded missing data due to broken or lost MEMS caps and instances where participants had >120% of expected bottle openings during the period between study visits, which could indicate cap malfunction or repeated openings without removing a dose. Participants were considered to have high PrEP adherence during periods where MEMS data indicated that $\geq 80\%$ of expected openings occurred between quarterly study visits. This cutoff corresponds to 5-6 doses per week and plasma tenofovir concentrations >40 ng/mL, which is consistent with steady-state daily dosing and has been associated with high levels of protection against HIV.^{79,80} In this cohort, MEMS data were highly correlated with blood plasma tenofovir concentrations in a random sample of 140 participants.^{69,81}

Statistical analyses

We used descriptive statistics to summarize the sample of HIV-uninfected participants by gender and compared participant characteristics during periods of probable depression and those without probable depression using generalized estimating equations (GEE) extension to logistic regression. The multivariable model of factors associated with probable depression included any variables for which the univariable p-value was ≤ 0.10 .

To assess the effect of depression on low PrEP adherence, we used GEE with a log link, Poisson distribution, and robust standard errors to estimate risk ratios. Our primary model included “probable depression” as a categorical (yes/no) exposure, as has been done in studies of depressive symptoms and ART adherence to allow for a meaningful interpretation of results.^{49,82,83} Study site, age, and time-dependent measures of stigma, social support, fertility intentions, and any condomless sex acts since the prior study visit were included in the models based on *a priori* knowledge that these factors may be related to both depression and PrEP adherence.^{15,16,22} We assessed several additional covariates for confounding, including education, income, marital status, partnership duration, time known to be in an HIV serodiscordant relationship, and parity (measured at enrollment), as well as time-dependent measures of sexually transmitted infection symptoms, heavy alcohol use, current relationship status, relationship satisfaction with study partner, reported abuse, and plasma HIV RNA viral load (\log_{10} copies/mL) and CD4 count (cells/ μ l) of the partner living with HIV. Of these covariates, any that resulted in a substantial change in the effect estimate (>10%) were included in the multivariable model. Separate models were run for men and women.

We also conducted several sensitivity analyses of our primary GEE models to explore whether our findings were robust to changes in depression and adherence definitions. First, we examined the dose-response relationship between depression and PrEP adherence by varying the HSCL-D score cutoff to 1.60 and 1.50. Second, we defined PrEP adherence with cutoffs of $\geq 70\%$, $\geq 85\%$, and $\geq 90\%$ of expected openings using MEMS data. Third, we ran our models among the subset of participants with plasma tenofovir levels (N=140) and defined our adherence outcome using a cutoff of 35 ng/mL.

We repeated our primary analyses using marginal structural models to adjust for time-dependent confounding by stigma, social support, and sexual risk behavior (Figure 2).⁸⁴ We computed stabilized inverse probability weights using logistic regression to predict the probability of categorical depression exposure at each visit.⁸⁵ The weights were calculated with baseline measures of marital status, age, heavy alcohol use, relationship satisfaction with study partner, and plasma HIV RNA viral load of the partner living with HIV, as well as HSCL-D score at the prior visit (exposure history) and time-dependent measures of stigma, social support, and condomless sex. Exposure weights were computed separately for women (mean 0.99, range 0.23-3.13) and men (mean 1.00, range 0.49-1.91) and were not truncated. These weights were included in regression models with a log link, Poisson distribution, and robust standard errors.

All analyses were conducted using SAS 9.4 (Cary, North Carolina, USA).

Ethical statement

Protocols were approved by ethical review boards at the University of Washington and collaborating institutions in Kenya and Uganda. All participants provided written informed consent in their preferred language.

RESULTS

Participant characteristics

The Partners Demonstration Project enrolled 1013 HIV-uninfected individuals, including 334 (33.0%) women and 679 (67.0%) men. The median age at enrollment was 30 years (interquartile range [IQR] 26, 36 years).⁶⁹ The median reported duration of partnership was 5.9 years (IQR 1.9, 11.6) for women and 2.4 years (IQR 0.8-5.8) for men (Table 1). Most participants reported learning that they were in an HIV serodiscordant relationship shortly before study enrollment (median time= 1.2 months). Approximately 198 women (59.3%) and 458 men (67.5%) reported at least one condomless sex act with their study partner in the month prior to enrollment and the median plasma HIV RNA viral load for participants' partners living with HIV was 4.6 log₁₀ copies/mL (IQR 3.8, 5.0).

During the two year study period, 982 participants initiated PrEP, a majority at enrollment (98.2% of women and 97.1% of men). In addition, 233 women (74.9%) and 425 men (70.7%) had a partner initiate ART within the first six months of follow-up. Retention rates were high throughout the study (>83% at all visits) and 962 participants had at least one follow-up visit after PrEP initiation. More than half of the participants stopped PrEP by their 12-month visit (N=196; 58.7% for women and N=372; 54.8% for men). The most frequent reason for stopping PrEP during follow-up was ≥6 months of ART use by the partner living with HIV (N=519; 51.3%).

Prevalence and factors associated with depression

A total of 103 HIV-uninfected participants (10.2%) had probable depression at enrollment and this proportion decreased during study follow-up. Among women, 11.7%, 8.2%, and 3.1% were classified as having probable depression at enrollment, 12-, and 24-month visits, respectively (p-value for trend <0.001). Among men, 9.4%, 2.6%, and 2.0% were classified as having probable depression at each of the annual visits (p-value for trend <0.001). In a multivariable model, being female (adjusted odds ratio [OR] 2.16, 95% CI 1.35-3.43), being unmarried (aOR 2.77, 95% CI 1.33-5.77), reporting condomless sex in the prior month (aOR 1.33, 95% CI 1.01-1.77), and having a partner with higher plasma HIV RNA viral load (aOR 1.16, 95% CI 1.04-1.31) were all independently associated with higher odds of probable depression during the study (Table 2). Several psychosocial and behavioral characteristics were also associated with probable depression during follow-up. Higher levels of HIV-related stigma (aOR 1.11, 95% CI 1.04-1.19), heavy alcohol use (aOR 1.83, 95% CI 1.18-2.82), lower levels of social support (aOR 0.72, 95% CI 0.52-1.00), lower reported relationship satisfaction with a study partner (aOR 0.91, 95% CI 0.89-0.94), and reporting abuse from a study partner (aOR 2.73, 95% CI 1.48-5.02) were more likely during periods with probable depression than during periods without probable depression.

Depression and PrEP adherence

The analysis of depression and PrEP adherence included 903 participants, after excluding those who did not initiate PrEP (N=28), did not have a follow-up visit during the analysis period (N=23), or did not have a visit where adherence could be calculated

due to PrEP discontinuation, missing MEMS data, and MEMS adherence data >120% for all visits when measured (N=59).

Among women, low (<80%) PrEP adherence was detected at 26.9% of included visits and occurred more often during periods when probable depression was reported (41.1% of visits) relative to periods without depression (25.9% of visits; adjusted risk ratio [aRR] 1.77, 95% CI 1.14-2.77, Table 3). These results were in agreement with marginal structural model findings (aRR 1.53, 95% CI 1.05-2.23, Table 3). The strength of the association between depression and PrEP adherence decreased when the HSCL-D score cutoff was changed to 1.60 in the GEE model (aRR: 1.61, 95% CI: 1.05-2.48) and was no longer statistically significant when the HSCL-D cutoff was changed to 1.50. Our findings were robust to changes in the outcome variable and remained statistically significant for adherence cutoffs of 70%, 85%, and 90% (aRR estimates ranged from 1.53-1.87). In the model with plasma TFV levels, the direction of the association between depression and adherence remained (aRR: 1.21, 95% CI: 0.93-1.58), but the magnitude of the estimate was attenuated likely due to the smaller number of observations.

Among men, low adherence to PrEP was detected at 35.8% of visits when probable depression was reported and 30.9% of visits without depression. The frequency of low PrEP adherence was not associated with probable depression in the GEE ($p=0.50$) or marginal structural model analyses ($p=0.32$, Table 3). We also did not detect significant associations between depression and adherence in any sensitivity analyses.

DISCUSSION

In this PrEP demonstration project with HIV-uninfected individuals in mutually disclosed HIV serodiscordant partnerships in East Africa, depression was significantly associated with low PrEP adherence among women, but was not related to PrEP adherence among men. This finding is particularly important given that in this cohort, as well as other sub-Saharan African settings, the burden of depression is greater among women than men and women may have more difficulty adhering to oral PrEP than men.^{11,12,21,86} However, overall adherence was high in this sample even among participants with probable depression, and only 4 participants seroconverted during follow-up, suggesting that depressive symptoms may not be sufficient to eliminate the benefit of PrEP in the cohort.⁶⁹

Overall, few participants (10.2%) endorsed symptoms consistent with depression at enrollment and the prevalence of probable depression decreased over time for men and women. During follow-up, probable depression was associated with gender, marital status, viral load, condomless sex, stigma, alcohol use, social support, relationship satisfaction, and abuse. Other studies in sub-Saharan Africa have found similar associations, and the relationships between depression, risky sexual behavior, abuse, and other psychosocial and behavioral variables are likely bidirectional and dynamic.^{35,51,87}

Consistent with our findings, an analysis with the iPrEx OLE cohort found that the effect of depressive symptoms on PrEP adherence differed between men and TGW.⁴⁹ Moreover, research on the relationship between depression and ART adherence among adults living with HIV in sub-Saharan Africa has shown that depression is associated with poorer ART adherence and this relationship is stronger for women than for men.⁶⁰

These findings on the moderating role of gender in the relationship between depression and adherence could be explained in part by traditional gender roles in these settings. Women in sub-Saharan Africa are typically viewed as caregivers with primary responsibilities for household tasks, which are often prioritized above their self-care.^{88,89} This situation may be particularly true in our cohort of serodiscordant couples with HIV-uninfected women who could be caring for their partners living with HIV, although this has not been a predominant theme in our qualitative work.⁹⁰ Other qualitative research with HIV serodiscordant couples has shown that men may feel their masculinity is threatened by their female partners' use of ART or PrEP and, as a result, may attempt to control their partners' medication use.⁸⁸ Traditional gender roles and relationship power dynamics could influence access to mental healthcare and severity of depression, thereby strengthening an association between depression and low PrEP adherence over time particularly for women. The potential influence of gendered power dynamics on health and HIV prevention behaviors also supports our finding that relationship satisfaction was strongly associated with both depression and PrEP adherence in this sample.

We classified PrEP adherence using MEMS data and participants were considered to have low adherence for a given visit if MEMS data indicated that <80% of bottle openings occurred. This 80% threshold corresponds to approximately 5-6 PrEP doses per week, which we assumed was sufficient to protect against HIV acquisition in this cohort. However, pharmacokinetic minimum levels of PrEP adherence have not yet been established for women or heterosexual men and, while prior studies have found associations between high levels of adherence and low HIV incidence, recent data

suggest that PrEP may be less forgiving to missed doses in vaginal than rectal exposure.^{79,91,92} In order to address these uncertainties about effective levels of PrEP, we repeated our analyses using various PrEP adherence cutoffs and plasma TFV levels and found similar results.

The strengths of this study included the large, prospective cohort with participants from urban and rural African settings and the use of a validated depression screening tool and electronic monitoring devices to monitor medication use. Overall retention rates were high in the sample which minimized bias due to differential attrition by depressive symptom severity. Limitations of this study included annual depression measurement, which reduced our ability to analyze more frequent changes in depression status. Depressive symptoms could have been influenced by social desirability bias, but interviews were conducted with trained counselors to minimize this issue. In addition, there may be non-differential misclassification of probable depression status with respect to PrEP adherence, which would be expected to attenuate our model estimates. Finally, participants were all in stable HIV serodiscordant relationships at enrollment and our findings may not be generalizable to other high-risk populations.

Future research on links between depression and PrEP adherence should consider potential intervention opportunities to incorporate mental health services with PrEP delivery, particularly for women. Several models that integrate depression interventions into existing healthcare programs are being implemented in sub-Saharan Africa. For example, a “measurement-based care model” for antidepressant delivery, which encourages case managers to screen individuals for depression using brief tools and track their antidepressant adherence during regular clinic visits, has been

successfully deployed in HIV clinics in Cameroon and Uganda.^{93,94} Psychotherapy interventions, such as cognitive behavioral therapy, have also been adapted for lay healthcare worker delivery in HIV, antenatal, and primary healthcare clinics throughout sub-Saharan Africa and have been shown to reduce depression and improve ART adherence after 6-8 months among adults living with HIV.⁹⁵ The successes of these programs suggest that depression screening tools and adapted interventions can be implemented in busy healthcare settings, and similar intervention approaches could be tailored to HIV-uninfected adults seeking PrEP to potentially improve PrEP adherence in the subset with depressive symptoms.

In conclusion, depressive symptoms were relatively uncommon in our study and appear to have negatively impacted PrEP adherence among high-risk, HIV-uninfected women, but not among men. These findings highlight a need for future studies to continue exploring psychosocial barriers to PrEP adherence by gender. Additional research is also necessary to understand the potential mechanisms by which depression influences adherence to preventive therapies and whether there are modifiable factors mediating this relationship. Our study supports the integration of regular depression screening and treatment into PrEP delivery programs which may reduce the burden of depression and improve PrEP effectiveness among African women.

ACKNOWLEDGMENTS

The authors thank the couples who participated in the study and the teams at the four study sites and the University of Washington that supported data collection and management for this work.

Partners Demonstration Project Team

Coordinating Center (University of Washington) and collaborating investigators (Harvard Medical School, Johns Hopkins University, Massachusetts General Hospital):

Jared Baeten (protocol chair), Connie Celum (protocol co-chair), Renee Heffron (project director), Deborah Donnell (statistician), Ruanne Barnabas, Jessica Haberer, Harald Haugen, Craig Hendrix, Lara Kidoguchi, Mark Marzinke, Susan Morrison, Jennifer Morton, Norma Ware, Monique Wyatt

Project sites:

Kabwohe, Uganda (Kabwohe Clinical Research Centre): Stephen Asiimwe, Edna Tindimwebwa

Kampala, Uganda (Makerere University): Elly Katabira, Nulu Bulya

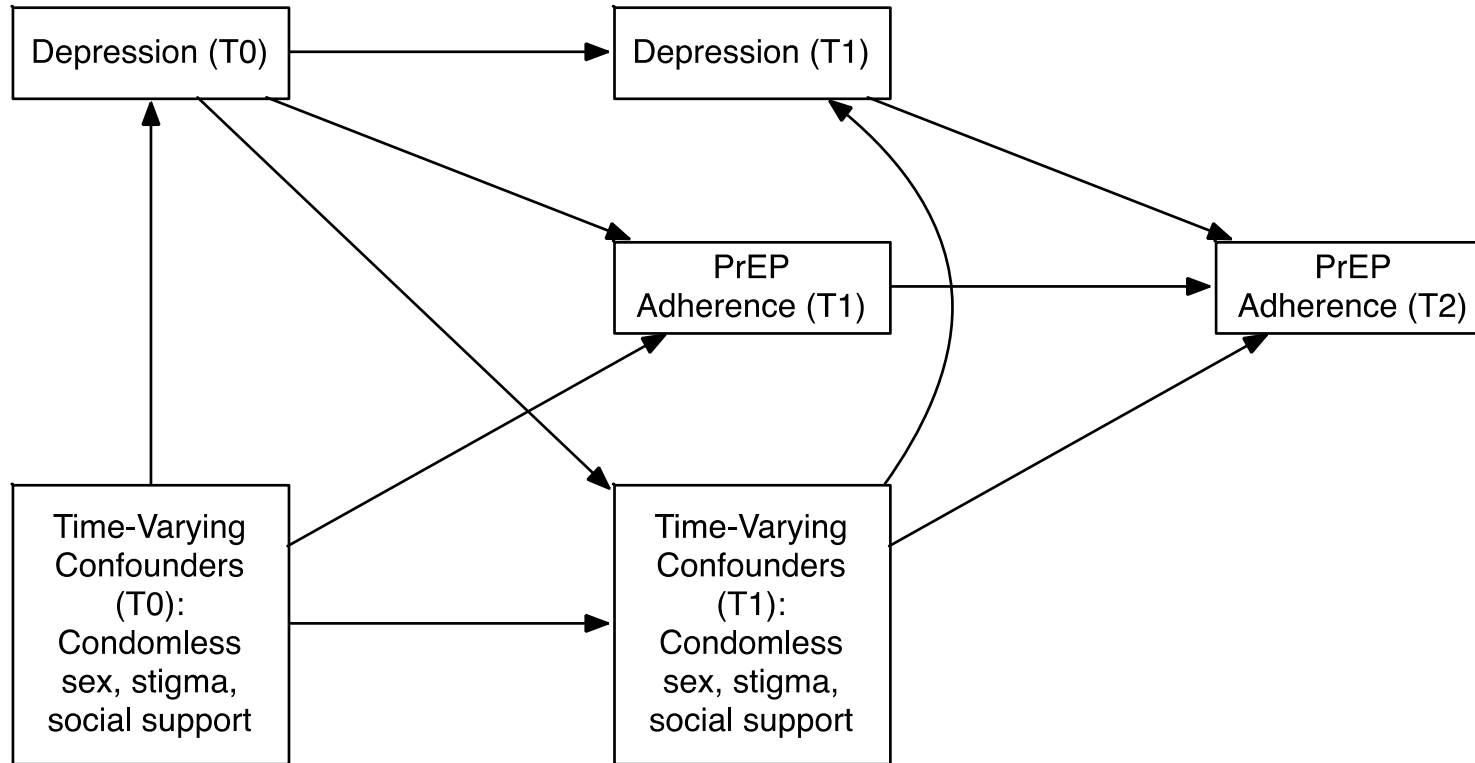
Kisumu, Kenya (Kenya Medical Research Institute): Elizabeth Bukusi, Josephine Odoyo

Thika, Kenya (Kenya Medical Research Institute, University of Washington): Nelly

Rwamba Mugo, Kenneth Ngure

Data Management was provided by DF/Net Research, Inc. (Seattle, WA). PrEP medication was donated by Gilead Sciences.

Figure 2. Hypothesized relationships between depression, PrEP adherence, and time-varying confounding variables during study follow-up



T0= Enrollment; T1= Quarterly follow-up visits; T2= Final study visit
PrEP= pre-exposure prophylaxis

Table 1. Characteristics of the study sample at enrollment (N=1013 unless otherwise indicated)

	HIV-uninfected women (N=334)	HIV-uninfected men (N=679)
Age, years	29 (24-35)	30 (26-37)
Unmarried	9 (2.7)	32 (4.7)
Education, years	8 (5-11)	8 (7-12)
Any income reported	217 (65.0)	653 (96.2)
Relationship duration with study partner, years	5.9 (1.9-11.6)	2.4 (0.8-5.8)
Time known to be in an HIV serodiscordant relationship, years	0.1 (0.1-0.6)	0.1 (0.0-0.2)
Number of children with study partner	1 (0-2)	0 (0-1)
Number of more children desired	1 (0-2)	2 (1-3)
Timing of next pregnancy (N=887 non-pregnant participants)		
Currently trying to get pregnant	23 (6.9)	41 (6.0)
Not currently trying to get pregnant	185 (55.4)	514 (75.7)
Number of sex acts with study partner	4.5 (3.0-8.0)	6.0 (3.0-12.0)
Any condomless sex with study partner	198 (59.3)	458 (67.5)
Any sex with outside partner(s)	5 (1.5)	79 (11.6)
STI symptoms	20 (6.0)	11 (1.6)
CD4 count (cells/ μ l) of partner living with HIV	403 (221-595)	451 (285-660)
Plasma HIV RNA (\log_{10} copies/mL) of partner living with HIV	4.8 (4.3-5.3)	4.4 (3.5-4.9)
Probable depression ¹	39 (11.7)	64 (9.4)
HIV-related stigma	6.0 (4.0-8.0)	8.0 (5.0-9.0)
Heavy alcohol use	50 (15.0)	152 (22.4)
Social support	3.6 (3.2-3.9)	3.7 (3.2-4.0)
Relationship satisfaction with study partner	31.0 (27.0-34.0)	32.0 (28.0-35.0)
Happiness in relationship (N=1012) ²		
Happy	292 (87.4)	621 (91.6)
Unhappy	42 (12.6)	57 (8.4)
Reported abuse	1 (0.3)	2 (0.3)

Data are presented as number (%) for categorical variables and median (interquartile range [IQR]) for continuous variables. STI=sexually transmitted infection

¹Cognitive, behavioral disengagement, and somatic depressive symptoms were assessed with a Likert response scale ranging from 1 ("Not at all") to 4 ("Extremely"). A mean score >1.75 was indicative of "probable depression".

²Happiness in the relationship was assessed with a single item.

Table 2. Associations between participant characteristics and probable depression during study follow-up (n=1013)

	Frequency of visits ¹		Factors associated with probable depression			
	Probable depression ² (N=431 visits)	No probable depression (N=8386 visits)	Univariable OR (95% CI)	p-value	Multivariable OR ³ (95% CI)	p-value
Demographic characteristics						
Female	219 (50.8)	2770 (33.0)	2.41 (1.61-3.61)	<0.001	2.16 (1.35-3.43)	0.001
Age, years	30 (25-35)	30 (25-35)	1.00 (0.97-1.02)	0.84		
Unmarried	31 (7.2)	291 (3.5)	2.12 (0.92-4.90)	0.08	2.77 (1.33-5.77)	0.01
Education, years	9 (7-12)	8 (6-12)	1.02 (0.97-1.08)	0.42		
Any income reported	335 (77.7)	7256 (86.5)	0.56 (0.33-0.94)	0.03	0.84 (0.48-1.47)	0.54
Couple characteristics						
Relationship duration with study partner, years	3.4 (0.7-8.2)	3.5 (1.1-8.1)	1.00 (0.97-1.03)	0.87		
Time known to be in an HIV serodiscordant relationship, years	0.1 (0.0-0.2)	0.1 (0.1-0.3)	1.04 (0.80-1.36)	0.77		
Number of children with study partner	0 (0-1)	0 (0-2)	1.03 (0.88-1.22)	0.69		
Number of more children desired	1 (0-2)	1 (0-2)	0.94 (0.83-1.05)	0.28		
Currently pregnant or trying to become pregnant	71 (18.2)	1320 (19.4)	0.86 (0.61-1.22)	0.40		
Currently in relationship with study partner at this visit	369 (85.6)	7329 (87.5)	0.91 (0.56-1.48)	0.70		
Sexual behavior since prior visit						
Number of sex acts with study partner	3 (1-8)	4 (1-8)	0.98 (0.96-1.01)	0.19		
Any condomless sex with study partner	152 (35.9)	2547 (30.7)	1.34 (1.02-1.77)	0.04	1.33 (1.01-1.77)	0.04
Any sex with outside partner(s)	43 (10.0)	988 (11.8)	0.95 (0.62-1.46)	0.82		
STI symptoms	25 (5.8)	228 (2.7)	1.55 (0.74-3.24)	0.24		
HIV-related characteristics						
CD4 count (cells/ μ l) of partner living with HIV	471 (293-611)	511 (344-712)	1.00 (0.99-1.00)	0.03	1.00 (0.99-1.00)	0.54
Plasma HIV RNA (log ₁₀ copies/mL) of partner living with HIV	4.1 (1.6-4.8)	2.2 (1.5-4.4)	1.28 (1.15-1.42)	<0.001	1.16 (1.04-1.31)	0.01
Partner living with HIV on ART at this visit	256 (61.1)	5975 (73.9)	0.56 (0.40-0.78)	<0.001	0.74 (0.51-1.07)	0.11
Psychosocial and behavioral characteristics						
HIV-related stigma	8.0 (6.0-10.0)	7.0 (4.0-8.0)	1.13 (1.06-1.20)	<0.001	1.11 (1.04-1.19)	0.01
Heavy alcohol use	125 (29.0)	1465 (17.5)	1.66 (1.10-2.51)	0.02	1.83 (1.18-2.82)	0.01
Social support	3.5 (2.8-4.0)	3.8 (3.4-4.0)	0.48 (0.36-0.64)	<0.001	0.72 (0.52-1.00)	0.05
Relationship satisfaction with study partner	27.0 (21.0-31.0)	32.0 (28.0-35.0)	0.89 (0.87-0.91)	<0.001	0.91 (0.89-0.94)	<0.001
Happy in relationship with study partner	328 (76.6)	7596 (90.6)	0.37 (0.25-0.56)	<0.001	0.70 (0.45-1.10)	0.12
Reported abuse	11 (2.6)	39 (0.5)	4.31 (2.16-8.59)	<0.001	2.73 (1.48-5.02)	0.01

OR=Odds Ratio; CI=Confidence Interval; STI=sexually transmitted infection; ART=antiretroviral therapy

¹Data are n/N(%) or median (IQR). The number of data points assessed is the total number of visits with each characteristic during study follow-up, stratified by probable depression.

²Cognitive, behavioral disengagement, and somatic depressive symptoms were assessed with a Likert response scale ranging from 1 ("Not at all") to 4 ("Extremely"). A mean score >1.75 was indicative of "probable depression".

³Multivariable models adjusted for study site and all other factors associated with probable depression in the univariable models, as determined by $p\text{-value} \leq 0.10$.

Table 3. Associations between depression and low PrEP adherence¹ during study follow-up (n=903 participants)

		Unadjusted GEE Analysis		Adjusted GEE Analysis ³		Adjusted MSM Analysis ⁴	
HIV-uninfected women (N=312)							
	Visits with low PrEP adherence ² (N=386/1433 visits)	RR (95% CI)	p-value	aRR (95% CI)	p-value	aRR (95%CI)	p-value
Probable depression ⁵	39 (41.1)	1.46 (1.05-2.03)	0.02	1.77 (1.14-2.77)	0.01	1.53 (1.05-2.23)	0.03
No probable depression	347 (25.9)	REF	REF	REF	REF	REF	REF
HIV-uninfected men (N=591)							
	Visits with low PrEP adherence ² (N= 890/2865 visits)	RR (95% CI)	p-value	aRR (95% CI)	p-value	aRR (95%CI)	p-value
Probable depression ⁵	29 (35.8)	1.16 (0.75-1.81)	0.49	1.18 (0.73-1.91)	0.50	1.28 (0.78-2.12)	0.32
No probable depression	861 (30.9)	REF	REF	REF	REF	REF	REF

GEE=Generalized Estimating Equations; MSM=Marginal Structural Models; RR=Risk Ratio; aRR=adjusted Risk Ratio; CI=Confidence Interval

¹Participants were considered to have low adherence if they opened their pill bottles <80% of the expected days between study visits, based on MEMs caps data.

²Data are n/N(%) or median (IQR)

³GEE models adjusted for study site, age, stigma, social support, fertility intentions, and condomless sex with their study partner since the prior visit, which were selected *a priori*, as well as relationship satisfaction with study partner which resulted in a >10% change in the unadjusted RR in models for both men and women.

⁴Weighted marginal structural model is adjusted for marital status, age, heavy alcohol use, relationship satisfaction, plasma HIV RNA concentration in the partner living with HIV, and depression history.

⁵Defined as HSCL-D mean score >1.75

Chapter 3. The Effect of Depression on Adherence to HIV Pre-Exposure Prophylaxis Adherence among High-Risk South African Women in HPTN 067/ADAPT

Citation: Velloza J, Heffron R, Amico KR, Rowhani-Rahbar A, Hughes JP, Li M, Dye BJ, Celum C, Bekker LG, Grant RM, HPTN 067/ADAPT Study Team. The Effect of Depression on HIV Pre-Exposure Prophylaxis Adherence among High-Risk South African Women in HPTN 067/ADAPT. AIDS (under review).

The effect of depression on adherence to HIV pre-exposure prophylaxis among high-risk South African women in HPTN 067/ADAPT

Jennifer Velloza, MPH^{1,2}, Renee Heffron, MPH, PhD^{1,2}, K. Rivet Amico, PhD³, Ali Rowhani-Rahbar, MD, MPH, PhD¹, James P. Hughes, PhD^{4,5}, Maoji Li, MMath⁴, Bonnie J. Dye, MPH⁶, Connie Celum, MD, MPH², Linda-Gail Bekker, MBChB, PhD⁷, Robert M. Grant, MD, MPH^{8,9}; HPTN 067/ADAPT Study Team

Affiliations:

¹University of Washington, Department of Epidemiology, Seattle, WA, United States

²University of Washington, Department of Global Health, Seattle, WA, United States

³University of Michigan, Ann Arbor, MI, United States

⁴Fred Hutchinson Cancer Research Center, Seattle, WA, United States

⁵University of Washington, Department of Biostatistics, Seattle, WA, United States

⁶FHI 360, Durham, NC, United States

⁷The Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa

⁸University of California at San Francisco, San Francisco, CA, United States

⁹Gladstone Institute of Virology and Immunology, University of California at San Francisco, San Francisco, CA, United States

Corresponding Author:

Jennifer Velloza, MPH

International Clinical Research Center

University of Washington

Box 359927

325 Ninth Avenue

Seattle, WA 98104

Phone: 917-392-3561; Fax: 206-520-3831; Email: jvelloza@uw.edu

Conflicts of Interest & Source of Funding: RMG has been a site investigator for clinical trials funded by GlaxoSmithKline (GSK; managed by ViiV Healthcare) and Gilead Sciences to the Gladstone Institutes and the San Francisco AIDS Foundation. KRA received an unrestricted educational grant to the University of Michigan from Gilead Sciences (2015-2017). All other authors report no potential conflicts of interest.

This work was supported by award numbers UM1-AI068619, UM1-AI068617, UM1-AI068613, and R01 AI118575, from the NIH (National Institute of Allergy and Infectious Diseases [NIAID], National Institute of Mental Health [NIMH], and National Institute on Drug Abuse [NIDA]) to HPTN. This work was also supported in part by the Emory-CDC HIV/AIDS Clinical Trials Unit award number UM1AI069418 from the NIH (NIAID). JV was supported by the NIMH of the NIH (grant F31 MH113420). Gilead Sciences donated study medication to the NIH to support this study. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIAID, the National Institutes of Health, or the U.S. Centers for Disease Control and Prevention. The use of a trademark name herein does not indicate government endorsement.

Running Head: Depression and oral PrEP adherence

ABSTRACT

Background: Oral pre-exposure prophylaxis (PrEP) is highly efficacious in women when used daily but low adherence undermines effectiveness. Depression, which is common in African women, has been associated with low PrEP adherence and prior literature suggests it may negatively impact PrEP use through psychosocial factors like stigma but this has not yet been explored.

Methods: We analyzed data from South African women who participated in HPTN 067, an open-label oral PrEP trial conducted from 2011-2013. Participants were randomized to daily, time-driven, or event-driven PrEP regimens. Study visits occurred at 4, 12, and 24 weeks post-randomization. PrEP adherence was measured via Wisepill™ devices and self-report data collected at weekly interviews. We considered participants “adherent” at their 24-week visit if Wisepill™ and interview data indicated that $\geq 80\%$ of expected doses were taken in the prior month. Depressive symptoms were assessed at baseline using the 20-item Center for Epidemiological Studies-Depression (CES-D) scale; scores ≥ 16 indicate likely depression. We used marginal structural models to estimate the direct effect of likely depression at baseline on PrEP adherence at week 24 after controlling for confounders and mediating effects of stigma, social support, and PrEP optimism.

Results: At baseline, 79 (45.4%) of 174 women had likely depression. At week 24, 53.0% (N=87) of participants had high PrEP adherence. High adherence occurred less often among women with likely depression (N=35; 44.3%) compared with those without (N=52; 54.7%; adjusted relative risk [aRR]: 0.79; 95% confidence interval [CI]: 0.63-0.99). We found a direct effect of depression on adherence in models accounting for the mediating influence of stigma (aRR: 0.74; 95% CI: 0.51-0.97) and PrEP optimism (aRR: 0.75; 95% CI: 0.55-0.99).

Conclusions: Depression was common and associated with lower PrEP adherence among South African women. Depression screening and services integrated with PrEP delivery may improve PrEP effectiveness among African women.

Word count: 299/300

Keywords: Depression; HIV; Pre-exposure prophylaxis; Africa; Women; Mediation

INTRODUCTION

Daily oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) pre-exposure prophylaxis (PrEP) is >90% effective in preventing HIV transmission when adherence is high.^{1,3,4,6} While open-label and demonstration projects have shown that women at high risk for HIV are generally able to adhere to daily oral PrEP regimens, these studies also reported waning PrEP adherence over time.^{13,14} Qualitative studies have identified important psychosocial barriers to regular pill-taking for women in the context of placebo-controlled and early open-label PrEP trials including anticipated and experienced stigma, lack of social support, concerns about safety, and low perceptions of HIV risk and PrEP effectiveness.^{16,18} Mental health conditions, including depression, are also known barriers to healthcare engagement and medication adherence, and recent analyses have documented an influence of depressive symptoms on PrEP non-adherence.^{49,96}

Depression is highly prevalent worldwide, particularly among women who are 1.5-3 times more likely to experience lifetime depression than men.²¹ In addition, studies in the United States and sub-Saharan Africa have found that depressive symptoms are related to sexual behaviors, anticipated HIV-related stigma, and poor instrumental and emotional social support.^{35,51} HIV-infected women with elevated depressive symptoms often report higher levels of anticipated HIV-related stigma and lower social support than those without depression.⁹⁷ Depression, stigma, and social support can directly influence HIV treatment adherence and healthcare engagement,^{39,98} and these variables may indirectly influence HIV outcomes through their effects on one another and on optimism about HIV treatment approaches.^{39,98,99} Overall, this body of research

provides strong evidence of the high prevalence of depression among people living with HIV, the influence of depression on stigma, social support, and treatment optimism, and the potential for these factors to influence HIV acquisition and treatment adherence.

While the role of depression on PrEP adherence is gaining recognition,^{49,96,100} the complexity of the mechanism by which depression and other psychosocial barriers influence PrEP use remains poorly understood. To contribute information to this gap, we: 1) evaluated the total effect of depression on PrEP adherence and 2) explored whether the relationship between depression and adherence remained after accounting for potential psychosocial mediators among a cohort of 174 HIV-uninfected women participating in an open-label randomized trial in South Africa. We hypothesized that depression would be associated with low PrEP adherence and that the strength of this association would be altered by controlling for anticipated HIV-related stigma, instrumental social support, and optimism about PrEP efficacy.

METHODS

Study design and participants

The HIV Prevention Trials Network (HPTN) 067/Alternative Dosing to Augment PrEP Pill Taking (ADAPT) study was a randomized, open-label trial of daily versus intermittent oral emtricitabine/tenofovir (FTC/TDF)-based PrEP conducted from 2011-2014. The study enrolled high-risk women in Cape Town, South Africa and transgender women and men who have sex with men (MSM) in Bangkok and Harlem.^{13,101} This analysis is limited to cisgender female African participants because of the higher prevalence of depression among women,²¹ links between depression and PrEP

adherence in African women,⁹⁶ and pharmacokinetic data indicating that PrEP may be less forgiving to missed doses for vaginal than rectal HIV exposure.⁷⁹ Eligible women were HIV-antibody negative, ≥ 18 years old, literate in English or Xhosa, and had at least one risk factor for HIV in the six months prior to enrollment (e.g., sex with more than one partner, history of sexually transmitted infection).

Enrolled participants completed a five-week period of once a week directly-observed-dosing and were then randomly assigned to one of three FTC/TDF PrEP dosing regimens: daily (one tablet every day); time-driven (one tablet twice a week, plus a post-sex dose); and event-driven (one tablet before and after sex).¹³ Although we based the time- and event-driven regimens on available animal model data at the time when HPTN 067/ADAPT was designed, models now suggest that more regular PrEP dosing is likely needed to achieve protective drug concentrations in vaginal tissue.⁷⁹ Regimens were assigned in a 1:1:1 ratio for each site. After randomization and counseling about their dosing regimen, participants received a one-month supply of PrEP in an electronic dose monitoring device (Wisepill™). Follow-up visits occurred at 4, 12, and 24 weeks post-randomization and participants received HIV testing, counseling, and PrEP refills.

Data collection

Participants completed computer-assisted self-interviewing (CASI) surveys (in English or Xhosa) to provide data on depression, drug and alcohol use, HIV risk perception, sexual behavior, social support, stigma related to HIV and PrEP, and optimism about PrEP effectiveness.

Alcohol use was measured using the validated Alcohol Use Disorders Identification Test (AUDIT) scale (range 0-40; score ≥ 8 indicates heavy alcohol use).¹⁰² Illicit drug use was measured using the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) scale and was coded as a binary variable (any or none).¹⁰³ HIV risk perception was measured with a visual analogue scale item asking participants about the chance that they will get HIV at some point in their life. Responses ranged from 0 (no chance) to 8 (very high chance). A score ≥ 6 indicated high risk perception.

Depression was measured at the baseline and 24-week visits with the 20-item version of the Center for Epidemiologic Studies-Depression scale (CES-D).¹⁰⁴ A sum score ≥ 16 was indicative of likely depression (range 0-60). This cutoff value has been previously validated with women in sub-Saharan Africa and corresponds well with clinical depression diagnosis.¹⁰⁴

Anticipated HIV-related stigma was measured at the 12-week visit with two items asking participants whether they are worried that someone will see them taking a pill and think they have HIV. Those who endorsed either item were considered to anticipate stigma. Instrumental social support was measured at the 12-week visit with two items asking whether participants receive help taking PrEP from 1) family or friends or 2) from study staff. Those who endorsed either item were considered to have instrumental social support related to PrEP. PrEP optimism was measured at the 12-week visit with five items asking about the degree to which participants feel that PrEP protects them from a HIV. Scores from the Likert response scales were summed and classified into a binary variable around the “neither agree nor disagree” response (1= high levels of PrEP optimism; 0= low levels of PrEP optimism).

PrEP use was measured with Wisepill™ electronic monitoring devices that record a date-time stamp with every closure and transmit the data to a cloud-based database. Trained staff also conducted weekly in-person or phone interviews to collect dates, times, and types of sex ‘events’ in the prior week. These data were used to calculate the expected number of PrEP doses for participants in the event-driven and time-driven arms. Weekly interviews were also used to adjust Wisepill™ recorded times for doses removed and taken later or for openings not associated with pill-taking.

Adherence was defined as the percentage of PrEP doses taken out of expected doses during the period between 20 and 24 weeks. The number of expected doses excluded days for which PrEP was not dispensed due to missed visits, protocol-defined stops, or refill refusals. Participants were considered to have high adherence at the 24-week visit if $\geq 80\%$ of expected doses were taken in the prior month. This cutoff corresponds to 5-6 doses per week and has been associated with high levels of plasma drug concentrations and protection against HIV.^{79,80} We excluded visits when event-driven arm participants were not expected to have taken PrEP doses (N=13).

Statistical analyses

We estimated the population-level total effect of depression on PrEP adherence using marginal structural models to adjust for confounding variables. We first computed stabilized inverse probability weights using logistic regression to predict the probability of having likely depression. These exposure weights were calculated with age, marital status, education, alcohol and drug use, HIV risk perception, and condomless sex, identified *a priori* because of their known associations with depression and adherence.¹⁵

These weights were included in regression models with a log link, binomial distribution, and robust standard errors to estimate relative risks.

We similarly used marginal structural models to estimate controlled direct effects of depression on PrEP adherence separately for each mediator. This modeling approach allowed us to quantify the magnitude of the association between depression and PrEP adherence that remained after removing any downstream influence of anticipated stigma, instrumental social support, and PrEP optimism on adherence, while also accounting for mediator-outcome confounders that were affected by the exposure. The controlled direct effect estimates the amount that PrEP adherence would change, on average, if everyone in the population changed from not depressed to depressed and the mediators were held at a fixed level. We hypothesized that depression was related to anticipated HIV-related stigma, instrumental social support to take PrEP, and PrEP optimism at week 12, which in turn influenced PrEP adherence at week 24 (Figure 3). We calculated stabilized inverse probability weights for each mediator using the depression exposure and the same variables from the exposure weight models. We then multiplied the mediator weights by the exposure weights to calculate total weights for each mediator. The total weights were included in regression models and we ran separate regression models for each mediator.

Before conducting our analyses, we used Monte Carlo Markov Chain (MCMC) models to impute missing confounder and mediator variable data over six datasets. For binary variables, imputed data were rounded to the nearest whole number. We ran our models on the full sample in each imputed dataset and combined the resulting estimates using Rubin's method.

We conducted several additional analyses to explore whether our findings were robust to changes in variable measurement and imputation procedures. First, we repeated our marginal structural model analyses using a binomial distribution and identity link to estimate risk differences for the total and direct effects. Second, we tested for the presence of moderated-mediation between the exposure and each of the mediators by calculating controlled direct effects with interaction terms in the models. Third, we examined the dose-response relationship for the total effect by varying the definition of PrEP adherence to $\geq 70\%$ and $\geq 95\%$ of expected PrEP doses. Fourth, we restricted our total and direct effect models to participants in the daily arm only (N=57) and those who had complete mediator and confounder data available (N=158). Finally, we conducted quantitative bias analysis to estimate the potential influence of a binary unmeasured confounder of the relationship between mediators and PrEP adherence. We specified a range of bias parameter values (e.g., the prevalence of intimate partner violence in the population and its influence on PrEP) and examined the bounds within which our findings remained significant.

All analyses were conducted using SAS 9.4 (Cary, North Carolina, USA).

Ethical statement

Ethical approval was obtained by the Human Research Ethics Committee (HREC) in South Africa and the protocol was reviewed by the National Institutes of Health (NIH) Division of AIDS (DAIDS) prior to implementation. Participants provided written informed consent in their preferred language. The protocol was registered at ClinicalTrials.gov (identifier NCT01327651).

RESULTS

Participant characteristics

A total of 178 HIV-uninfected South African women were enrolled and randomized in the HPTN 067 study. Among the 174 women (97.8%) with CES-D scores at baseline, 57 (32.8%) were randomized to daily PrEP, 58 (33.3%) were in the time-driven arm, and 59 (33.9%) were in the event-driven dosing arm (Table 4). Almost half of the participants (N=79; 45.4%) had CES-D scores ≥ 16 . The median age at enrollment was 26 years (interquartile range [IQR] 21, 37 years). CES-D scores remained consistent throughout study follow-up and 46.7% of participants had scores ≥ 16 at their final study visit (N=77 of 164 participants retained). Among four women who seroconverted during follow-up, none had likely depression at baseline and only one had high PrEP adherence at the 12-week visit.

Retention rates were high throughout follow-up (>90% attended all visits) and did not differ by arm or CES-D scores. Prior to imputation, we had complete exposure, mediator, and outcome data for 159 (91.4%) participants. Week 12 visit data on all mediators were available for 162 of 174 participants (93.1%). Approximately 16.0% of participants (N=26) reported high levels of PrEP optimism, 14.2% (N=23) reported anticipated HIV-related stigma, and 31.5% (N=51) reported instrumental social support related to PrEP use at week 12. Missing mediator and confounder data were not associated with depression or PrEP adherence. We had PrEP adherence data at week 24 for 164 participants (94.3%).

Total effect of depression on PrEP adherence

High PrEP adherence ($\geq 80\%$) was detected among 53.0% of 164 participants with week 24 adherence data ($N=87$) and occurred less often among women with depression than among women without depression (44.3% versus 54.7%, chi-squared test statistic: 2.78, p -value: 0.09). After adjusting for confounders, women with depression were less likely to have high PrEP adherence than women without depression (adjusted risk ratio [aRR]: 0.79, 95% confidence interval [CI]: 0.63, 0.99, Table 5). Our findings were robust to changes in the sample: the total effect remained statistically significant for participants who had complete data available prior to imputation (aRR: 0.77, 95% CI: 0.56, 1.00) and was a similar magnitude for participants in the daily dosing arm (aRR: 0.71, 95% CI: 0.41, 1.24). The strength of the association decreased with PrEP adherence cutoffs of 70% (aRR: 0.89, 95% CI: 0.76, 1.03) and 95% (aRR: 0.91, 95% CI: 0.77, 1.09) of expected doses. There were 15 fewer participants with high PrEP adherence per 100 participants with depression compared to participants without depression (adjusted risk difference [aRD]: -0.15, 95% CI: -0.31, 0.01; Table 5).

Controlled direct effect of depression on PrEP adherence

In our model using anticipated stigma as a mediator of the association between depression and PrEP adherence, we estimated a statistically significant controlled direct effect of 0.74 (95% CI: 0.51, 0.97; Table 6), which was quite similar to the total effect estimate. The point estimates for the direct effect did not change considerably in models with an interaction term between depression and HIV-related stigma (aRR among those without stigma: 0.74, 95% CI: 0.52-1.05; aRR among those with stigma: 0.75, 95% CI: 0.29-1.98). There were 18 fewer participants with high PrEP adherence per 100

participants with depression compared to participants without depression, while holding stigma values fixed (aRD: -0.18, 95% CI: -0.35, -0.01, p-value: 0.04).

Considering instrumental social support as a mediator, we estimated controlled direct effect point estimates that were similar to the total effect on both the relative (aRR: 0.77, 95% CI: 0.57, 1.03) and absolute scales (aRD: -0.15, 95% CI: -0.32, 0.02), although without statistical significance (Table 6). We did not detect a meaningful interaction effect between depression and social support (aRR among those without social support: 0.79, 95% CI: 0.55-1.13; aRR among those with social support: 0.72, 95% CI: 0.27-1.92). The controlled direct effect was also not substantially changed when PrEP optimism was included as the mediating factor: we found a statistically significant direct effect on the relative scale (aRR: 0.75, 95% CI: 0.55, 0.99) but not on the absolute scale (aRD: -0.15, 95% CI: -0.32, 0.01). However, the controlled direct effect point estimates changed when including an interaction term between depression and PrEP optimism (aRR among those without optimism: 0.69, 95% CI: 0.50-0.98; aRR among those with optimism: 1.19, 95% CI: 0.37-2.03).

Our controlled direct effect coefficients were robust to changes in the definition of PrEP adherence, although they were no longer statistically significant when PrEP adherence was defined as $\geq 95\%$ of expected doses or in the sample of daily arm participants. They were similar in magnitude and statistical significance among those with complete data before imputation. Our bias analysis indicated that an unmeasured confounder of the mediator and outcome relationship would need to have a 35% prevalence difference between depressed and non-depressed individuals and a strong

effect on PrEP adherence (RR ≥ 2.00) to alter our findings of a statistically significant controlled direct effect.

DISCUSSION

In this open-label randomized evaluation of PrEP dosing regimens in South Africa, women with depression were less adherent to PrEP. Anticipated stigma, instrumental social support, and optimism were not mediators of this association. This finding is particularly important given that in this cohort and other sub-Saharan African settings the burden of depression is quite high among women and women have been found to experience difficulty adhering to daily oral PrEP over time.^{13,21}

Consistent with these findings, another recent analysis found that depressive symptoms had a strong negative influence on PrEP adherence among women in Kenya and Uganda.⁹⁶ A study in the United States reported that depression was associated with low PrEP adherence among MSM.¹⁰⁰ Work from the iPrEX OLE team found that depression may have a stronger effect on adherence for women than men, pointing to possible gender differences in depression severity or the mechanism by which depression influences adherence.⁴⁹ Links between depression and antiretroviral therapy and oral contraceptive adherence have also been established.^{24,36(p)} These data suggest that the relationship between depression and adherence may be generalized across medications and settings.

The mechanisms for the association between depression and daily medication use are not well-understood. Depression could lead to lower healthcare engagement and is a predictor of feelings of social isolation and lower trust in sexual partners and

medical personnel.¹⁰⁵ Among individuals at risk of HIV, these feelings could lead to changes in perceived HIV risk, self-care, anticipated stigma related to HIV or PrEP, and instrumental and emotional social support to continue using daily PrEP.^{16,39,105}

Depression has also been linked with changes in sexual behavior. In Eastern Africa, depressive symptoms were associated with increased condomless sex and partners, but other analyses found that depression was related to reduced frequency of sexual intercourse.^{106,107} Within the context of PrEP delivery, these dynamic changes in sexual behavior related to depression could affect a woman's need and desires for PrEP. In this analysis, we did not find a mediated effect of the relationship between depression and PrEP adherence by stigma, social support, or optimism about PrEP effectiveness after controlling for sexual behavior. There are two potential explanations for our results: 1) these variables truly do not mediate the relationship between depression and PrEP adherence or the direct association between depression and adherence is stronger than any indirect association through these factors; or 2) these variables do mediate the relationship but were mismeasured or measured too infrequently for us to detect a change in the controlled direct effect. While our results have interestingly pointed to a robust association between depression and PrEP adherence, future studies are needed to understand the mechanism of this effect.

The strengths of this study include the prospective cohort which allowed us to establish temporality of the association between depression, PrEP adherence, and potential mediators. Data on depressive symptoms were collected using a validated screening tool and data on PrEP use were rigorously collected with electronic monitoring devices and adjusted using weekly interview data. Overall retention rates

were high in the sample and bias due to differential attrition by depressive symptoms was likely minimal.

Limitations of this study included a small sample size and infrequent measurement of depression and mediators which reduced our ability to assess change over time. However, CES-D scores were stable between baseline and Week 24 indicating that depression may have remained consistent. We were unable to examine serial mediation because the mediators were all measured at the same visit. Scales for stigma, social support, and PrEP-related optimism were adapted from instruments for ART use but had not been previously validated and the binary classification of these mediators may have resulted in measurement error. In addition, there may be non-differential misclassification of binary depression status with respect to adherence, which would have attenuated our estimates. The HPTN 067 protocol was not designed with this analysis in mind, and there are limitations of unmeasured (e.g., intimate partner violence), infrequently measured (e.g., drug and alcohol use), and potentially mismeasured confounders. In estimating the controlled direct effect, we were particularly concerned about unmeasured confounding of the exposure and mediator and mediator and outcome relationships. However, sensitivity analyses indicated that a confounder would need to have a strong association with the outcome and be relatively common in our population to alter conclusions. PrEP adherence was measured via electronic device and self-report, both of which may be biased. We could not examine effects on continuous PrEP dosing or drug concentrations because participants in the event-driven and time-driven arms had less consistent PrEP use by design. Finally, our

findings may not be generalizable to populations accessing PrEP through public programs.

The controlled direct effect estimate allows us to understand the public health relevance of intervening on stigma, social support, and PrEP optimism among a population of high-risk women taking PrEP. Our results showing the robust effect of depression on lower PrEP adherence point to a potential need for future interventions to incorporate mental health services with PrEP delivery for women. Moreover, interventions targeting stigma, social support, and optimism about PrEP effectiveness may not have a substantial impact at improving PrEP adherence in this population. Interventions integrating depression care into existing ART and prenatal care programs are being implemented with success in sub-Saharan Africa which suggests that depression services can be implemented in busy healthcare settings.⁹⁴ While additional research is necessary to understand the mechanisms by which depression influences PrEP adherence, our results support the integration of regular depression screening, referral, and treatment into PrEP delivery programs which may reduce the burden of depression, improve PrEP effectiveness, and prevent PrEP from becoming a missed public health opportunity among African women.

Word Count: 3500/3500

ACKNOWLEDGMENTS

The authors thank the individuals who participated in the study, the team at the Emavundleni Clinical Research Site in Cape Town, South Africa, and the HIV Prevention Trials Network that supported data collection and management for this work.

TABLES AND FIGURES

Figure 3. Directed acyclic graph of the relationships between depressive symptoms, mediators, and PrEP adherence over follow-up

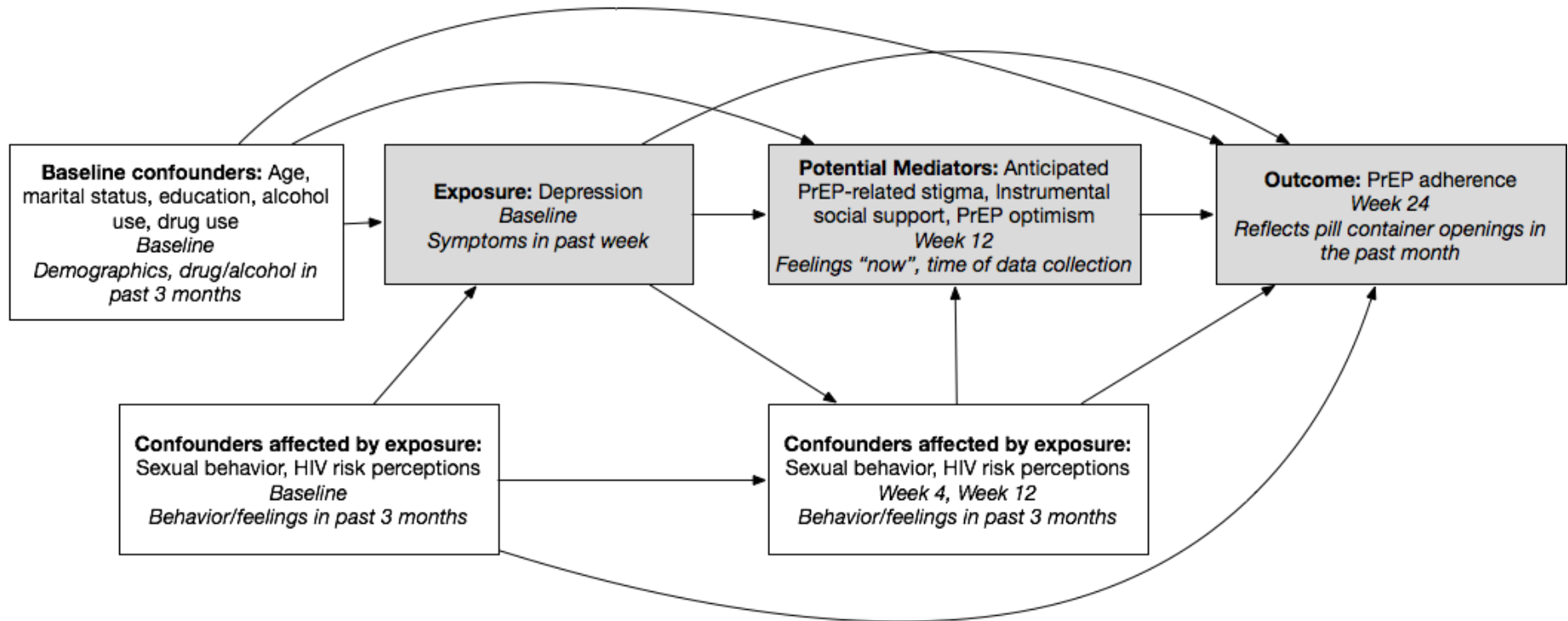


Table 4. Characteristics of the study sample, by study arm (N= 174 unless otherwise indicated)

Characteristic	CES-D Score	
	CES-D <16 (N=95; 54.6%)	CES-D ≥16 (N=79; 45.4%)
Randomized arm		
Daily	30 (31.6%)	27 (34.2%)
Time-driven	35 (36.8%)	23 (29.1%)
Event-driven	30 (31.6%)	29 (36.7%)
≤25 years old	56 (59.0%)	31 (39.2%)
Never married	75 (79.0%)	66 (83.5%)
Secondary education completed	42 (44.2%)	18 (22.8%)
Black ethnic origin	94 (99.0%)	79 (100.0%)
Number of sex partners, 3 months prior to enrollment	1 (1-1)	1 (1-1)
Number of vaginal or anal sex acts, 3 months prior to enrollment	5 (2-11)	4 (1-6)
Any sex without a condom, 3 months prior to enrollment (N=167)	58 (62.4%)	43 (58.1%)
Transactional sex (N=172)	5 (5.3%)	11 (14.1%)
Drug use	8 (8.4%)	14 (17.7%)
AUDIT score ≥8	24 (25.3%)	28 (35.4%)
HIV risk perceptions		
Low chance of becoming HIV infected	57 (60.0%)	41 (51.9%)
High chance of becoming HIV infected	5 (5.3%)	13 (16.5%)
Unknown chance of becoming HIV infected	33 (34.7%)	25 (31.7%)
Anticipated stigma at Week 12 (N=162)	9 (10.2%)	14 (18.9%)
Instrumental social support at Week 12 (N=162)	27 (30.7%)	24 (32.4%)
PrEP optimism at Week 12 (N=162)	12 (13.6%)	14 (18.9%)

Data are presented as number (%) for categorical variables and median (interquartile range [IQR]) for continuous variables. CES-D= Center for Epidemiologic Studies Depression scale; AUDIT= Alcohol Use Disorders Identification Test

Table 5. Total effect estimates for the association between depression and PrEP adherence (N=164 participants with PrEP adherence data available at Week 24)¹

	Visits with high PrEP adherence¹ (N=87; 53.0%)	Relative scale²		Absolute scale²	
		RR (95% CI)	p-value	aRD (95% CI)	p-value
Depression	35 (44.3%)	0.79 (0.63, 0.99)	0.05	-0.15 (-0.31, 0.01)	0.07
No depression	52 (54.7%)	REF	REF	REF	REF

aRR= adjusted relative risk; aRD= adjusted risk difference; 95% CI= 95% confidence interval

¹Participants were considered adherent to PrEP if their adjusted Wisepill data indicated that they had taken $\geq 80\%$ of expected pills at the Week 24 study visit

²Stabilized inverse probability weights account for confounding by the sets of baseline confounders (age, marital status, education, alcohol use, drug use) and longitudinal confounders (any unprotected sex, HIV risk perceptions; weight mean=0.99; range=0.47-2.38)

Table 6. Controlled direct effect estimates for the association between depression and PrEP adherence¹ for each mediator (N=164 participants with PrEP adherence data available at Week 24)

Exposure	Mediator	Outcome	Relative scale ²		Absolute scale ²	
			aRR (95% CI)	p-value	aRD (95% CI)	p-value
Depression	Stigma	PrEP adherence	0.74 (0.51, 0.97)	0.02	-0.18 (-0.35, -0.01)	0.04
Depression	Social support	PrEP adherence	0.77 (0.57, 1.03)	0.07	-0.15 (-0.32, 0.02)	0.09
Depression	PrEP optimism	PrEP adherence	0.75 (0.55, 0.99)	0.05	-0.15 (-0.32, 0.01)	0.08

aRR= adjusted relative risk; RD= adjusted risk difference; 95% CI= 95% confidence interval

¹Participants were considered adherent to PrEP if their adjusted Wisepill data indicated that they had taken ≥80% of expected pills at the Week 24 study visit

²Stabilized inverse probability weights account for confounding by the sets of confounders and mediator (depression weight: mean=0.99; range=0.47-2.38; stigma weight: mean=0.98; range=0.41-3.12; social support weight: mean=0.99; range=0.38-3.12; optimism weight: mean=0.98; range=0.38-2.50)

Chapter 4. The Influence of HIV-Related Stigma on PrEP Disclosure and Adherence among Adolescent Girls and Young Women in HPTN 082: A Qualitative Study

TITLE PAGE**The influence of HIV-related stigma on PrEP disclosure and adherence among adolescent girls and young women in HPTN 082: a qualitative study**

Jennifer Velloza, MPH^{1,2}, Nomhle Khoza³, Fiona Scorgie, PhD³, Miria Chitukuta⁴, Prisca Mutero⁴, Kudzai Mutiti⁴, Nomvuyo Mangxilana⁵, Lumka Nobula⁵, Michelle A. Bulterys, BA^{1,2}, Millicent Atujuna, PhD⁵, Sybil Hosek, PhD⁶, Renee Heffron, MPH, PhD^{1,2}, Connie Celum, MD, MPH^{1,2,7}, Sinead Delany-Moretlwe, MBChB, PhD³ for the HPTN 082 study group

Affiliations:

¹University of Washington, Department of Epidemiology, Seattle, WA, United States

²University of Washington, Department of Global Health, Seattle, WA, United States

³Wits Reproductive Health & HIV Institute (Wits RHI), Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

⁴University of Zimbabwe College of Health Sciences Clinical Trials Research Centre, Harare, Zimbabwe

⁵The Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa

⁶Stroger Hospital of Cook County, Department of Psychiatry, Chicago, United States

⁷University of Washington, Department of Medicine, Seattle, United States

Corresponding Author:

Jennifer Velloza, MPH
International Clinical Research Center
University of Washington
Box 359927
325 Ninth Avenue
Seattle, WA 98104
Phone: 917-392-3561
Fax: 206-520-3831
Email: jvelloza@uw.edu

Conflicts of Interest & Source of Funding: The authors report no potential conflicts of interest.

This work was supported by award numbers UM1-AI068619, UM1-AI068617, and UM1-AI068613, from the NIH (National Institute of Allergy and Infectious Diseases [NIAID]) to HPTN. JV was supported by the NIMH of the NIH (grant F31 MH113420). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Running Head: Stigma, disclosure, and oral PrEP adherence

Target Journal: JIAS

ABSTRACT

BACKGROUND: Oral pre-exposure prophylaxis (PrEP) is highly efficacious, however, low adherence undermines efficacy. Stigma and disclosure concerns were key barriers to PrEP adherence for adolescent girls and young women (AGYW) in clinical trials, but this has not been explored in open-label studies.

METHODS: HPTN 082 was an open-label PrEP study among AGYW (ages 16-24) in Harare, Zimbabwe and Cape Town and Johannesburg, South Africa from 2016-2018. Serial in-depth interviews were conducted among a purposive sub-sample of 67 AGYW to explore experiences of stigma, disclosure, and PrEP adherence — dynamic constructs that often change over time. Participants were interviewed after their 13-week and 26-week study visits. We analyzed data by coding transcripts and using memo-writing and diagramming to summarize themes.

RESULTS: AGYW described two types of stigma, particularly during the first interview: stigma related to sexual activity (e.g., “people say I’m a prostitute”) and being perceived to be living with HIV because of taking antiretrovirals (e.g., “my husband’s friends say I’m HIV infected”). Stigma was both anticipated and experienced and was often mentioned in relation to product disclosure. Participants who anticipated stigma were reluctant to disclose PrEP use and reported adherence challenges. Disclosure also regularly resulted in stigmatizing experiences. Across all sites, negative descriptions of stigma and disclosure issues were more common in the first interview than the second. By the second interview, participants often described disclosure as an “empowering” way to combat community-level PrEP stigma and many became “community PrEP ambassadors”, which improved their ability to take PrEP and encourage others to use PrEP. These empowering disclosure experiences were facilitated by ongoing HPTN 082 study activities (e.g., counseling sessions, adherence clubs) when they could discuss PrEP-related stigma, disclosure, and PrEP adherence issues.

CONCLUSIONS: Stigma and disclosure issues were initial concerns for African AGYW initiating PrEP but many were empowered to disclose PrEP use over time, which helped them cope with stigma and feel more able to take PrEP regularly. PrEP programs can foster disclosure through community and clinic-based discussion, adherence clubs, and activities normalizing sexual behavior and PrEP use, which can reduce stigma and improve PrEP adherence and thus effectiveness.

Word count: 350/350

KEYWORDS: Stigma; Disclosure; HIV; Pre-exposure prophylaxis; Africa; Women

INTRODUCTION

Daily oral tenofovir-based pre-exposure prophylaxis (PrEP) is >90% effective in preventing HIV transmission when taken with high adherence.^{1,3,4,6,12,108} Daily adherence however, can be challenging, as observed among women at high risk for HIV who participated in blinded, placebo randomized controlled trials of oral and topical tenofovir-based PrEP.^{16,108,109} Suboptimal adherence in the trials was largely attributed to concerns around product safety, effectiveness, and anticipated and experienced stigma around PrEP use.^{16,108,109} “Anticipated stigma” in this context includes fears about negative societal reactions to PrEP use, while “experienced stigma” describes social discrimination actually resulting from PrEP use.^{15,16,109,110} In some contexts, PrEP has been stigmatized because of the medication’s more familiar use to treat HIV, and individuals may be mistakenly labeled as “HIV positive” if they are seen with PrEP pills.^{56,111,112} People have also expressed concerns that PrEP use could promote sexual promiscuity and high-risk sexual activity, which can lead to stigma around sexual activity among AGYW.^{56,113,114}

Since the efficacy trials, open-label and implementation projects have found that women with substantial HIV risk use PrEP regularly when they know they are using a safe and effective prevention product.^{13,14,18} These studies also report waning adherence and/or PrEP discontinuation over time, with stigma remaining as a barrier to effective PrEP use during periods of HIV risk in many settings.^{13,14,18} Stigma can be particularly high in contexts where community knowledge and awareness about PrEP is low, gender and cultural norms dictate that women should not be sexually active or should practice monogamy, and where PrEP is marketed primarily as a tool for key

populations.^{113,115–117} Quantitative analyses among men who have sex with men (MSM) have found that stigma significantly reduces PrEP uptake and adherence.^{113,118–120} Stigma may influence PrEP adherence after PrEP use is intentionally or unintentionally disclosed, and qualitative work in sub-Saharan Africa describes women's need to discretely use HIV prevention products, hide their products at home, and miss product doses because of concerns around anticipated and experienced stigma.^{18,115,121}

The influence of stigma on disclosure and PrEP use has not been well-explored among adolescent girls and young women (AGYW) in sub-Saharan Africa, whose experiences of stigma, disclosure, and PrEP use may be quite different than those in older female or MSM populations. Moreover, PrEP-related stigma, attitudes toward PrEP use, and experiences with disclosure could dynamically shift over time as community knowledge of PrEP increases and PrEP becomes more normative, although this has not yet been studied.^{116,122,123} To contribute to this gap, we conducted a qualitative analysis to describe experiences of PrEP-related stigma and changes in PrEP stigma, disclosure, and adherence over time using serial, in-depth interview data from AGYW in South Africa and Zimbabwe, as part of a larger PrEP randomized controlled trial conducted during an evolving period of national PrEP roll-out in both countries.

METHODS

Study design and participants

The HIV Prevention Trials Network (HPTN) 082/HERS study was a randomized, open-label clinical trial assessing characteristics of AGYW who accept and adhere to

daily oral emtricitabine/tenofovir (FTC/TDF)-based PrEP. Importantly, this study was conducted when national PrEP guidelines and initial demonstration projects in South Africa and Zimbabwe focused on female sex workers (FSWs). During the trial, these programs were subsequently expanded to include AGYW from the general population accompanied by public demand-creation activities (e.g., radio and television campaigns, advertisements). The study enrolled sexually active young women, ages 16-25, in Johannesburg and Cape Town, South Africa and Harare, Zimbabwe and was conducted from 2016-2018. Eligible women were HIV- negative, literate in one or more of the study languages (English, isiXhosa, isiZulu, SeSotho, Shona), sexually active (reporting vaginal or anal intercourse in the month prior to screening), and at high risk of HIV as determined by an empiric risk score previously used in this setting.¹²⁴

Participants were screened, enrolled, and offered daily oral PrEP at enrollment. Those who accepted PrEP were then randomly assigned in a 1:1 ratio, stratified by site, to one of two PrEP adherence support interventions: 1) a standard adherence package that included adherence support sessions, weekly short message service (SMS) reminder messages, and monthly in-person adherence support clubs (control arm), or 2) all standard adherence package components plus counseling based on observed PrEP drug levels measured during the previous study visit (“drug-level feedback”, intervention arm). Follow-up visits occurred at 4, 8, 13, 26, 39, and 52 weeks post-enrollment and participants underwent HIV testing and counseling and PrEP refills at all visits. Those who declined PrEP at enrollment were followed over time to continually offer PrEP and standard of care HIV prevention counseling. PrEP adherence was measured during follow-up using dried blood spots (DBS). Intracellular tenofovir

diphosphate (TFV-DP) levels in DBS were batch tested at the University of Cape Town Pharmacology laboratory, which participated in validation with the University of Colorado laboratory that developed the assay.¹²⁵

Qualitative sampling and recruitment

Participants were purposively recruited for this qualitative sub-study from the cohort enrolled in HPTN 082/HERS. We planned to recruit up to 25 participants per study site, a sample size adequate to achieve saturation of key themes. As much as possible, we stratified participant selection by three groups: those who accepted PrEP and adhered well to PrEP by week 4, those who accepted PrEP but had difficulty adhering to PrEP by week 4, and those who continually declined PrEP through the first 12 weeks of follow-up. At each site, we also selected approximately 2-4 participants who were considered to be “interesting cases”, such as participants who had a protocol-defined PrEP stop (e.g., due to pregnancy, creatinine levels, or a potential HIV seroconversion).

Potential participants were recruited by phone or upon arrival for HPTN 082 study visits. All participants were asked to complete one interview after their 13-week study visit and a second interview after their 26-week study visit. Interviews were scheduled either on the day of the routine HPTN 082 study visit or on another day at the participant’s convenience. Study staff contacted participants by phone for appointment reminders and rescheduling.

Data collection

Semi-structured in-depth interview guides were developed based on literature reviews and prior experiences with research on PrEP delivery and HIV prevention.

Guides were translated into all study languages and were revised throughout data collection to improve question clarity and response quality. The 13-week interview guide included questions and probes related to: 1) PrEP information in the community, 2) motivations to participate and take PrEP, 3) facilitators and barriers to PrEP uptake, 4) PrEP disclosure experiences, 5) PrEP adherence and difficulties taking PrEP, and 6) influence of family, friends, and sexual partner(s) on PrEP use. Interviews conducted with PrEP decliners also explored reasons for not taking PrEP. The 26-week interview covered similar topics and asked about changes that were experienced in these themes since the prior interview. Participants were also asked about their experiences with the HPTN 082/HERS interventions.

Interviews were carried out by female qualitative researchers with prior experience conducting in-depth interviews among AGYW in each site's local language. Interviewers were not involved in providing clinical care for participants and they received training on the study guides prior to data collection. Participants were informed that their participation in the interviews would not affect their clinical care or study participation. Interviews were conducted in participants' preferred language and were audio-recorded. Each interview lasted approximately 45 minutes and was conducted in a quiet, private area of the study site. Interview recordings were transcribed and translated into English. Transcripts were reviewed by the sites' qualitative teams to check for accuracy.

Data analysis

We analyzed data using thematic and case-specific approaches. For our thematic analysis, we used the constant comparative method where we developed an

initial codebook from themes arising in the data and refined the codebook through team discussions during the coding process.⁵⁸ Transcripts were imported into NVivo (versions 11 and 12; QSR International, Melbourne, Australia) and each transcript was coded independently by one member of the study team (JV, NK, FS, MB, PM, LM, NM, MA, or SH). One member of the study team (FS) reviewed coding for approximately 20% of the transcripts and disagreements in code application were resolved through discussion until consensus was reached. We iteratively analyzed the data by reviewing the codes, writing analytic memos, and using diagramming techniques to identify key themes across transcripts and participant characteristics. The analytical work included in-person workshops with study team members from all three sites.

We also utilized a case-specific analytic approach to identify changes in participants' narratives over time. After reviewing interview transcripts and coded text, one team member (JV) developed a participant-level matrix of key themes from the 13-week and 26-week interviews. We examined themes in the matrix by site, demographics, and reported PrEP use and wrote summary memos on longitudinal patterns in the qualitative data.

Ethical statement

This qualitative study received ethical approval from review boards at the University of the Witwatersrand, University of Zimbabwe, University of Cape Town, University of California – San Francisco, and University of Washington, as part of the HPTN 082/HERS study. All participants provided written informed consent (or assent with consent from a parent or legal guardian if <18 years old) in their preferred language

prior to participation. The protocol was registered at ClinicalTrials.gov (identifier NCT02732730).

RESULTS

Participant characteristics

67 women were enrolled in this qualitative sub-study, of 451 participants in HPTN 082. We interviewed 25 (37.3%) women from the Harare site, 20 (29.9%) from Cape Town, and 22 (32.8%) from Johannesburg (Table 7). The median age in the sample was 21 years (interquartile range [IQR] 19, 22). There was high retention between the first and second interviews, with 57 (85.1%) participants completing both in-depth interviews.

Stigma experiences, PrEP disclosure, and PrEP use

Three main themes emerged related to: 1) concerns around and experiences of stigma related to PrEP use; 2) the negative influence of stigma on PrEP disclosure and PrEP adherence; and 3) the role of disclosure as a strategy to combat stigma and improve PrEP use over time (Figure 4; Table 8).

Concerns around stigma and experiences of stigma related to PrEP use

AGYW described two main types of stigma related to PrEP use: HIV stigma arising when PrEP was mistaken for HIV treatment and sexual stigma when PrEP was thought to promote risky sexual behaviors. Participants described anticipated and experienced (e.g., name calling, loss of friends and partners, eviction) HIV stigma from someone seeing their pill bottles and assuming they were living with HIV. The pill bottles

were quite similar to medication bottles for antiretroviral therapy (ART) and it was difficult for participants to explain that their pills were for prevention rather than treatment if someone saw the bottle or heard the pills rattle (Table 8).

HIV stigma was feared and experienced from male partners, family members, friends, and others in their community. Participants were told by family and friends that they did not want to be associated with someone taking antiretroviral medications and a few participants described instances where they were evicted from their homes (“it was difficult...[my aunt] arranged that I leave because I kept on taking pills”), lost important relationships in their lives, or felt socially isolated because of their PrEP use (“I felt out of place...people would talk and you will be the topic of discussion”). Participants also commonly said their male partners feared that their PrEP use would “out them” as being HIV-infected (“he thought that I was implying that he had AIDS”) and their partners did not want them to use PrEP because they would be teased for being with someone who was taking antiretroviral medications.

In addition to these HIV stigma experiences, participants also commonly discussed sexual stigma arising from PrEP use. They described how male partners, family members, and friends called them “whores” and “prostitutes” and how it was common for their male partners to accuse them of having other sexual partners because of their PrEP use (Table 8). Participants were concerned about how partners and others in the community would view their sexual behavior because of their PrEP use. Anticipated sexual stigma was a particularly common worry among those who were religious and did not want to be ostracized from their church for their sexual behavior or those who lived with family members who did not know they were sexually active.

Participants who were in a new relationship or marriage also feared sexual stigma because they felt that their PrEP use could indicate that they had numerous sexual partners.

Negative influence of stigma on PrEP disclosure and PrEP adherence

Stigma was mentioned in relation to PrEP disclosure across all three study sites. Anticipated stigma prevented participants from disclosing their PrEP use and resulted in them delaying PrEP disclosure (Table 8). Many participants who did disclose their PrEP use (either intentionally or accidentally) experienced stigma from partners, family members, and friends; however, these negative disclosure experiences were more commonly discussed during their first interview.

HIV and sexual stigma around PrEP use and related disclosure issues were described as barriers to regular PrEP use, particularly early on in study participation. Participants discussed feelings of embarrassment from their pill bottles being seen by others or pills heard rattling in the bottles and the teasing and name-calling they experienced as a result of PrEP use. Several said that they stopped using PrEP (“I stopped after they laughed at me...I stopped when people were saying they are ARVs”), refused their PrEP pill bottles during clinic visits, or did not carry their PrEP bottles with them when they traveled (“it’s embarrassing, what people will say...I just left them”) to avoid these negative experiences in the future.

Disclosure as a strategy to combat stigma and improve PrEP use over time

By their second interview, most participants had some experiences with disclosure to family and friends. Many described disclosure as a powerful way to combat stigma around PrEP in their households and communities, increase community knowledge about PrEP, and improve their own PrEP use (Table 8). While participants acknowledged that they would not be able to convince everyone about the prevention benefits of PrEP (“there are people you cannot change”), they did talk about the importance of telling those with whom they lived about their product use before they found the pill bottles and came to their own assumptions about PrEP. This allowed them to share their knowledge about PrEP while preventing rumors and stigmatizing experiences. Disclosure was typically linked with improved PrEP use because as participants were able to explain PrEP and convince people in their lives of the HIV prevention benefits of PrEP, these supportive individuals helped remind and encourage them to take their daily pills (“if you tell them about PrEP, they will encourage you to keep taking because they see it as a good idea to protect your life”). Disclosure also helped participants improve PrEP use because they were no longer embarrassed about carrying pills and taking PrEP in front of other people.

In addition to PrEP disclosure in their households, some participants talked about proactively discussing PrEP more broadly, in their communities. One participant in particular referred to herself as a “PrEP ambassador”, and described how she shared knowledge about PrEP widely in her community. Participants felt that this broader disclosure of PrEP use and more widespread knowledge about PrEP for HIV protection could help reduce levels of HIV and sexual stigma in their communities.

Intervention opportunities to combat stigma and improve disclosure skills

Participants discussed several HPTN 082 activities that helped to change their stigma experiences, disclosure skills, and PrEP use over time, which highlight potentially successful intervention approaches to combat stigma and facilitate PrEP adherence (Figure 5; Table 8). During the first interview, participants commonly described negative social consequences of stigma around PrEP use (e.g., break-ups with partners, discrimination), much of which resulted from unintended product disclosure. However, by the second interview, many participants discussed increased community understanding and knowledge around PrEP, improved confidence in skills around product disclosure, and increased support from others to use PrEP. Participants from Harare more commonly described community-wide changes in knowledge and support around PrEP, while those from Cape Town and Johannesburg talked more about changes in PrEP knowledge in their smaller community of family and friends where they were disseminating information about PrEP alongside the study staff.

Participants attributed changes in stigma, knowledge, and support around PrEP to HPTN 082 study activities, including community outreach campaigns led by HPTN 082 study staff, informational brochures and t-shirts to raise awareness about PrEP, and discrete pill carrying cases that looked like compact mirrors to conceal product use and prevent pills from rattling during instances when they did not want their PrEP use to be unintentionally disclosed (Table 8). The study also offered monthly in-person adherence clubs at each of the three sites, which were an opportunity for participants to come together and share their experiences and challenges with stigma, disclosure, and PrEP use. Participants across all three sites said that they felt supported by others at the clubs which helped improve their morale and self-reported PrEP adherence.

National PrEP campaigns, particularly in South Africa, were also seen by participants as helping to change knowledge and awareness of PrEP and reduce stigma around product use over time, which facilitated improvements in PrEP use.

DISCUSSION

In this qualitative analysis of AGYWs' experiences in an open-label randomized study of PrEP adherence support strategies in South Africa and Zimbabwe, we found that participants described anticipated and experienced stigma related to HIV and sexual activity. Stigma was a barrier to product disclosure and PrEP use particularly during their early study participation. Over the course of the study, however, women became more comfortable disclosing PrEP use to those around them. Study-supported activities to improve disclosure skills and increase social support and PrEP visibility (e.g., informational materials, study T-shirts, adherence clubs) were cited as helping to reduce stigma around PrEP use and improve self-reported PrEP adherence. Results from this study highlight the importance of acknowledging difficulties with stigmatizing experiences and product disclosure for AGYW and developing intervention approaches to empower young women around PrEP use, particularly early on when they are first considering PrEP as an HIV prevention option.

While this work is unique in its focus on African AGYW, our findings are largely consistent with those from other PrEP studies conducted with adult populations in sub-Saharan Africa.^{16,18,126} Women in South Africa have discussed the importance of male partners' and family members' support as a facilitator of PrEP use, and have described PrEP stigma, relationship power dynamics, and issues around product disclosure as

barriers to PrEP use in trial contexts.¹²⁶ They have also reported trying to conceal or discontinue PrEP to maintain social relationships and partnerships.^{16,126} Similar concerns about stigma and disclosure have been described in programmatic PrEP delivery settings as well, particularly when PrEP is marketed for “high-risk populations” during periods of sexual activity.^{127,128} Mediation analyses have shown that stigma has a direct negative association on PrEP adherence and an indirect influence on PrEP use through fears about disclosure and self-efficacy, highlighting the importance of both stigma and disclosure on regular PrEP use.¹¹⁸

The longitudinal nature of our qualitative data collection allows us to describe dynamic changes in narratives around stigma, disclosure, and PrEP adherence in their first 3-6 months of PrEP use, and provides a different perspective than if we had only interviewed individuals when they recently started PrEP or at the end of their study participation. Events in the broader socio-cultural context also likely impacted PrEP use. During HPTN 082, national PrEP programs in South Africa and Zimbabwe evolved from a focus on FSWs to include AGYW in the general population in selected urban and peri-urban centers. More media discussion about PrEP during this period may have influenced AGYW’s stigma and disclosure experiences.^{116,129,130} Efforts to create demand around PrEP and integrate PrEP within antenatal, primary care, and sexual and reproductive health services in both countries also gained traction during the study period and will continue to increase awareness and acceptability of PrEP in sub-Saharan Africa in the future.¹³¹⁻¹³⁴ Studies among people living with HIV have shown that HIV-related stigma decreases over time in communities as they scale up treatment services and community outreach campaigns and similar trends will likely be seen for

PrEP stigma among high-risk individuals in the future.^{135,136,137} In short, our work is uniquely positioned to describe changing experiences of PrEP stigma, disclosure, and adherence among HIV-uninfected young women during a period of rapid growth in PrEP availability in South Africa and Zimbabwe. While quantitative methods are typically used to examine changes over time, serial in-depth interviews allowed us to capture a more nuanced understanding of these dynamic constructs.¹³⁸

These results highlight opportunities for future PrEP programs to improve product effectiveness by addressing community stigma around PrEP and concerns around disclosure. Broad in-person and social media marketing campaigns that improve PrEP knowledge and brand PrEP around wellness and empowerment, rather than HIV risk, can counter misconceptions and stigmatizing narratives around PrEP.^{116,139,140}

Adolescent-friendly and de-medicalized PrEP delivery approaches (e.g., online PrEP ordering, initiations at pharmacies) can also help separate PrEP from ART delivery and change perceptions that PrEP is only for individuals with risky sexual behavior.^{133,141-144}

Social support interventions are likely key strategies to improve PrEP effectiveness among youth and in-person adherence clubs have been previously found to improve ART adherence among adolescents living with HIV.¹⁴⁵ Adherence clubs may provide opportunities for young people to discuss stigmatizing experiences, cope with stigma and concerns about product use, and learn empowering skills around discrete product use or PrEP disclosure.

The strengths of this study include the large qualitative sample size from three different study sites and high retention between the first and second serial interviews which allowed us to achieve saturation of themes and observe changes in narratives

over time. All interviews were conducted by trained interviewers who had previous experience working with AGYW at the study sites. We had a large team of coders and analysts who provided different, context-specific, perspectives on the data and enriched the thematic analysis process. This study also had a number of limitations. We relied on self-reported information about PrEP use during the interviews and this information may be biased. While women discussed changes in stigma and disclosure experiences as a result of community outreach and adherence clubs, it is difficult to definitively attribute these changes to study activities or national PrEP roll-out. Given the qualitative nature of this study, we also cannot determine the magnitude of stigma changes over time or statistical differences in stigma, disclosure, and PrEP adherence between study sites and time points. All AGYW were participants in the parent HPTN 082 trial and our findings may not be generalizable to a population of young women seeking PrEP in a programmatic delivery setting. Future work should explore themes around stigma, disclosure, and adherence in the context of more real-world PrEP delivery.

CONCLUSIONS

In conclusion, AGYW in our study described PrEP stigma related to HIV and sexual behavior and stigma negatively influenced PrEP disclosure, uptake, and adherence particularly early on in the study. For those coping with stigma, product disclosure became a tool for empowerment for many women to change community beliefs around PrEP and improve PrEP use throughout follow-up. Changes in stigma levels, disclosure experiences, and PrEP use over time highlight opportunities for future PrEP programs to improve product effectiveness through broad marketing and

community education campaigns, empowerment and social support interventions, and adolescent-friendly healthcare services.

Word Count: 3886/3500

ACKNOWLEDGMENTS

The authors thank the individuals who participated in the study, the teams at the Johannesburg, South Africa, Cape Town, South Africa, and Harare, Zimbabwe study sites, and the HIV Prevention Trials Network that supported data collection and management for this work. We would also like to thank the HPTN 082 qualitative team members who were involved in data collection, coding, and data management, including Petina Musara, Lerato Makhale, and Kudzai Matambanadzo.

Table 7. Characteristics of the HPTN 082 study sample at enrollment¹

Characteristic	
Site	
Spilhaus, Harare, Zimbabwe	25 (37.3%)
Emavundleni, Cape Town, South Africa	20 (29.9%)
Ward 21, Johannesburg, South Africa	22 (32.8%)
Age	21 (19-23)
Education (N=57)	
Completed secondary school or higher	40 (70.2%)
Some secondary school	16 (28.1%)
Completed primary school	1 (1.8%)
Employment status (N=65)	
Employed	11 (16.9%)
Unemployed	30 (46.2%)
Current student (either secondary or tertiary education)	24 (36.9%)
Relationship status	
Single, no sexual partners	16 (24.6%)
Dating (at least one sexual partner but casual)	12 (18.5%)
In a relationship (at least one main serious partner)	32 (49.2%)
Married	7 (10.8%)
Living with:	
Parents (with or without siblings or own children)	41 (61.2%)
Partner (with or without other roommates or own children)	10 (14.9%)
Other	13 (19.4%)
Alone	3 (4.5%)
PrEP use Week 13 interview (N=66)	
Accepted PrEP at enrollment and started PrEP immediately	49 (74.2%)
Delayed taking PrEP for a period after initially accepting PrEP	6 (9.1%)
Discontinued PrEP after taking PrEP for a period	1 (1.5%)
Declined PrEP	10 (15.2%)
PrEP use at Week 26 interview (N=63)	
Accepted PrEP and continuing PrEP use since a prior visit	41 (65.1%)
Delayed taking PrEP for a period after initially accepting PrEP	4 (6.3%)
Discontinued PrEP after taking PrEP for a period	4 (6.3%)
Protocol-defined PrEP product hold	3 (4.8%)
Declined PrEP	11 (17.5%)

PrEP=pre-exposure prophylaxis

¹Data are presented as median (interquartile range) for continuous variables and frequency (percentage) for categorical variables

Table 8. Representative quotations from IDI transcripts

Main Theme	Subtheme(s)	Representative quotations
Concerns around stigma and experiences of stigma related to PrEP use	Stigma from PrEP being mistaken for ART	<i>“This [pill] bottle that they give us, it’s the same bottle as those of ARVs, some people will think you are lying, she is taking the AIDS pills. So I feel bad and it’s not easy for to prove for a person.”</i> (Johannesburg participant, age 25, IDI 1)
	Experienced HIV stigma from male partners	<i>“During the first days when I started taking Truvada, my husband and his friends got in...When people left he said, ‘My friends were laughing at me that your wife has been taking ARVs.’ It stirs quarrels in marriages...He came back angry, so annoyed. He said, ‘I am being labeled that I am sleeping with you and you are labeled that you have HIV.’”</i> (Harare participant, age 20, IDI 1)
	Experienced sexual stigma from male partners	<i>“Guys take it that you are this whore, you are sleeping around and that is why you are going to protect yourself. My ex-boyfriend was saying I am a whore, why am I taking PrEP?”</i> (Johannesburg participant, age 24, IDI 1)
	Anticipated sexual stigma from male partners	<i>“I wanted to tell him (male partner) but I thought that he is going to judge me and say I want to sleep around.”</i> (Cape Town participant, age 20, IDI 2)
Negative influence of stigma on PrEP disclosure and PrEP adherence	Concerns about stigma prevent PrEP disclosure	<i>“If I were to tell him that I am using PrEP he would not understand. He would shout, he would think that I have AIDS. So that is why I chose not to tell him and just leave it. If I tell him I might as well just lose him.”</i> (Cape Town participant, age 18, IDI 2)
	Stigma as a result of intentional PrEP disclosure	<i>“The guy I was with dumped me for using PrEP...I showed him PrEP and he thought it was ARVs. He was saying I am cheating, why am I using these pills.”</i> (Johannesburg participant, age 24, IDI 1)
	Stigma as a result of unintentional PrEP disclosure	<i>“I carry my pills everywhere I go. But they make a sound, people look at you wondering why this person is carrying the pills ...that container would humiliate us in the streets.”</i> (Harare participant, age 17, IDI 2)
	Stigma and related disclosure issues were barriers to PrEP adherence	<i>“When I started taking pills for the first time, I stopped taking them. When I had taken them for some time, my [PrEP bottle] was seen by others and I was laughed at in the community...I felt quite low. I came and told the [clinic] staff that I want to stop.”</i> (Harare participant, age 23, IDI 1)
Disclosure as a strategy to combat stigma and improve PrEP use over time	Disclosure to family and friends as a way to prevent stigma and reduce PrEP misconceptions	<i>“I used to be scared to share with my relatives, but now I sat down with them to explain just like it is explained to use by the [study staff]...because if you get the container and just take the pills people [who see the pills] will not understand you.”</i> (Harare participant, age 23, IDI 2)
	Disclosure to change community knowledge about PrEP and find others to support their PrEP use	<i>“It’s very easy [to take PrEP now] because now I don’t forget. At home, I get that support because my brother usually says that I mustn’t forget to take PrEP, so it has become a norm to me. He says that it’s a pill that prevents against the HIV virus...he knows it from me. He was shocked [when I first told him]...but he came back from</i>

	<p>Disclosure to improve PrEP adherence</p> <p>Disclosure to family and friends to support daily pill-taking</p> <p>Importance of broader disclosure to the community</p>	<p><i>school and then he told me that his teacher had a picture with PrEP on it and was chatting with other teachers.” (Cape Town participant, age 19, IDI 2)</i></p> <p><i>“I explained it to them (people at home) and told them about PrEP. When they began to understand, they also realized that I am serious about it. There are a lot of people who I would explain to... When they realized that I was serious about it, I didn’t forget [anymore]. I take my pills on time. They ended up encouraging me. For example, like I said when it’s time if I am outside they call me and say, ‘Come it’s time, your phone alarm is ringing.’” (Harare participant, age 17, IDI 2)</i></p> <p><i>“I was telling [my friends] about PrEP, explaining everything that you find in the study. I told them on purpose. I wanted to feel comfortable whenever taking the pill even if I am with them. They are not saying anything back about the pill and [they support me].” (Johannesburg participant, age 25, IDI 2)</i></p> <p><i>“I want to be the change. I want to announce PrEP so that many people can know about it and feel there’s a need to take PrEP.” (Cape Town participant, age 22, IDI 1)</i></p>
<p>Intervention opportunities to combat stigma and improve disclosure skills</p>	<p>HPTN 082 adherence clubs as a place to process stigma experiences and feel social support to improve PrEP adherence</p> <p>HPTN 082 activities to promote knowledge and reduce stigma around PrEP</p> <p>National PrEP campaigns to improve knowledge and reduce stigma around PrEP</p> <p>National PrEP campaigns to motivate participants to take PrEP</p>	<p><i>“At adherence clubs...we meet, share our life experiences. If I share that I was laughed at by people saying I have AIDS, someone will say, ‘No, being laughed at is common, just ignore it’. We are giving each other advice. When you are home you will still be in pain that people laughed at you and can actually think of stopping the pill. But you hear someone encouraging you...there are many who testified that they were also being laughed at. It is me who knows the reason I need to take the pill...ignore what other people say.” (Harare participant, age 23, IDI 2)</i></p> <p><i>“I am now dignified...Now I have observed that no one shouts a thing even if I pass by, all people will be quiet. Through the T-shirt, I thank this T-shirt and the sisters (study staff) here. They help explain PrEP to the community and that is how they understood.” (Harare participant, age 23, IDI 2)</i></p> <p><i>“[People] ended up believing that this thing about PrEP is true. They saw it on magazines. And there are advertisements with PrEP on it and that is how they understood it.” (Cape Town participant, age 19, IDI 2)</i></p> <p><i>“It influenced me to continue with what I am doing. They are now talking about [PrEP] on TV and the radio. At Jozi FM (local radio station) I heard them talk about it. [It motivated me] to continue with it.” (Johannesburg participant, age 25, IDI 2)</i></p>

Figure 4. Key qualitative themes on the relationship between stigma, disclosure, and PrEP adherence in the HPTN 082 sample

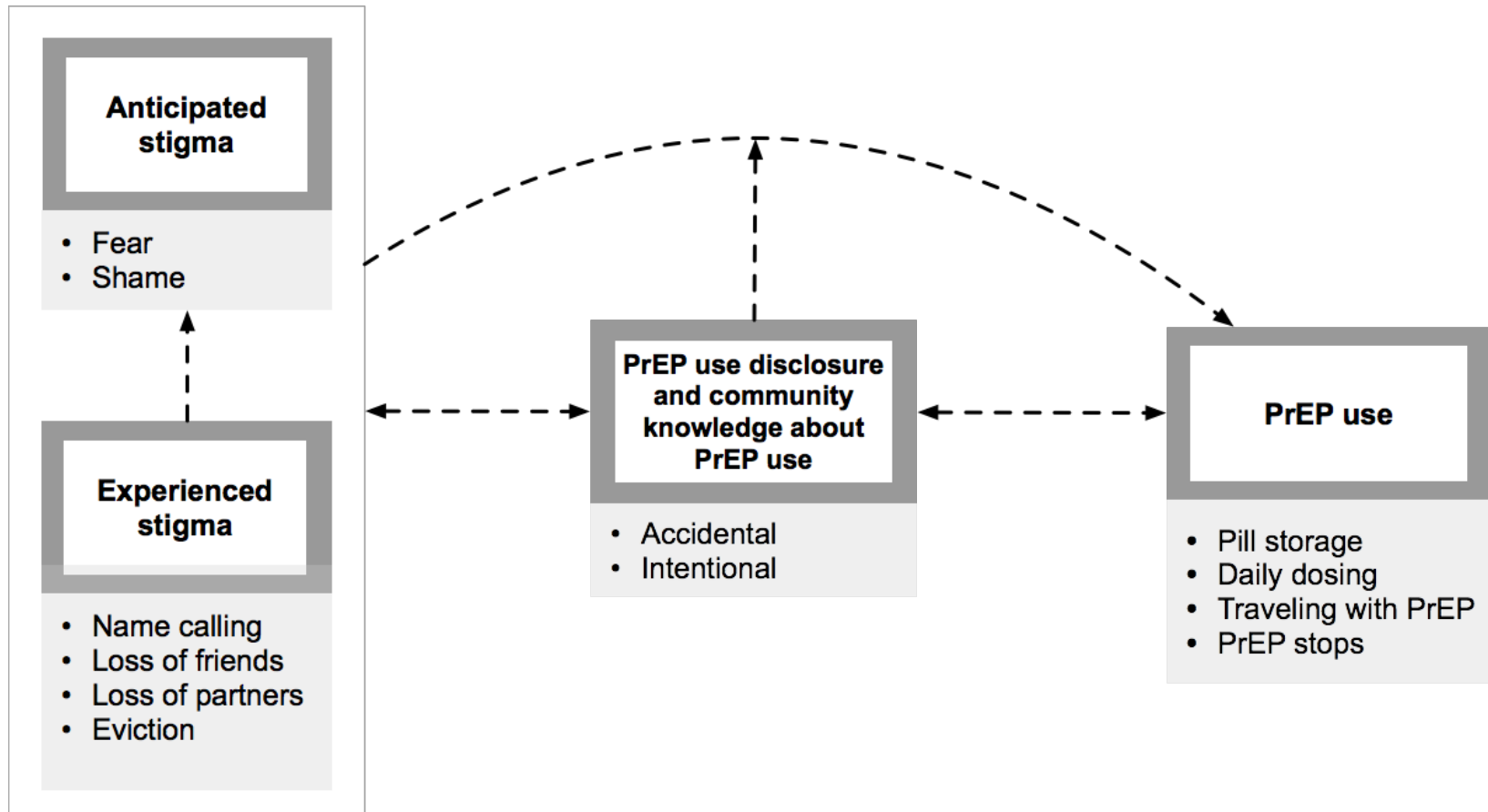
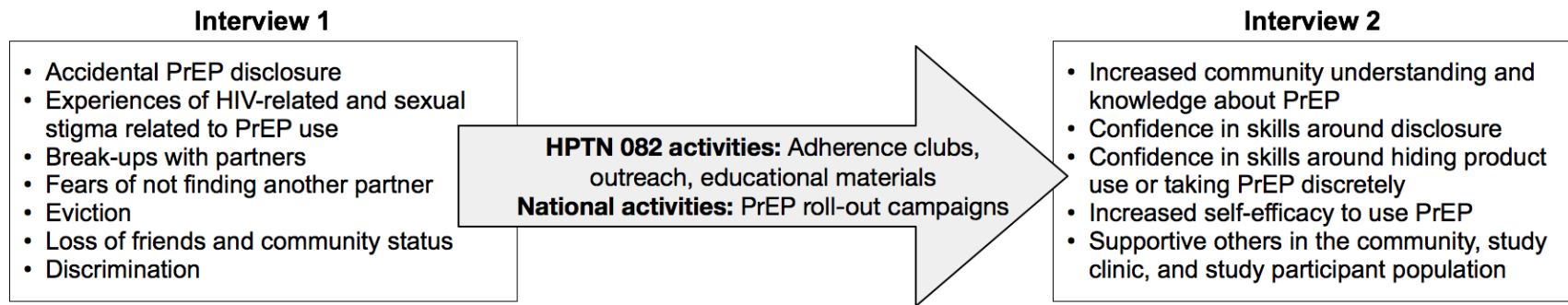


Figure 5. Changes in stigma, disclosure, and PrEP experiences over time attributed to HPTN 082 intervention and national activities



Chapter 5. Cognitive Testing of the PHQ-9 for Depression Screening among Pregnant and Postpartum Women in Kenya

Citation: Velloza J, Njoroge N, Ngure K, Thuo N, Kiptinness C, Momanyi R, Ayub S, Gakuo S, Mugo N, Simoni J, Heffron R. Cognitive Testing of the PHQ-9 for Depression Screening among Pregnant and Postpartum Women in Kenya. *BMC Women's Health* (under review).

Cognitive testing of the PHQ-9 for depression screening among pregnant and postpartum women in Kenya

Authors:

Jennifer Velloza^{1,2}, John Njoroge³, Kenneth Ngure^{3,4}, Nicholas Thuo³, Catherine Kiptinness³, Richard Momanyi³, Snaidah Ayub³, Stephen Gakuo³, Nelly Mugo^{1,3,5}, Jane Simoni^{1,6}, Renee Heffron^{1,2}

Affiliations:

¹University of Washington, Department of Global Health, Seattle, USA

²University of Washington, Department of Epidemiology, Seattle, USA

³Partners in Health and Research Development, Nairobi, Kenya

⁴Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya

⁵Center for Clinical Research, Kenya Medical Research Institute, Nairobi, Kenya

⁶University of Washington, Department of Psychology, Seattle, USA

Corresponding Author:

Renee Heffron, PhD, MPH

International Clinical Research Center

University of Washington

Box 359927

325 Ninth Avenue

Seattle, WA 98104

Phone: 206-520-3800

Fax: 206-520-3831

Email: rheffron@uw.edu

Running Head: PHQ-9 depression screening among Kenyan women

ABSTRACT

Background: Approximately 35-50% African women experience depression during pregnancy or postpartum, which is associated with maternal and child mortality and HIV acquisition. Screening is a critical first step for identifying women with perinatal depression and linking them to care. The Patient Health Questionnaire-9 (PHQ-9) screening tool has been previously validated and extensively used, but it remains unclear whether items are well understood and culturally appropriate among pregnant and postpartum Kenyan women.

Methods: We administered the Kiswahili or English PHQ-9 (based on preference) to 29 pregnant and postpartum women in Thika, Kenya. Following administration, we conducted cognitive interviews with a purposive sample of 20 women. We used analytic memos and data matrices to identify themes around scale acceptability, comprehension, and decision and response processes.

Results: Most participants preferred to answer the PHQ-9 in Kiswahili (N=18; 62%). Among the 20 interview participants, 12 (60%) had scores ≥ 5 , indicating depressive symptoms. Overall, participants found the scale acceptable as an interviewer-administered tool. Participants reported few problems related to comprehension but had difficulty answering items not relevant to their lives (e.g., “watching television”) and double-barreled items (e.g., “poor appetite or overeating”). They were hesitant to endorse items related to “duties as a wife and mother” and suicidal ideation. Most participants had difficulty distinguishing between response options of “several days” and “more than half the days”.

Conclusions: We detected several problems related to PHQ-9 comprehension, decision processes, and response processes. We provide recommended changes to instructions and item wording to improve PHQ-9 validity among Kenyan women.

KEYWORDS

Depression; PHQ-9; Pregnancy; Kenya; Women

INTRODUCTION

Major depressive disorder (MDD) is highly prevalent among women worldwide.^{67,149,150} In sub-Saharan Africa, women are 75% more likely to experience lifetime depression and twice as likely to experience 12-month depression than men.²¹ Pregnant and postpartum women have even greater risk of depression and approximately 35-50% of African women meet the criteria for MDD during these periods (“perinatal depression”).^{22,23} Perinatal depression has been associated with HIV risk behaviors (e.g., unprotected sex, substance use) and HIV acquisition, and prior research has documented overlapping epidemics of HIV risk and depression in pregnant and postpartum African women.^{29–34} Depressive symptom screening is a critical first step for identifying pregnant and postpartum women with likely MDD and linking them to care, particularly in resource-limited settings such as Kenya where it is often not possible to conduct clinical diagnostic interviews (the “gold-standard” for MDD diagnosis) due to shortages in clinician or counselor time, financial resources, and trained mental health personnel. In this context, screening could be integrated in HIV and reproductive health clinics to improve patient access to mental health treatment services.^{151–153}

A wide variety of depressive symptom screening tools have been developed to provide a basis for a diagnosis of “likely” or “probable” MDD and triage patients for mental health services.⁶¹ The most commonly used screening tool is the Patient Health Questionnaire-9 item (PHQ-9) which has been validated in a wide variety of settings including Kenya, can be administered quickly, accurately measures perinatal depression, and directly relates to the nine Diagnostic and Statistical Manual of Mental

Health Disorders (DSM-5) criteria for MDD diagnosis.^{61,62,154,155} The PHQ-9 is often used in the general population, facilitating comparisons between pregnant and postpartum women and other groups of women, and it is already recommended for widespread use in primary care, reproductive health, and HIV clinics by the Kenyan Ministry of Health.⁶¹

In Kenya, the PHQ-9 has been previously translated into Swahili and scoring cut-offs have been quantitatively validated against DSM-5 MDD diagnostic criteria.^{63,156} However, research has shown that the PHQ-9 may not perform well among women with lower education levels or those who did not learn English as a first language, and work remains necessary to adapt the PHQ-9, ensure that items are understood as intended and culturally relevant, and facilitate the incorporation of cultural idioms of depression for pregnant and postpartum Kenyan women.^{61,157–159} This novel study sought to use cognitive interviewing techniques to inform local adaptation of the PHQ-9 for perinatal depression screening among pregnant and postpartum women in Kenya, in the context of an HIV prevention and care clinic. We also qualitatively explored conceptualization of depression and factors affecting depressive symptoms to inform future work integrating depression screening with HIV and reproductive healthcare in Kenya.

MATERIALS AND METHODS

Study setting and design

This cross-sectional study was conducted from August 2017 – March 2018 in an HIV prevention and care clinic in Thika, Kenya. The main objectives were to explore PHQ-9 scale acceptability, item comprehension, response and decision processes in

answering the items, and feasibility of interviewer-administered delivery in the context of an HIV prevention and treatment intervention.

Participant recruitment

Women were recruited to participate from the Safer Conception Intervention for Partners (SCIP) study (clinicaltrials.gov #NCT03030768), which included 74 mutually-disclosed HIV serodiscordant couples with immediate fertility intentions.¹⁶⁰ SCIP was a pilot intervention study of a comprehensive safer conception package, including integrated antiretroviral therapy (ART), pre-exposure prophylaxis (PrEP), menstrual cycle tracking, and referral for other safer conception services.¹⁶⁰ Active female SCIP participants were eligible to participate in this ancillary study if they were currently pregnant or recently postpartum (delivered a live baby within the last six months) at the time of protocol approval. Participants were approached during their routine SCIP study visits by a counselor who confirmed their eligibility and obtained written informed consent. We enrolled women regardless of their HIV status and pregnancy trimester and included a sufficient sample size of participants to elicit a range of PHQ-9 scores.

PHQ-9 translation

Kenyan counselors from the clinic site translated the PHQ-9 from English into Kiswahili and Kikuyu. We based the Kiswahili translation on previous work conducted with Kenyan adults and included regional expressions for the local context.¹⁵⁶ The Kikuyu version was developed by the study's clinical psychologist (JNM) and reviewed for accuracy by two other Kikuyu-speaking staff members. Versions were back-translated into English and reviewed by mental health professionals in Kenya and the

United States to ensure that the translated items maintained fidelity to meaning of the English items.

Data collection

Data collection occurred in two phases. In Phase 1, a study counselor administered the PHQ-9 to consenting participants. The items were read aloud in their preferred language (English, Kiswahili, or Kikuyu) and counselors were instructed to read the items exactly as written. After completing the paper form, counselors summed the individual item scores (range: 0-27) and classified participants as having no depressive symptoms (score <5), minimal symptoms (score 5-14), or moderate to severe symptoms (score >14) using previously validated cut-offs.¹⁶¹ Counselors also completed debriefing reports summarizing words that participants' did not understand, any definitions or word substitutions that they provided, and general comments about the overall PHQ-9 administration experience.

In Phase 2, a Kenyan clinical psychologist conducted cognitive interviews with a purposive sample of 20 participants to elicit themes related to PHQ-9 acceptability, item comprehension, and recommended changes to PHQ-9 item wording. These participants were selected to achieve representation of individuals with different PHQ-9 scores, levels of education, preferred languages of administration, pregnancy and postpartum stages, and HIV status. Approximately 20 interviews were sufficient to achieve saturation of key themes. Participants were initially recommended for cognitive interviews by the counselor who administered their PHQ-9. The counselor brought the completed PHQ-9 and debriefing report to the psychologist, who approached potential participants, explained the purpose of the interviews, and reminded participants that

interview participation would not affect their participation in the SCIP study or their clinical care.

Semi-structured cognitive interview guides included scripted probes related to question comprehension (understanding of what the question asking), decision processes (motivation to respond accurately, sensitivity to the questions), and response processes (match between the participant's desired answer and response options) for each PHQ-9 item.⁵⁹ We also asked participants to describe their experiences completing the survey, perceptions of what the scale was trying to measure, and recommended changes to the items. Finally, we asked general probes about participants' conceptualization of mood and factors related to depressive symptoms. We piloted the guide with staff to ensure cultural appropriateness and clarity of questions, and final guide was translated into Kiswahili and Kikuyu.

Interviews were conducted immediately after the PHQ-9 administration to reduce recall issues. In cases when we were unable to conduct the interviews immediately after PHQ-9 data collection, we refreshed participants on the items and their responses prior to the interview. Interviews were conducted in English, Kiswahili, and/or Kikuyu and lasted approximately 45 minutes. Data collection took place in a quiet, private area and interviewers took detailed notes on debriefing forms. All interviews were audio-recorded, transcribed, and translated into English. Participants who endorsed depressive symptoms were referred to further mental health evaluation and individuals who were deemed to be a harm to themselves or others were immediately linked to medical care with close follow up from study staff.

Data analysis

We used descriptive statistics to summarize the sample by HIV and pregnancy status. These quantitative analyses were conducted using SAS 9.4 (Cary, North Carolina, USA).

Qualitative analyses were focused on understanding key themes around participants' comprehension, decision processes, and response processes based on the model of Willis and colleagues.⁵⁹ We conducted a multi-stage analysis, whereby we first developed participant-level analytic memos summarizing themes from the interviews and debriefing reports for each PHQ-9 item.¹⁶² These memos included representative quotations, and we consulted the original Kiswahili and Kikuyu interviews to accurately convey participants' views. We summarized data from these memos in matrix format to identify issues with each PHQ-9 item by participant demographics (HIV status, pregnant or postpartum status, education, PHQ-9 score, and language of administration).¹⁶³ Issues with the items were assigned to one of three categories: question comprehension; decision processes; or response processes. In addition, we reviewed transcripts and participant-level memos to identify general themes related to scale administration and acceptability (summarized in a separate matrix), and wrote analytic memos on participants' conceptualization of depressive symptoms and factors related to mood. All analytic memos and matrices were reviewed by the primary analyst (JV), a secondary analyst (NT, RM, or SA), and the study clinical psychologist (JM), and we sought broader feedback on our results from HIV and reproductive health care providers in Kenya. Discrepancies in findings were resolved by discussion. Based on these analyses and team discussions, we drafted revised versions of the PHQ-9 for future testing among pregnant and postpartum Kenyan women.

Ethical approval

Protocols were approved by ethical review boards at the University of Washington and Kenya Medical Research Institute (KEMRI). All participants provided written informed consent in their preferred languages.

RESULTS

Participant characteristics

We approached 30 women and enrolled 29 (96.7%) for PHQ-9 administration. Of these, 16 (55.2%) were postpartum and 13 (44.8%) were living with HIV (Table 9). The median level of education was 8 years (IQR 8, 12). Most participants preferred to have the PHQ-9 administered in Kiswahili (N=18; 62.1%). Approximately 11 women (37.9%) had PHQ-9 scores <5, 17 (58.6%) had scores between 5-14, and 1 (3.5%) had a score >14. The most commonly endorsed PHQ-9 item asked about “little interest or pleasure in doing things” (N=17; 58.6%) and 4 participants (13.8%) endorsed the item regarding suicidal ideation in the prior two weeks.

From the sample of 29 women, we purposively selected 20 (69.0%) to complete cognitive interviews, all of whom agreed to participate. These participants had a median of 10.5 years of education (IQR 8, 12), and preferred to conduct the interview in Kiswahili (N=6; 30.0%) or a mix of two or more languages (N=12; 60%). The majority were postpartum (N=12; 60.0%) and 8 (40.0%) were living with HIV. A total of 8 (40.0%) participants had PHQ-9 scores <5, 11 (55.0%) had PHQ-9 scores between 5-14, and 1 (5.0%) had a PHQ-9 score >14.

PHQ-9 comprehension, decision processes, and response processes

Almost all interview participants reported that the PHQ-9 was acceptable and “easy to complete” because they felt that “it is measuring those things that most women experience”. Several said that the PHQ-9 could serve as an intervention for depressive symptoms because the questions helped to normalize mental health issues and made them feel that someone was interested in their lives:

“The questions make me feel at peace. They are a source of comfort. It makes me feel that I am not alone in this because when I am given this question, I know there are others who also have [depression] and that is comforting. You (the interviewer) are also a source of comfort.” (Pregnant, HIV-infected woman with a PHQ-9 score of 2)

When asked whether they would prefer the PHQ-9 as a self- or interviewer-administered questionnaire, most participants said that they would rather it be interviewer-administered because they enjoyed talking with the interviewer and wanted to be able to ask clarifying questions (“when alone I may fail to understand some parts, but if we are two we can discuss about it”).

Item comprehension

Participants were able to understand the content and wording of most items, in both the English and Kiswahili versions, but had some difficulties distinguishing between concepts asked in different questions and relating the concepts to their own lives (Table 10). For item 1 (“little interest or pleasure in doing things”), participants discussed tasks that they felt it was their duty to complete but that they typically do not enjoy (e.g., “house chores”, “work”, forced “sex” with a partner, “taking care of children”). Their lack of enjoyment of these tasks was often reported as a constant in their lives, rather than

being related to recent mood issues, and most participants endorsed this item even if their experience of little interest or pleasure was not limited only to the past two weeks. This lends context to the quantitative data which showed that item 1 was the most commonly endorsed PHQ-9 item. Similarly, participants interpreted item 4 (“tired or little energy”) as having little energy specifically to do house chores and found this item to be repetitive with question 1. For question 7, participants had difficulties relating “trouble concentrating” to the examples provided, particularly if they did not own a television or regularly read the newspaper, and they more often talked about trouble concentrating as it related to their ability to “complete housework” or “attend church”. Finally, among those who completed the English PHQ-9, the word “fidgety” was almost universally not understood. All other items were well comprehended and participants were able describe the concepts in their own words (often switching among English, Kiswahili, and Kikuyu) during the cognitive interview. Participants generally understood the purpose of the questionnaire and were able to disentangle pregnancy and HIV symptoms from depressive symptoms (e.g., “I am hungry all the time but it is because of this pregnancy”).

Decision processes

Participants reported social desirability bias as a reason for difficulty in accurately answering five of the PHQ-9 questions (Table 10). Specifically, several participants were hesitant to endorse items 1, 4, and 6 because it would be an admission to both the interviewer and themselves that they had failed to complete their “duties” as a wife and mother. While most participants found items 2 (“feeling down, depressed, or hopeless”) and 9 (“thoughts that you would be better off dead”) acceptable and culturally

appropriate, a few participants who described themselves as “church going” said that they would not endorse those items because “even if I feel those feelings I know I should turn to God for acceptance.”

Response processes

Response process problems were the most commonly reported issues. Participants had difficulty responding to the double-barreled questions in items 3 (“trouble falling asleep, staying asleep, or sleeping too much”), 5 (“poor appetite or overeating”), and 8 (“moving or speaking so slowly...or the opposite”) if they had only experienced one type of symptom mentioned in the question or if they experienced that issue for only part of a day (e.g., difficulty sleeping during a nap but not at night; Table 10). In addition, participants were hesitant to choose a response to item 7 (“trouble concentrating”) if they experienced difficulty concentrating in other areas of their lives besides watching television or reading (e.g., difficulty interacting with friends in peer groups or “chamas”, completing chores, praying). When asked about their overall feelings on the response options, participants who experienced several symptoms and who had higher PHQ-9 scores (PHQ-9 score >5) reported difficulties choosing between “several days” and “more than half the days” and keeping all four of the response options in mind while answering a question. Participants also had challenges identifying a two-week period (some identified a shorter time period while others considered the whole prior month) and choosing a response option when a problem did not occur on consecutive days during that period.

Suggested changes to the PHQ-9

Based on our qualitative findings and team discussions, we propose several changes to the English and Kiswahili PHQ-9 tools that will potentially mitigate issues around comprehension, decision processes, and response processes while still preserving the meaning and content of the validated scale items (Figure 6). First, changing the word “little” to “less” in item 1 may help participants distinguish between tasks that they typically do not enjoy doing and those that they have recently been less interested in. Second, additional instructions for items 3, 6, and 8 may help participants select an answer choice regardless of whether they experienced only one of the symptoms included in the double-barreled questions. Third, more culturally relevant examples for item 7 are important for allowing participants to identify with the question and choose an appropriate response. Finally, we propose removing the word “fidgety” from the English version of the PHQ-9 item 8 when it is delivered to comparable patient populations.

We have also developed additional instructional language for describing the two-week reference time period and response options (Figure 6) and a visual aid to help participants understand the difference between the response options (Figure 7) in settings where the PHQ-9 is to be delivered as an interviewer-administered tool.

Conceptualization of depressive symptoms and factors related to mood

In addition to these findings on specific PHQ-9 items, five themes emerged related to conceptualization of depressive symptoms and factors related to mood (Table 11). “Depression” was typically well-understood and when participants were asked to explain depression in their own words they often used cultural idioms including “thinking too much”, “feeling moodless”, “feeling like your head will burst”, and “having a lot of

disturbing thoughts.” Depressive symptoms were also thought to be quite transient during pregnancy (“tomorrow you will find that your mind is stable and you are back to normal”) and were related to external stressors including responsibilities as a wife and a mother, relationship with a partner, and one’s HIV status. For example, several participants described feeling depressed when they failed to take care of house chores, when they were concerned with food security or their child’s education, or when they were fighting with their partners. One participant described an experience when she had suicide intent and “bought poison” after she fought with her partner because she worried that “he will leave me at some point”. Participants living with HIV described times when they experienced depressive symptoms because they were worried about transmitting HIV to their child (“you keep thinking about your child’s results”), they experienced HIV-related stigma (“society stigmatizes [HIV-infected people] so they get depression”), or they thought their partner would leave them because of their HIV status (“I think about my husband leaving me because he probably sees me differently”). When specifically talking about feeling like a failure or letting one’s family down, several participants discussed their family’s disappointment when they acquired HIV or learned they were pregnant and had to drop out of school. Finally, those who experienced depression often talked about the importance of prayer and religious coping for improving mood (“you tell God that He’s in control...and you begin to feel peace”). Religious convictions were also discussed as a barrier to harming oneself (“let Him take you when the time comes instead of doing yourself harm”).

DISCUSSION

In this study among pregnant and postpartum women in Kenya, the PHQ-9 was acceptable as an interviewer-administered screening tool and items were generally well comprehended. However, some items lacked full comprehension and we recommend key changes for these items and additional instructions for double-barreled questions. Participants also reported difficulty choosing between several response options and we have developed a visual aid for use in similar settings where the PHQ-9 is interviewer-administered. These results provide encouraging findings on the broader use of the PHQ-9 for depression screening among pregnant and postpartum women in Kenya, and highlight opportunities to improve scale validity as its use is being currently scaled-up by the Kenyan Ministry of Health.

Previous qualitative studies of PHQ-9 comprehension and decision and response processes have similarly reported that patients may have difficulty identifying appropriate responses, particularly when they have experienced a symptom for at least some time in the prior two weeks, and the PHQ-9 response choices may not accurately capture their symptom severity.^{164,165} Patients have described difficulty selecting responses when their symptoms fluctuated prior to the clinic visit and they also experienced some social desirability and recall bias in selecting response options.¹⁶⁵ These findings may help to explain why PHQ-9 scores in this sample were lower than expected and few women had scores >14 (the cut-off typically used to identify moderate to severe depressive symptoms), despite describing significant depressive symptoms and suicide ideation during the interviews.⁶¹ Other studies of the PHQ-9 in Asia and Africa have identified a PHQ-9 score of 10 as the optimal cutoff for identifying patients with MDD in resource-limited settings,^{64,166,167} and we would have classified an

additional five women with moderate to severe depressive symptoms using this cutoff. Future research is necessary to improve both item and instruction wording and guidance around clinically relevant cut-off scores in Kenya.

Previous studies of depression screening have debated whether to include the sensitive and potentially stigmatizing item related to suicidal ideation, despite known associations between depressive symptoms and suicide.^{168,169} While we found some evidence of social desirability bias related to this item, participants did not object to inclusion of the question or find it uncomfortable to answer. In addition, participants who endorsed this item accurately described times when they had thoughts of committing suicide, indicating that the item was well comprehended despite previous findings about its misinterpretation.¹⁷⁰ Women in our cohort reported hesitancy to endorse feelings of suicidal ideation particularly if they were religious, commensurate with other studies in East Africa that have described the influence of religious beliefs on suicidal ideation and behavior.^{171,172} Religious adults in Uganda and Ghana have described suicide as being “unacceptable” and against God’s rule, but still sympathized with and tried to help individuals in their community with suicidal ideation.^{171,172} However, healthcare staff administering the PHQ-9 may need additional training on asking about suicidal ideation in a nonjudgmental manner, identifying referral locations for mental healthcare, and linking individuals to immediate care.^{173,174}

PHQ-9 items related to somatic depressive symptoms (e.g. issues with appetite or sleeping) may be difficult to distinguish from symptoms of HIV or pregnancy.^{159,168} We did not detect a difference in our cognitive interview findings or PHQ-9 scores by HIV status or pregnancy or postpartum stage, and pregnant women were often able to

distinguish somatic symptoms related to their pregnancy (e.g., nausea in the first trimester, trouble sleeping with a newborn baby) from those related to depression. Other research has shown that there may be little benefit to removing somatic items and these items are likely especially important in identifying depressive symptoms among East African women who experience or talk about somatic depressive symptoms more often than men and women in Western settings.^{158,168,175–179}

The strengths of this study included the two-stage data collection from a well-established cohort of pregnant and postpartum women who were already comfortable talking with study staff. We also had strong referral systems to link patients with a mental healthcare provider as needed and no adverse events were reported during the study. Limitations included our small sample size of individuals with immediate fertility intentions who were in stable, mutually-disclosed HIV serodiscordant relationships. We only had one individual with a PHQ-9 >14 and our results may not be generalizable to a population of women newly diagnosed with HIV or those who have unintended pregnancies. We did not have resources to conduct clinical diagnostic interviews for MDD diagnosis or follow-up cognitive interviews after developing scale revisions. We did not compare PHQ-9 scores with the Edinburgh Postnatal Depression Scale, which is also commonly used for perinatal depression screening, but recent studies have found that it performs similarly to the PHQ-9 in pregnant and postpartum populations.^{180–182} Future large-scale validation studies using the revised PHQ-9 among pregnant and postpartum women in East Africa are necessary. Finally, there remains a need to conduct provider training and provide support on the best approaches to administer

PHQ-9 items in a culturally appropriate and understanding manner and ensure that appropriate referral services are available and accessible to patients.

CONCLUSIONS

The PHQ-9 is an acceptable and well-comprehended screening tool for perinatal depression among HIV-infected and uninfected women in Kenya. However, we detected several shortcomings in its comprehension and the associated processes for decision and response. In light of this, we provide recommendations for PHQ-9 item wording, response option instructions, and a participant-facing visual aid. This work highlights the importance of using cognitive interviewing methods to understand participants' understanding of depressive symptom screening tools and conceptualization of factors related to mood. Further refinement of the PHQ-9 tool and integration of depression screening into HIV and reproductive healthcare has the potential to improve maternal and child health outcomes.

ACKNOWLEDGEMENTS

The authors thank the couples who participated in the study and the teams at the study site and the University of Washington that supported data collection and management for this work.

Safer Conception Intervention for Partners Team:

Coordinating Center (University of Washington: Renee Heffron (protocol chair), Justice Quame-Amaglo, Jennifer Velloza, Harald Haugen, Susan Morrison, Jennifer Morton, Katherine K. Thomas

Thika, Kenya (Kenya Medical Research Institute, University of Washington): Nelly Mugo, Kenneth Ngure, Catherine Kiptinness, John Njoroge, Nicholas Thuo, Stephen Gakuo, Peter Mogere, Peter Michira, Richard Momanyi, Peterson Mwaniki, Lawrence Mwihaki, Grace Kimemia, Linda Oluoch, Bhavna Chohan, James Munyao, Snaida Ayub, Lawrence Mwaniki, Mary Kimani, Sarah Mbugua, Njambi Njuguna, Elizabeth Irungu

AUTHOR DISCLOSURE STATEMENT

The authors declare that they have no conflicts of interest to disclose.

Table 9. Participant characteristics for Phases 2 and 3

Characteristic	Frequency	
	Phase 2, PHQ-9 Administration (N=29)	Phase 3, Cognitive Interview (N=20)
Age, years	29.7 (26.4-33.7)	29.3 (25.2-33.3)
Any income reported	19 (65.5%)	12 (60.0%)
Education, years	8.0 (8.0-12.0)	10.5 (8.0-12.0)
Literate	29 (100.0%)	20 (100.0%)
Preferred language of PHQ-9		
English	14 (48.3%)	12 (60.0%)
Kiswahili	15 (51.7%)	8 (40.0%)
Kikuyu	0 (0.0%)	0 (0.0%)
Preferred language of PHQ-9		
English	NA	0 (0.0%)
Kiswahili		6 (30.0%)
Kikuyu		2 (10.0%)
Mix of two or more languages		12 (60.0%)
Married or in a relationship	27 (93.1%)	20 (100.0%)
Partnership duration, years	1.6 (0.8-6.2)	1.3 (0.5-5.6)
Number of prior children	1 (1-2)	1 (0-2)
Any unprotected sex with current partner in prior month	7 (24.1%)	5 (25.0%)
Any sex with outside partner in prior month	1 (3.5%)	0 (0.0%)
HIV-infected	13 (44.8%)	8 (40.0%)
On ART, participants living with HIV only	13 (100.0%)	8 (100.0%)
On PrEP, HIV-uninfected participants only	14 (87.5%)	12 (100.0%)
Pregnancy status		
1 st Trimester	6 (20.7%)	3 (15.0%)
2 nd Trimester	5 (17.2%)	3 (15.0%)
3 rd Trimester	2 (6.9%)	2 (10.0%)
Postpartum	16 (55.2%)	12 (60.0%)
Frequency of individual PHQ-9 items		
Little interest or pleasure	17 (58.6%)	12 (60.0%)
Feeling down, depressed, hopeless	16 (55.2%)	11 (55.0%)
Trouble sleeping too little or too much	21 (72.4%)	14 (70.0%)
Tired or little energy	15 (51.7%)	11 (55.0%)
Poor appetite or overeating	18 (62.1%)	14 (70.0%)
Feeling bad about yourself	7 (24.1%)	6 (30.0%)
Trouble concentrating	9 (31.0%)	7 (35.0%)
Moving slowly or feeling restless	7 (24.1%)	6 (30.0%)
Thoughts of suicide or self-harm	4 (13.8%)	2 (10.0%)
Median PHQ-9 score	5 (3-9)	5 (3-9.5)
PHQ-9 scoring categories		
<5	11 (37.9%)	8 (40.0%)
5-14	17 (58.6%)	11 (55.0%)
>14	1 (3.5%)	1 (5.0%)

Data are number (%) or median (IQR). PHQ-9= Patient Health Questionnaire 9-item. ART= antiretroviral therapy. PrEP= pre-exposure prophylaxis.

Table 10. Summary of findings by PHQ-9 item and types of cognitive process problems discussed

Item	Comprehension problems: <i>What does the participant think the question is asking?</i>	Decision process problems: <i>Does the participant want to tell the truth and/or devote mental energy to the question?</i>	Response process problems: <i>Can the participant map her internal answer with a given answer choice?</i>
1. Little interest or pleasure in doing things	Often related it to tasks that women feel they should do but don't enjoy (e.g., household chores, work)	Reluctance to endorse this item if it meant failing to perform "duties"	None
2. Feeling down, depressed, hopeless	None	Some hesitation to endorse if participants felt they should "turn to God for acceptance" when experiencing these feelings	None
3. Trouble falling asleep, staying asleep, or sleeping too much	None	None	Difficulty responding for those who experienced only one type of sleep issue, or if it occurred for part of a day (e.g., during a nap)
4. Tired or little energy	Comprehended similarly to item 1 and participants discussed feeling little energy to do household chores or work	Reluctance to endorse this item if it meant failing to perform "duties"	None
5. Poor appetite or overeating	None	None	Participants were generally not sure how to respond if they experienced only one type of appetite issue, or if it occurred for part of a day (e.g., during a midday meal)
6. Feeling bad about yourself—or that you are a failure or have let your family down	None	Reluctance to endorse this item if it meant failing to perform "duties"	None
7. Trouble concentrating on things such as reading the newspaper or watching television	Comprehension difficulties among participants who could not relate to given examples	None	Difficulty responding for those who experienced this issue for only part of a day, or if they did not own a television or read the newspaper regularly
8. Moving or speaking so slowly that other people could have noticed, or the opposite—being so fidgety or restless that you have been moving around more than usual	Difficulty understanding the word "fidgety" on the English PHQ-9 (a direct translation of this word was not available for the Kiswahili PHQ-9 translation).	None	Difficulty responding for those who experienced only one type of issue, or if it occurred for part of a day
9. Thoughts that you would be better off dead or of hurting yourself in some way	None	Some hesitation to endorse if participants felt they should "turn to God for acceptance" when experiencing these feelings	None

Figure 6. Suggested English and Kiswahili PHQ-9 revisions

PHQ-9 FORM FOR PREGNANT AND POSTPARTUM WOMEN IN KENYA - ENGLISH				
<p>Over the last 2 weeks, how often have you been bothered by any of the following problems?</p> <p>Please think about the last 14 days, from [INSERT DAY OF WEEK AND CALENDAR DATE] TO [INSERT DAY OF WEEK AND CALENDAR DATE] (<i>Show calendar here</i>). We would like to know how often during this 14-day period you were bothered by the following problems. There are four possible answer choices for each question – not at all, several days, more than half the days, and nearly every day. (<i>Use visual aid here to explain choices</i>).</p>				
	Not at all	Several days	More than half the days	Nearly every day
1. Little Less interest or pleasure in doing things				
2. Feeling down, depressed, or hopeless				
3. Trouble falling or staying asleep, staying asleep, or sleeping too much [Instruction: Please select an answer choice regardless of which of these problems you may have had.]				
4. Feeling tired or having little energy				
5. Poor appetite or overeating [Instruction: Please select an answer choice regardless of which of these problems you may have had.]				
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down				
7. Trouble concentrating on things, such as reading the newspaper or watching television listening to the radio, praying, going to church, spending time in chamas, or completing housework or other tasks.				
8. Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual [Instruction: Please select an answer choice regardless of which of these problems you may have had.]				
9. Thoughts that you would be better off dead or of hurting yourself in some way				
<p>10. If you checked off <u>any</u> problems, how <u>difficult</u> have these problems made it for you to do your work, take care of things at home, or get along with other people?</p> <p><input type="checkbox"/> Not difficult at all <input type="checkbox"/> Somewhat difficult <input type="checkbox"/> Very difficult <input type="checkbox"/> Extremely difficult</p>				
<p>Tafadhali fikiria: Kwa muda wa majuma mawili yaliyopita, ni mara ngapi umekuwa ukisumbuliwa na matatizo yoyote yanayofuata?:</p> <p>Tafadhali fikiria: Kwa muda wa majuma mawili yaliyopita, kuanzia [SIKU YA WIKI NA TAREHE] hadi (SIKU YA WIKI NA TAREHE) (<i>onyesha mteja kalenda</i>) tungependa kujua ni mara ngapi umekuwa ukisumbuliwa na matatizo yoyote kama haya yanayofuata? Kuna majibu manne kwa kila swali-sikusumbuka hata kidogo, siku nyingi, zaidi ya nusu ya muda wote, karibu kila siku. (<i>Tumia mifano kuelezea chaguo</i>)</p>				
	Sikusu mbuka hata kidogo	Siku nyingi	Zaidi ya nusu ya muda wote	Karibu kila siku
1. Kuwa na hamu chache ama kidogo ya kufanya mambo/kukosa raha yakufanya mambo				
1. Kukosa raha au kuwa na hamu iliyopunguka kuliko hapo awali				
2. Kujihisi kuwa na huzuni au kukosa matumaini				
3. Shida kupata usingizi au kushindwa kupata usingizi baada ya kuamka au kulala kupita kiasi. [Maagizo: Tafadhali chagua jibu bila kujali matatizo haya ambayo huenda umewahi kuwa nayo]				
4. Kuhisi uchovu au kuwa na nguvu kidogo				
5. Kukosa hamu ya kula chakula au kula kupita kiasi [Maagizo: Tafadhali chagua jibu bila kujali matatizo haya ambayo huenda umewahi kuwa nayo]				
6. Kuwa na hisia mbaya kujihusu- ama kujiona kama umeshindwa maishani ama umejikose ama umekosea familia yako				
7. Kuwa na shida kufuatilia vitu kwa makini, kama; kusoma gazeti ama kutazama runinga/televishoni kusikiliza radio, kuomba, kushiriki kwa chama au kumaliza kazi ya nyumba au kazi zingine				
8. Kusongea au kuzungumza pole pole san ahata ingeweza kuonekana kwa watu wengine. Ama kinyume – kuwa na mashaka/wasiwasi au kutotulia kiasi, hata umekuwa ukitembea tembea sana kuliko kawaida [Maagizo: Tafadhali chagua jibu bila kujali matatizo haya ambayo huenda umewahi kuwa nayo]				
9. Mawazo kuwa ungalikuwa umekufa ingekuwa bora au kutaka kujidhuru kwa njia yoyote ile.				
<p>10. Ikiwa ulikiri kuwa na tatizo lolote hapo juu, je ni kwa jinsi gani matatizo haya yamefanya iwe vigumu kufanya kazi yako, kushughulika mambo nyumbani ama kusikizana na wengine</p> <p><input type="checkbox"/> Haijakuwa vigumu hata kidogo <input type="checkbox"/> Imekuwa vigumu kiasi <input type="checkbox"/> Imekuwa vigumu <input type="checkbox"/> Imekuwa vigumu sana</p>				

Table 11. Summary of key themes related to conceptualization of mood and factors related to depressive symptoms

Key theme	Representative quotations
<p>“Depression” is described with specific cultural idioms including “thinking too much”, “feeling moodless”, and “feeling like your head will burst”</p>	<p>“You feel like your head is going to burst, you are thinking about a lot of issues. You are feeling so depressed.” <i>Pregnant, HIV-uninfected, spoke in Kiswahili and English, PHQ-9 score of 8</i></p> <p>“Depression is when you are having a lot of disturbing thoughts.” <i>Postpartum, HIV-infected, spoke in Kiswahili and English, had a PHQ-9 score of 2</i></p>
<p>Depressive symptoms are common but transient during pregnancy and postpartum periods</p>	<p>“If you find that for two days you don’t feel the same way you were a few days ago, you get a counselor to talk to you because we women, we feel so moodless when we are pregnant and it’s not intentional. Sometimes you will find your husband asking for food and you tell him to go and get for himself the food and this is just because you are moodless, it’s not because you want to. But tomorrow you will find that your mind is stable and you are back to normal.” <i>Pregnant, HIV-uninfected, spoke in Kiswahili and English, PHQ-9 score of 8</i></p>
<p>Depressive symptoms are related to external stressors including responsibilities as a wife and mother, relationship with a partner, and one’s HIV status</p>	<p>“Sometimes one feels they are down because you want to do that thing but you don’t make it. Like you can see I want to wash dishes but I don’t feel like it so I will feel like I am down. Yes, the house is dirty, what the husband will think, you see?” <i>Pregnant, HIV-uninfected, spoke in Kikuyu, Kiswahili, and English, PHQ-9 score of 4</i></p> <p>“Sometimes you find that you are quarrelling with your husband. You find that the children have been chased away from school for school fees, no food is in your house. You feel you are so stressed...if it’s eating, there is no mood to eat. When people talk to you, you feel that today you have no mood.” <i>Pregnant, HIV-uninfected, spoke in Kiswahili and English, PHQ-9 score of 8</i></p> <p>“I might wake up and sit with my husband, we might start chatting and then you find we have disagreed over a small issue, or he asks me to do something and then I tell him that I will not be able to do it but he insists. That issue affects me and I see as if he is forcing me to do something that I don’t want to do. I feel bad about it...I keep getting depressed because of these issues. Sometimes I lose hope as to whether we will stay together or if he will leave me at some point. There was a time when we had a disagreement and I found myself going to get poison to take. Luckily he came home and so I did not take it. I find myself thinking about it [still].” <i>Pregnant, HIV-infected, spoke in Kiswahili and English, PHQ-9 score of 9</i></p> <p>“Most of the time, the way I am (HIV-positive), you keep thinking about your child’s results...My child has already been tested for [HIV] and I had a lot in my mind about the results. Something else that can bother my mind is when you live discordant, I think about my husband leaving me because he probably sees me differently.” <i>Postpartum, HIV-infected, spoke in Kiswahili and English, PHQ-9 score of 5</i></p> <p>“Mostly what can make a person die is not using [HIV] medication wrongly, it is lack of counseling and stigma from HIV negative people because they can be using medicine well but those around them stigmatize them or society stigmatizes them so they get depression or stress. It is mainly about feeling like a failure especially when you look at your age mates, when you compare your life and see that their lives are better.” <i>Postpartum, HIV-infected, spoke in Kiswahili, PHQ-9 score of 17</i></p>

<p>Unintended pregnancy and HIV diagnosis can cause women to feel they've let their families down</p>	<p>"I can use an example, whereby we have a family, they had a girl child, so the girl child fails to finish her education, she gets pregnant. For me that can be a failure. Disappointing the family." <i>Postpartum, HIV-uninfected, spoke in Kiswahili and English, PHQ-9 score of 3</i></p> <p>"Mostly it's about being HIV positive so it makes me think I have let people down, so I feel like even if I do something good, I doubt that anyone will see as if I have achieved anything." <i>Postpartum, HIV-infected, spoke in Kiswahili, PHQ-9 score of 17</i></p>
<p>Religious coping is important for participants who experience depressive symptoms, feelings of hopelessness, or suicidal ideation</p>	<p>"[Depression] is when you say that you have lost hope. What can I say, like I had said earlier, you should just thank God...When I experience the things I have told you and I am not able to eat, I ask God to help me. If I face any difficulty, God will help me." <i>Pregnant, HIV-uninfected, spoke in Kikuyu, PHQ-9 score of 8</i></p> <p>"With depression it's something that has really gotten to you, that's weighing heavily on the mind and you feel that thing might bring harm to your body. However, after some days you can get into a state of acceptance, you begin to see that God is there, you pray, you tell God that He's in control, that He's the one that can intervene and you being to feel peace." <i>Pregnant, HIV-uninfected, spoke in Kiswahili, PHQ-9 score of 8</i></p> <p>"[When talking to someone with suicidal intent], I would comfort them and tell them because it was God who created you let Him take you when the time comes, instead of doing yourself harm which could mean that you are correcting God". <i>Pregnant, HIV-infected, spoke in Kiswahili and Kikuyu, PHQ-9 score of 2</i></p>

Chapter 6. Discussion

The work included in this dissertation is the first of its kind to consider depression and related psychosocial factors as determinants of PrEP use for young women and it generally contributes to a better understanding of the links between mental health and HIV risk. Here, we have leveraged data from four different HIV prevention trials and demonstration projects to look at the impact of mental health on PrEP adherence for HIV serodiscordant couples, young women, and pregnant and postpartum women. Leveraging techniques from longitudinal clinical epidemiology, causal inference, and qualitative analysis, this body of work consistently highlights the negative effect of depressive symptoms and stigma on PrEP adherence and the importance of integrated mental health, empowerment-based, and PrEP delivery interventions. Such interventions could build on the strengths of existing HIV service platforms to improve mental health screening and treatment and PrEP effectiveness for women in sub-Saharan Africa.

Interpretations of the links between depression, psychosocial factors, and PrEP use

In Chapters 2 and 3 we report that depressive symptoms have a strong negative influence on PrEP adherence both for women in HIV serodiscordant relationships and other high-risk women. Similar findings have also been reported in two other PrEP trials conducted with men who have sex with men and transgender women.^{49,100} Studies conducted with populations living with HIV and women of reproductive age have also found negative associations between depressive symptoms and adherence to daily ART and oral contraceptive pills.^{24,27,36} We explored three potential pathways to explain this relationship between depressive symptoms and PrEP adherence in Chapter 3. Our

findings suggest that depressive symptoms do not impact PrEP adherence through mediating influences of stigma, social support, and optimism around PrEP use. We also examined hypotheses of moderated-mediation, by examining whether there were significant interactions between depression and each of these mediating variables in our models, and conducted a number of sensitivity analyses. These additional analyses also did not change our main findings on the direct relationship between depression and PrEP adherence among women. This work may reflect a true, strong direct effect of depression on PrEP adherence; however, it is also possible that we were not able to observe an indirect effect of depression on adherence through these psychosocial mediators because they were infrequently measured or mismeasured in our analysis sample.

There are several other possible behavioral and biological mechanisms for the relationship between depression and PrEP adherence. Results from neuroimaging studies suggest that changes to dopamine signaling and nucleus accumbens function, proinflammatory responses, and brain structures associated with reward processing could mediate the pathway between depression and adherence to health promotion behaviors including HIV pre-exposure prophylaxis use (PrEP).^{183–185} In addition, observational data show that depression influences feelings of social isolation and rejection, sexual drive, and trust in others, all of which could reduce PrEP uptake and adherence and the need for regular PrEP use.^{186–189} While the potential pathway between depression, social isolation and rejection, and PrEP adherence was not supported in our mediation analysis in Chapter 3, qualitative work from Chapter 4 highlights the importance of perceived social support and stigma on regular PrEP use for adolescent girls and young women. This serial in-depth interview data also highlight

the potential for increases in community knowledge and awareness of PrEP to reduce PrEP-related stigma, improve feelings of self-esteem, mental health, and well-being, and empower young women to consistently use PrEP during periods of risk.

Our analyses in Chapters 2-4 generally support one another and frame a story about the potential links between depressive symptoms and PrEP adherence among women. The consistency of our findings across multiple different data sources, study settings, and analysis techniques enables us to draw conclusions about the importance of psychosocial factors on PrEP use for women. However, it is important to note that each chapter used data from a different PrEP trial with a unique parent study design and cohort of participants.^{13,69,190,191} Moreover, each study measured depressive symptoms and PrEP adherence using different measures and the length of study follow-up and timing of data collection was inconsistent across the cohorts which limits our ability to directly compare results across studies. For example, women in HPTN 067 reported higher prevalence of depressive symptoms than those in the Partners Demonstration Project, but this could be reflective of the different screening tools used or the different study inclusion criteria around having a stable sexual partnership. Neither the Partners Demonstration Project nor HPTN 067 measured intimate partner violence (IPV) experiences longitudinally among all female participants and IPV may be a strong unmeasured confounder of the relationship between depression and PrEP adherence in both Chapters 2 and 3. Future studies are needed to continue exploring the mechanism by which depression influences PrEP adherence to understand whether stigma and social support might serve as mediators of this relationship in other cohorts where depression, IPV, sexual behavior, and other key confounders are more frequently measured.

Making the case for integrated mental health and PrEP service delivery

A causal interpretation of our results in Chapters 2 and 3 suggests that PrEP adherence is greater when depressive symptoms are reduced, thereby making PrEP a more effective biomedical HIV prevention strategy. Moreover, results from Chapter 4 highlight the need for empowerment-based interventions that improve women's feelings of social support and self-esteem, their overall mental health, and PrEP adherence. This dissertation research points to the need for future integrated PrEP delivery and mental health interventions which address women's HIV prevention needs alongside depressive symptoms, concerns about stigma and social support, and feelings of self-esteem and self-worth.

In sub-Saharan Africa, PrEP has been delivered in HIV, antenatal, maternal and child health, and primary care clinics targeting key populations (e.g. sex workers, men who have sex with men, serodiscordant couples). Community-based PrEP delivery programs have also been developed in several sub-Saharan African contexts including Kenya, South Africa, and Lesotho to increase PrEP availability in the broader population.^{132–134,148,192} These clinic- and community-based PrEP delivery settings may be key entry points for women in the healthcare system and present opportunities for mental health screening, referral, and treatment.¹⁹³ Women in sub-Saharan Africa and other resource-limited settings do not otherwise have many opportunities to discuss their mental health with healthcare providers and stigma around mental health conditions and shortages of trained mental health providers also are also regularly reported barriers to care.^{157,194} Studies conducted in Uganda, Tanzania, and South Africa have shown that

women with depression, anxiety, and post-traumatic stress often present to healthcare facilities with somatic depressive symptoms (e.g., upset stomach, trouble sleeping), and are more likely to talk about these physical symptoms even if they are experiencing cognitive depressive symptoms as well, which may influence the conditions for which they receive treatment.^{157,158,195} Pregnant and postpartum South African women report hesitation to discuss cognitive depressive symptoms, including suicidal ideation, because of internalized stigma and guilt related to their depression and concerns about becoming socially isolated from their community, family, or husband.^{196,197} Participants who experience depression more somatically or who primarily express somatic symptoms because they are thought to be less stigmatizing than cognitive symptoms are less likely to receive specialized mental health services.^{154,157,198,199} These individuals often first seek treatment at primary healthcare, HIV, or antenatal clinics or with traditional healers and are less likely to view depression as a disorder that requires professional mental health treatment.^{154,198,199} In addition, there is a shortage of trained mental health personnel in resource-limited settings and there remains a need for task-shifting and task-sharing of depression interventions that can be delivered by primary healthcare, HIV, or maternal health providers in settings where trained psychologists and psychiatrists are not available.²⁰⁰ We can more effectively deliver depression care and improve women's overall mental health if we include mental health screening, referral, and treatment as part of routine service delivery in these other clinic settings.²⁰¹ Moreover, as we saw in Chapter 5, women appreciate being asked about their mental health symptoms in a non-stigmatizing way within the context of PrEP service delivery and depression screening was a mental health intervention in itself in a context where women are not often able to

talk about their symptoms.

Women may also return for regular PrEP refill visits and medical appointments if they are simultaneously receiving care for their other broad healthcare needs. In Chapter 4, we saw that women wanted to be empowered as part of their healthcare experiences and enjoyed receiving social support and enhanced counseling interventions which improved both their PrEP use and self-esteem. Women-centered PrEP implementation projects have begun to integrate HIV prevention with other desired services including gender-based violence and empowerment interventions and job training which have further improved visit retention, PrEP uptake and adherence, and overall participant well-being.^{146–148,202} Depression interventions could follow a similar model of integration within PrEP delivery settings to improve mental health and HIV prevention outcomes while maintaining women's engagement in clinic services.

Mental health conditions are also taking their place on the world stage as leading causes of death and disability worldwide.^{30,203,204} A recent Lancet Commission on Global Mental Health and Sustainable Development has emphasized a need to provide mental health care for all individuals by considering mental health on a continuum from mild to severely disabling.²⁰³ Moreover, we can prevent mental health symptoms from worsening or developing altogether with interventions that can meet individuals' broad needs along the severity continuum.²⁰³ Integrated mental health services within HIV, primary care, and antenatal care settings may serve as primary and secondary prevention strategies and this coordinated care model provides a sustainable way to deliver mental health services broadly in resource-limited settings.^{30,203}

Future directions for the integration of mental health and HIV prevention services

The World Health Organization (WHO) guidance on PrEP implementation and delivery models for young women emphasizes the importance of holistic HIV prevention programs that are accessible for young people in sub-Saharan Africa and meet their broad healthcare needs.²⁰⁵ A systematic review that was published as part of this WHO report recommends enhanced counseling and frequent clinic visits, mHealth tools (e.g., two-way SMS messages, tablet-based applications), specially trained counselors, and peer support groups to improve PrEP uptake and adherence for young women.²⁰⁵ Mental healthcare can be integrated with these counseling and mHealth PrEP adherence support approaches and several studies have already demonstrated the feasibility, acceptability, and effectiveness of including such mental health interventions within HIV treatment interventions in sub-Saharan Africa.⁹⁵ We can look to these existing intervention approaches to identify strategies to integrate mental health care with PrEP delivery.

Successful integrated mental health and HIV interventions must first accurately identify individuals with symptoms of distress. For depression, the “gold-standard” for diagnosis is an open-ended, structured clinical diagnostic interview (SCID) with a trained clinical psychologist.¹⁶⁸ However, this is usually not possible in contexts with few psychologists or in busy HIV, primary care, and antenatal clinic settings.¹⁶⁸ Instead, several depressive symptom screening tools have been developed to provide a basis for “likely” or “probable” depression diagnosis and are typically used in resource-limited healthcare settings where there are insufficiencies in trained personal, private clinic space, and clinic staff time.⁶¹ Screening tools typically take less than 10 minutes to complete and are useful as a first-step in determining which patients should be allocated

further mental healthcare treatment.^{61,168} They are also particularly important in resource-limited settings as a strategy to triage individuals and allocate clinic staff time and resources to cases that need more attention.¹⁶⁸ The Patient Health Questionnaire-9 item (PHQ-9) is one of the most commonly used depressive symptom screening tools, and the items directly relate to the nine DSM-5 diagnostic criteria for major depressive disorder.^{61,62,154} The tool has been translated into multiple languages and quantitative studies have shown that elevated PHQ-9 scores correspond well with a DSM-5 diagnosis of major depressive disorder; however, qualitative analyses suggest that the tool may fail to recognize culturally relevant depressive symptoms and may not perform well in settings with low English literacy.^{61,158} Results presented in Chapter 5 show that the English and Kiswahili PHQ-9 versions are well comprehended and acceptable for depression screening among pregnant and postpartum women visiting an HIV care clinic in Kenya. We provided several suggestions to improve question clarity and instructional language to improve identification of women with elevated depressive symptoms in this setting. During our study, we also successfully linked four women with depressive symptoms and suicidal ideation to further mental healthcare. While this small pilot and cognitive interviewing study shows that depression screening can be integrated with HIV prevention services for women, more work is needed to test the performance of our revised PHQ-9 instrument and to examine the effect of screening and referral on mental health and HIV outcomes.

Treatment for mental health conditions typically includes psychotherapy, pharmacotherapy, or a combination of both. Psychotherapy interventions require substantial resources including trained psychologists and other personnel to deliver the

intervention, staff to supervise intervention delivery, and time for providers and patients to administer the required number of sessions. Enhanced training for nursing staff and general practitioners, task-shifting, and group-based interventions have been successfully utilized in resource-limited settings to reduce the burden of mental health disorders including depression and to build capacity to deliver psychotherapy treatment when faced with personnel and time constraints.^{95,206} The WHO Mental Health Gap Action Programme (mhGAP) and companion Intervention Guide outlines effective interventions for numerous mental health conditions including depression, alcohol use, and suicide and provides guidance for non-specialists including general practitioners and nursing staff to deliver various pharmacologic and psychotherapy interventions.^{207,208} Cognitive behavioral therapy (CBT) has been the most frequently used depression treatment approach in resource-limited settings and studies in South Africa and Pakistan have shown that it effectively treats depressive symptoms when delivered as 6-8 sessions by community healthcare workers in primary healthcare clinics, HIV clinics, and home visits.^{95,209,210} The main limitations of these adapted, task-shared CBT interventions were in providing adequate training and supervision to lay counselors and ensuring fidelity to CBT activities.^{95,209,210} Brief mental health interventions such as the “Friendship Bench”, which consists of six counseling sessions delivered by trained female lay health workers (“grandmother figures”) on a wooden bench outside of clinic settings, have also been successfully implemented in primary care settings in sub-Saharan Africa and are currently being scaled up to different settings.²¹¹ Group-based interventions are effective when delivered by lay counselors (who are supervised by trained psychologists) and a small pilot study of a six-session group based intervention delivered in Zimbabwe showed

promising findings on intervention feasibility, acceptability, and effectiveness.²¹² Finally, computer- and tablet-based applications have been developed to empower lay counselors and provide ART adherence counseling.^{213,214} These mHealth tools could potentially be adapted and expanded for HIV-uninfected, high-risk women to include mental health counseling modules as part of PrEP adherence support.

Pharmacotherapy is an important component of effective mental health treatment, but its use is often limited by availability of medication, access to trained personnel who can prescribe and dispense medication, and barriers to uptake and adherence. Approximately a quarter of low-income countries do not provide antidepressant medications in primary healthcare settings where patients with depression are often first seen and diagnosed and the supply of drugs is often irregular.²⁰⁰ Health systems evaluations of antidepressant medication availability in Southern and Western Africa found that amitriptyline was the most common medication in primary healthcare clinics, while the more effective and safer selective serotonin reuptake inhibitors (SSRIs) were limited to a few small-scale facilities.^{215,216} Primary healthcare and non-mental health specialists are also often hesitant to prescribe antidepressant medication, which requires knowledge of patient's symptoms, comorbidities, and any contraindications to the drug, as well as regular follow-up on side effects. The Measurement-Based Care Model (MBC) was developed to address gaps in pharmacotherapy service delivery by training lay Depression Care Managers (DCMs) to measure depressive symptoms and recommend antidepressant initiation and duration, switching, and side effect management procedures to primary care and HIV providers in Uganda and Cameroon.^{93,94,153,217} This approach has been effective at improving antidepressant treatment access and reducing

depressive symptoms among the general population and people living with HIV, and could also be included in PrEP delivery settings.

As the HIV prevention field moves toward integrating mental health screening, referral, and treatment services within the context of PrEP delivery, several key barriers need to be considered and addressed. As previously discussed, the availability of pharmacotherapy, lay counselors, and trained supervisors are systems-level bottlenecks for successful, sustainable mental health intervention implementation.²⁰³ Moreover, HIV, primary care, and antenatal clinics must allocate private spaces for intervention delivery, although this could include outdoor areas as was done with the “Friendship Bench” intervention model.²¹¹ Treatment of mental health conditions can be quite costly for the healthcare system, although global calls to action and the recognition of mental health as a human right has helped prioritize funds for global mental health implementation research and service delivery.²⁰³ In addition, both mental health conditions and HIV are highly stigmatized in many settings and, as we showed in Chapter 4, PrEP may be stigmatized for its association with HIV treatment and sexual behavior. Successful integrated delivery of mental health and HIV prevention services will require parallel community-wide campaigns to decrease stigma around these conditions, create service demand, and improve knowledge of and attitudes about mental health and HIV treatment and prevention options.

Expanding delivery of mental health care alongside upcoming longer-acting HIV prevention and vaccine products

In the future, promising new HIV prevention products, including new oral PrEP

formulations, long-acting rings, injectables, and implantable prophylaxis, as well as broadly neutralizing antibody and other vaccine approaches may become available. Regardless of formulation or route of administration, none of these prophylactic and vaccine options will be immune from the challenges of delivering oral PrEP – we will still need to engage high-risk women in the healthcare system and support them to use these approaches in the face of challenges with product adherence and routine clinic visits. Moreover, we have learned from PrEP and contraceptive delivery that product choice is extremely important and individuals want a range of HIV prevention options to meet their needs at different times in their lives.^{16,218,219} Young women seeking these new HIV prevention services as they become available will be similar to populations who have been receiving oral PrEP, and will likely also face high burdens of mental health conditions including elevated depression symptoms. Mental health interventions will need to be integrated with these longer-acting prevention options as well, and the field must consider new strategies to screen and engage individuals with mental health services in their communities when they do not need to come back to clinics as regularly for pill pick-ups. These interventions could include mobile van HIV testing and prophylaxis services alongside mental health screening and referral or mHealth approaches to mental health and HIV prevention counseling. Such integrated mental health and HIV prevention models are necessary to maximize the public health benefit of these new, long-acting HIV prevention products as they become available and to improve overall mental health and well-being for women living in high-risk communities.

Conclusion

In this dissertation, we show the results from three different studies examining links between mental health and related psychosocial factors on PrEP use for adolescent girls, young women, and HIV serodiscordant couples in sub-Saharan Africa (Chapters 2-4). African women are at high risk of both HIV and mental health conditions and this work highlights the ways in which depressive symptoms can influence HIV risk through its negative impact on adherence to daily, oral PrEP. Qualitative work in Chapter 4 showed that stigma and social support can also reduce PrEP use and influence women's self-esteem and feelings of self-worth. It is necessary to integrate mental health screening, referral, and treatment services and empowerment-based interventions within the context of PrEP delivery to improve mental health and well-being, increase PrEP adherence, and improve the effectiveness of this biomedical HIV prevention technology among high-risk women in sub-Saharan Africa. We begin to address this service-delivery gap in Chapter 5 by integrating depression screening within an HIV prevention and treatment intervention for pregnant and postpartum women in Kenya. We found that the PHQ-9 was well-comprehended and acceptable as a depression screening tool and women generally enjoyed being asked questions about their mental health, although new instructional language and a visual aid may improve depression screening in this setting. Other research groups have successfully integrated psychotherapy and pharmacotherapy depression interventions within the context of HIV treatment in resource-limited settings. Future interventions should build on this work to test new models of depression screening, referral, and treatment integrated with PrEP delivery in sub-Saharan Africa to reduce barriers to care and improve mental health and HIV outcomes among women. The past decade has already seen tremendous advances in HIV prevention technologies and

increased attention on global mental health, with the United Nations setting ambitious international targets for both increased PrEP uptake (through the UNAIDS) and improved mental health care and treatment (through the UN Sustainable Development Goals) by 2030. This dissertation work has contributed substantially to both the fields of HIV prevention and global mental health and has identified critical opportunities to breakdown healthcare delivery silos in order to address women's broad sexual and mental health care needs.

REFERENCES

1. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet*. 2016;387(10013):53-60.
2. Molina J-M, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *N Engl J Med*. 2015;373(23):2237-2246.
3. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. 2012;367(5):399-410.
4. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med*. 2012;367(5):423-434.
5. Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2013;381(9883):2083-2090.
6. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010;363(27):2587-2599.
7. *Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection in Kenya 2016*. Nairobi, Kenya: Ministry of Health, National AIDS & STI Control Programme; 2016.
8. *Medicines Control Council Approves Fixed-Dose Combination of Tenofovir Disoproxyl Fumarate and Emtricitabine for Pre-Exposure Prophylaxis of HIV*. Pretoria, South Africa: South African Department of Health; 2015.
9. Mugo NR, Ngure K, Kiragu M, Irungu E, Kilonzo N. The preexposure prophylaxis revolution; from clinical trials to programmatic implementation. *Curr Opin HIV AIDS*. 2016;11(1):80-86.
10. Marcus JL, Volk JE, Pinder J, et al. Successful Implementation of HIV Preexposure Prophylaxis: Lessons Learned From Three Clinical Settings. *Curr HIV/AIDS Rep*. 2016;13(2):116-124.
11. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med*. 2012;367(5):411-422.
12. Murrain JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med*. 2015;372(6):509-518.
13. Bekker L-G, Roux S, Sebastien E, et al. Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town Trial): a randomised, open-label, phase 2 trial. *Lancet HIV*. 2018;5(2):e68-e78.
14. Gill K, Dietrich J, Gray G, Pidwell T, Kayamba E, Bennie, Thola. Pluspills: an open label, safety and feasibility study of oral pre-exposure prophylaxis (PrEP) in 15-19 year old adolescents in two sites in South Africa. Presented at the: 9th International AIDS Society Conference on HIV Science; July 23, 2017; Paris, France.

15. Geary CW, Bukusi EA. Women and ARV-based HIV prevention - challenges and opportunities. *J Int AIDS Soc.* 2014;17(3 Suppl 2):19356.
16. van der Straten A, Stadler J, Montgomery E, et al. Women's experiences with oral and vaginal pre-exposure prophylaxis: the VOICE-C qualitative study in Johannesburg, South Africa. *PLoS One.* 2014;9(2):e89118.
17. Tobin SC. VOICE reveals the need to improve adherence in PrEP trials: *AIDS.* 2015;29(12):N9.
18. Amico KR, Wallace M, Bekker L-G, et al. Experiences with HPTN 067/ADAPT Study-Provided Open-Label PrEP Among Women in Cape Town: Facilitators and Barriers Within a Mutuality Framework. *AIDS Behav.* 2017;21(5):1361-1375.
19. Celum CL, Delany-Moretlwe S, McConnell M, et al. Rethinking HIV prevention to prepare for oral PrEP implementation for young African women. *J Int AIDS Soc.* 2015;18(4 Suppl 3):20227.
20. Krishnaratne S, Hensen B, Cordes J, Enstone J, Hargreaves JR. Interventions to strengthen the HIV prevention cascade: a systematic review of reviews. *Lancet HIV.* 2016;3(7):e307-317.
21. Tomlinson M, Grimsrud AT, Stein DJ, Williams DR, Myer L. The epidemiology of major depression in South Africa: Results from the South African Stress and Health study. *South Afr Med J.* 2009;99(5 Pt 2):367-373.
22. Tomlinson M, O'Connor MJ, le Roux IM, et al. Multiple risk factors during pregnancy in South Africa: the need for a horizontal approach to perinatal care. *Prev Sci.* 2014;15(3):277-282.
23. Stringer EM, Meltzer-Brody S, Kasaro M, et al. Depression, pregnancy, and HIV: the case to strengthen mental health services for pregnant and post-partum women in sub-Saharan Africa. *Lancet Psychiatry.* 2014;1(2):159-162.
24. Hall KS, White KO, Rickert VI, Reame N, Westhoff C. Influence of depressed mood and psychological stress symptoms on perceived oral contraceptive side effects and discontinuation in young minority women. *Contraception.* 2012;86(5):518-525.
25. Garbers S, Correa N, Tobier N, Blust S, Chiasson MA. Association Between Symptoms of Depression and Contraceptive Method Choices Among Low-Income Women at Urban Reproductive Health Centers. *Matern Child Health J.* 2010;14(1):102-109.
26. Hall KS, Castaño PM, Westhoff CL. The influence of oral contraceptive knowledge on oral contraceptive continuation among young women. *J Womens Health.* 2014;23(7):596-601.
27. Hall KS, Kusunoki Y, Gatny H, Barber J. The risk of unintended pregnancy among young women with mental health symptoms. *Soc Sci Med.* 2014;100:62-71.
28. Callegari LS, Zhao X, Nelson KM, Borrero S. Contraceptive adherence among women Veterans with mental illness and substance use disorder. *Contraception.* 2015;91(5):386-

29. Lennon CA, Huedo-Medina TB, Gerwien DP, Johnson BT. A role for depression in sexual risk reduction for women? A meta-analysis of HIV prevention trials with depression outcomes. *Soc Sci Med*. 2012;75(4):688-698.
30. Prince M, Patel V, Saxena S, et al. No health without mental health. *The Lancet*. 2007;370(9590):859-877.
31. Pitpitan EV, Kalichman SC, Eaton LA, et al. Co-occurring psychosocial problems and HIV risk among women attending drinking venues in a South African township: a syndemic approach. *Ann Behav Med*. 2013;45(2):153-162.
32. Sikkema KJ, Watt MH, Meade CS, et al. Mental health and HIV sexual risk behavior among patrons of alcohol serving venues in Cape Town, South Africa. *J Acquir Immune Defic Syndr*. 2011;57(3):230-237.
33. Nduna M, Jewkes RK, Dunkle KL, Shai NPJ, Colman I. Associations between depressive symptoms, sexual behaviour and relationship characteristics: a prospective cohort study of young women and men in the Eastern Cape, South Africa. *J Int AIDS Soc*. 2010;13:44.
34. Smit J, Myer L, Middelkoop K, et al. Mental health and sexual risk behaviours in a South African township: a community-based cross-sectional study. *Public Health*. 2006;120(6):534-542.
35. Rao D, Feldman BJ, Fredericksen RJ, et al. A Structural Equation Model of HIV-Related Stigma, Depressive Symptoms, and Medication Adherence. *AIDS Behav*. 2012;16(3):711-716.
36. Nakimuli-Mpungu E, Bass JK, Alexandre P, et al. Depression, alcohol use and adherence to antiretroviral therapy in sub-Saharan Africa: a systematic review. *AIDS Behav*. 2012;16(8):2101-2118.
37. Mayston R, Kinyanda E, Chishinga N, Prince M, Patel V. Mental disorder and the outcome of HIV/AIDS in low-income and middle-income countries: a systematic review. *AIDS*. 2012;26 Suppl 2:S117-135.
38. Sheth SS, Coleman J, Cannon T, et al. Association between depression and nonadherence to antiretroviral therapy in pregnant women with perinatally acquired HIV. *AIDS Care*. 2015;27(3):350-354.
39. Turan B, Smith W, Cohen MH, et al. Mechanisms for the Negative Effects of Internalized HIV-Related Stigma on Antiretroviral Therapy Adherence in Women: The Mediating Roles of Social Isolation and Depression. *J Acquir Immune Defic Syndr*. 2016;72(2):198-205.
40. Glanz K, Barbara K. Rimer, K. Viswanath. *Health Behavior and Health Education: Theory, Research, and Practice*. 4th Edition. San Francisco, CA: John Wiley & Sons, Inc.
41. Lund C, De Silva M, Plagerson S, et al. Poverty and mental disorders: breaking the cycle in low-income and middle-income countries. *Lancet*. 2011;378(9801):1502-1514.
42. Magidson JF, Dietrich J, Otwombe KN, Sikkema KJ, Katz IT, Gray GE. Psychosocial correlates of alcohol and other substance use among low-income adolescents in peri-

- urban Johannesburg, South Africa: A focus on gender differences. *J Health Psychol.* 2017;22(11):1415-1425.
43. Dillon G, Hussain R, Loxton D, Rahman S. Mental and Physical Health and Intimate Partner Violence against Women: A Review of the Literature. *Int J Fam Med.* 2013;2013:313909.
 44. Devries KM, Mak JY, Bacchus LJ, et al. Intimate partner violence and incident depressive symptoms and suicide attempts: a systematic review of longitudinal studies. *PLoS Med.* 2013;10(5):e1001439.
 45. Manning M, Bettencourt BA. Depression and medication adherence among breast cancer survivors: Bridging the gap with the theory of planned behaviour. *Psychol Health.* 2011;26(9):1173-1187.
 46. Lin EHB, Katon W, Von Korff M, et al. Relationship of Depression and Diabetes Self-Care, Medication Adherence, and Preventive Care. *Diabetes Care.* 2004;27(9):2154-2160.
 47. Wing RR, Phelan S, Tate D. The role of adherence in mediating the relationship between depression and health outcomes. *J Psychosom Res.* 2002;53(4):877-881.
 48. Johnson MO, Catz SL, Remien RH, et al. Theory-Guided, Empirically Supported Avenues for Intervention on HIV Medication Nonadherence: Findings from the Healthy Living Project. *AIDS Patient Care STDs.* 2003;17(12):645-656.
 49. Mehrotra ML, Glidden DV, McMahan V, et al. The Effect of Depressive Symptoms on Adherence to Daily Oral PrEP in Men who have Sex with Men and Transgender Women: A Marginal Structural Model Analysis of The iPrEx OLE Study. *AIDS Behav.* 2016;20(7):1527-1534.
 50. Mack N, Odhiambo J, Wong CM, Agot K. Barriers and facilitators to pre-exposure prophylaxis (PrEP) eligibility screening and ongoing HIV testing among target populations in Bondo and Rarieda, Kenya: results of a consultation with community stakeholders. *BMC Health Serv Res.* 2014;14:231.
 51. Gore-Felton C, Koopman C. Behavioral mediation of the relationship between psychosocial factors and HIV disease progression. *Psychosom Med.* 2008;70(5):569-574.
 52. VanderWeele TJ. Marginal Structural Models for the Estimation of Direct and Indirect Effects: *Epidemiology.* 2009;20(1):18-26.
 53. VanderWeele TJ. Mediation Analysis: A Practitioner's Guide. *Annu Rev Public Health.* 2016;37:17-32.
 54. Naimi AI, Kaufman JS, MacLehose RF. Mediation misgivings: ambiguous clinical and public health interpretations of natural direct and indirect effects. *Int J Epidemiol.* 2014;43(5):1656-1661.
 55. Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods.* 2013;18(2):137-150.

56. Golub SA. PrEP Stigma: Implicit and Explicit Drivers of Disparity. *Curr HIV/AIDS Rep*. 2018;15(2):190-197.
57. Sandelowski M, Barroso J, Voils CI. Using qualitative metasummary to synthesize qualitative and quantitative descriptive findings. *Res Nurs Health*. 2007;30(1):99-111.
58. Glaser B, Strauss A. *The Discovery of Grounded Theory, Strategies for Qualitative Research*. Chicago, IL: Aldine Publishing Company; 1967.
59. Willis GB. *Analysis of the Cognitive Interview in Questionnaire Design: Understanding Qualitative Research*. NY, New York, USA: Oxford University Press; 2015.
60. Nakimuli-Mpungu E, Mojtabai R, Alexandre PK, et al. Lifetime depressive disorders and adherence to anti-retroviral therapy in HIV-infected Ugandan adults: a case-control study. *J Affect Disord*. 2013;145(2):221-226.
61. Ali G-C, Ryan G, De Silva MJ. Validated Screening Tools for Common Mental Disorders in Low and Middle Income Countries: A Systematic Review. *PloS One*. 2016;11(6):e0156939.
62. Bhana A, Rathod SD, Selohilwe O, Kathree T, Petersen I. The validity of the Patient Health Questionnaire for screening depression in chronic care patients in primary health care in South Africa. *BMC Psychiatry*. 2015;15:118.
63. Monahan PO, Shacham E, Reece M, et al. Validity/reliability of PHQ-9 and PHQ-2 depression scales among adults living with HIV/AIDS in western Kenya. *J Gen Intern Med*. 2009;24(2):189-197.
64. Cholera R, Gaynes BN, Pence BW, et al. Validity of the Patient Health Questionnaire-9 to screen for depression in a high-HIV burden primary healthcare clinic in Johannesburg, South Africa. *J Affect Disord*. 2014;167:160-166.
65. Thomson KA, Baeten JM, Mugo NR, Bekker L-G, Celum CL, Heffron R. Tenofovir-based oral preexposure prophylaxis prevents HIV infection among women. *Curr Opin HIV Aids*. 2016;11(1):18-26.
66. Grant RM, Koester KA. What people want from sex and preexposure prophylaxis. *Curr Opin HIV AIDS*. 2016;11(1):3-9.
67. Kuehner C. Why is depression more common among women than among men? *Lancet Psychiatry*. 2017;4(2):146-158.
68. Joyce K, Diffenbacher G, Greene J, Sorokin Y. Internal and External Barriers to Obtaining Prenatal Care. *Soc Work Health Care*. 2008;9:89-96.
69. Heffron R, Ngure K, Odoyo J, et al. Pre-exposure prophylaxis for HIV-negative persons with partners living with HIV: uptake, use, and effectiveness in an open-label demonstration project in East Africa. *Gates Open Res*. 2017;1(3).
70. Psaros C, Haberer JE, Boum Y, et al. The Factor Structure and Presentation of Depression Among HIV-Positive Adults in Uganda. *AIDS Behav*. 2015;19(1):27-33.

71. Bolton P. Cross-cultural validity and reliability testing of a standard psychiatric assessment instrument without a gold standard. *J Nerv Ment Dis.* 2001;189(4):238-242.
72. Ashaba S, Kakuhi B, Vořechovská D, et al. Reliability, Validity, and Factor Structure of the Hopkins Symptom Checklist-25: Population-Based Study of Persons Living with HIV in Rural Uganda. *AIDS Behav.* 2018;22(5):1467-1474.
73. de Vaus D. *Analyzing Social Science Data: 50 Key Problems in Data Analysis.* London, United Kingdom: SAGE Publications; 2002.
74. Simon GE, Katon WJ, VonKorff M, et al. Cost-effectiveness of a collaborative care program for primary care patients with persistent depression. *Am J Psychiatry.* 2001;158(10):1638-1644.
75. Kalichman SC, Simbayi LC, Cloete A, Mthembu PP, Mkhonta RN, Ginindza T. Measuring AIDS stigmas in people living with HIV/AIDS: the Internalized AIDS-Related Stigma Scale. *AIDS Care.* 2009;21(1):87-93.
76. Cherpitel CJ, Ye Y, Bond J, et al. Cross-national performance of the RAPS4/RAPS4-QF for tolerance and heavy drinking: data from 13 countries. *J Stud Alcohol.* 2005;66(3):428-432.
77. Broadhead WE, Gehlbach SH, de Gruy FV, Kaplan BH. The Duke-UNC Functional Social Support Questionnaire. Measurement of social support in family medicine patients. *Med Care.* 1988;26(7):709-723.
78. Spanier G. Measuring dyadic adjustment: new scale for assessing the quality of marriage and similar dyads. *J Marriage Fam.* 1976;38(1):15-28.
79. Cottrell ML, Yang KH, Prince HMA, et al. A Translational Pharmacology Approach to Predicting Outcomes of Preexposure Prophylaxis Against HIV in Men and Women Using Tenofovir Disoproxil Fumarate With or Without Emtricitabine. *J Infect Dis.* 2016;214(1):55-64.
80. Haberer JE, Baeten JM, Campbell J, et al. Adherence to Antiretroviral Prophylaxis for HIV Prevention: A Substudy Cohort within a Clinical Trial of Serodiscordant Couples in East Africa. Siegfried N, ed. *PLoS Med.* 2013;10(9):e1001511.
81. Donnell D, Baeten JM, Bumpus NN, et al. HIV protective efficacy and correlates of tenofovir blood concentrations in a clinical trial of PrEP for HIV prevention. *J Acquir Immune Defic Syndr.* 2014;66(3):340-348.
82. Defechereux PA, Mehrotra M, Liu AY, et al. Depression and Oral FTC/TDF Pre-exposure Prophylaxis (PrEP) Among Men and Transgender Women Who Have Sex With Men (MSM/TGW). *AIDS Behav.* 2015;20(7):1478-1488.
83. Martinez P, Andia I, Emenyonu N, et al. Alcohol Use, Depressive Symptoms and the Receipt of Antiretroviral Therapy in Southwest Uganda. *AIDS Behav.* 2008;12(4):605-612.
84. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiol.* 2000;11(5):550-560.

85. Cole SR, Hernán MA. Constructing Inverse Probability Weights for Marginal Structural Models. *Am J Epidemiol.* 2008;168(6):656-664.
86. Haberer JE, Kidoguchi L, Heffron R, et al. Alignment of adherence and risk for HIV acquisition in a demonstration project of pre-exposure prophylaxis among HIV serodiscordant couples in Kenya and Uganda: a prospective analysis of prevention-effective adherence. *J Int AIDS Soc.* 2017;20(1).
87. Machisa MT, Christofides N, Jewkes R. Mental ill health in structural pathways to women's experiences of intimate partner violence. Tsai AC, ed. *PLOS ONE.* 2017;12(4):e0175240.
88. Carroll JJ, Ngunjiri K, Heffron R, Curran K, Mugo NR, Baeten JM. Gendered differences in the perceived risks and benefits of oral PrEP among HIV-serodiscordant couples in Kenya. *AIDS Care.* 2016;28(8):1000-1006.
89. Montgomery ET, Chidanyika A, Chipato T, van der Straten A. Sharing the trousers: gender roles and relationships in an HIV-prevention trial in Zimbabwe. *Cult Health Sex.* 2012;14(7):795-810.
90. Ware NC, Wyatt MA, Haberer JE, et al. What's love got to do with it? Explaining adherence to oral antiretroviral pre-exposure prophylaxis for HIV-serodiscordant couples. *J Acquir Immune Defic Syndr.* 2012;59(5):463-468.
91. Hanscom B, Janes HE, Guarino PD, et al. Preventing HIV-1 Infection in Women using Oral Pre-Exposure Prophylaxis: A Meta-analysis of Current Evidence. *J Acquir Immune Defic Syndr.* 2016;73(5):606-608.
92. Anderson PL, Kiser JJ, Gardner EM, Rower JE, Meditz A, Grant RM. Pharmacological considerations for tenofovir and emtricitabine to prevent HIV infection. *J Antimicrob Chemother.* 2011;66(2):240-250.
93. Adams JL, Gaynes BN, McGuinness T, Modi R, Willig J, Pence BW. Treating Depression Within the HIV "Medical Home": A Guided Algorithm for Antidepressant Management by HIV Clinicians. *AIDS Patient Care STDs.* 2012;26(11):647-654.
94. Pence BW, Gaynes BN, Atashili J, et al. Feasibility, Safety, Acceptability, and Preliminary Efficacy of Measurement-Based Care Depression Treatment for HIV Patients in Bamenda, Cameroon. *AIDS Behav.* 2014;18(6):1142-1151.
95. Sikkema KJ, Dennis AC, Watt MH, Choi KW, Yemeke TT, Joska JA. Improving mental health among people living with HIV: a review of intervention trials in low- and middle-income countries. *Glob Ment Health.* 2015;2.
96. Velloza J, Baeten JM, Haberer J, et al. Effect of Depression on Adherence to Oral PrEP Among Men and Women in East Africa. *J Acquir Immune Defic Syndr.* 2018;79(3):330-338.
97. Brittain K, Mellins CA, Phillips T, et al. Social Support, Stigma and Antenatal Depression Among HIV-Infected Pregnant Women in South Africa. *AIDS Behav.* 2017;21(1):274-282.

98. Shrestha R, Copenhaver M, Bazazi AR, Huedo-Medina TB, Krishnan A, Altice FL. A Moderated Mediation Model of HIV-Related Stigma, Depression, and Social Support on Health-Related Quality of Life among Incarcerated Malaysian Men with HIV and Opioid Dependence. *AIDS Behav.* 2017;21(4):1059-1069.
99. Levy ME, Phillips G, Magnus M, et al. A Longitudinal Analysis of Treatment Optimism and HIV Acquisition and Transmission Risk Behaviors Among Black Men Who Have Sex with Men in HPTN 061. *AIDS Behav.* 2017;21(10):2958-2972.
100. Pasipanodya EC, Jain S, Sun X, et al. Trajectories and Predictors of Longitudinal Preexposure Prophylaxis Adherence Among Men Who Have Sex With Men. *J Infect Dis.* 2018;218(10):1551-1559.
101. Grant RM, Mannheimer S, Hughes JP, et al. Daily and Nondaily Oral Preexposure Prophylaxis in Men and Transgender Women Who Have Sex With Men: The Human Immunodeficiency Virus Prevention Trials Network 067/ADAPT Study. *Clin Infect Dis.* 2018;66(11):1712-1721.
102. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. *AUDIT: The Alcohol Use Disorders Identification Test, Guidelines for Use in Primary Care.* World Health Organization; 2001.
http://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MSD_MSB_01.6a.pdf;jsessionid=97053AA2F4DA925B9A6D5367EF824127?sequence=1.
103. WHO ASSIST Working Group. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. *Addict.* 2002;97(9):1183-1194.
104. Natamba BK, Achan J, Arbach A, et al. Reliability and validity of the center for epidemiologic studies-depression scale in screening for depression among HIV-infected and -uninfected pregnant women attending antenatal services in northern Uganda: a cross-sectional study. *BMC Psychiatry.* 2014;14(1).
105. Atukunda EC, Musiimenta A, Musinguzi N, et al. Understanding Patterns of Social Support and Their Relationship to an ART Adherence Intervention Among Adults in Rural Southwestern Uganda. *AIDS Behav.* 2017;21(2):428-440.
106. Kiene SM, Lule H, Sileo KM, Silmi KP, Wanyenze RK. Depression, alcohol use, and intimate partner violence among outpatients in rural Uganda: vulnerabilities for HIV, STIs and high risk sexual behavior. *BMC Infect Dis.* 2017;17(1):88.
107. Frohlich P, Meston C. Sexual functioning and self-reported depressive symptoms among college women. *J Sex Res.* 2002;39(4):321-325.
108. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med.* 2012;367(5):411-422.
109. Corneli A, Perry B, McKenna K, et al. Participants' Explanations for Nonadherence in the FEM-PrEP Clinical Trial. *J Acquir Immune Defic Syndr.* 2016;71(4):452-461.

110. Link BG, Phelan JC. Stigma and its public health implications. *Lancet*. 2006;367(9509):528-529.
111. Golub SA, Gamarel KE, Surace A. Demographic Differences in PrEP-Related Stereotypes: Implications for Implementation. *AIDS Behav*. 2017;21(5):1229-1235.
112. Biello KB, Oldenburg CE, Mitty JA, et al. The “Safe Sex” Conundrum: Anticipated Stigma From Sexual Partners as a Barrier to PrEP Use Among Substance Using MSM Engaging in Transactional Sex. *AIDS Behav*. 2017;21(1):300-306.
113. Eaton LA, Kalichman SC, Price D, Finneran S, Allen A, Maksut J. Stigma and Conspiracy Beliefs Related to Pre-exposure Prophylaxis (PrEP) and Interest in Using PrEP Among Black and White Men and Transgender Women Who Have Sex with Men. *AIDS Behav*. 2017;21(5):1236-1246.
114. Dubov A, Galbo P, Altice FL, Fraenkel L. Stigma and Shame Experiences by MSM Who Take PrEP for HIV Prevention: A Qualitative Study. *Am J Mens Health*. 2018;12(6):1843-1854.
115. Pintye J, Beima-Sofie KM, Makabong'O PA, et al. HIV-Uninfected Kenyan Adolescent and Young Women Share Perspectives on Using Pre-Exposure Prophylaxis During Pregnancy. *AIDS Patient Care STDs*. 2018;32(12):538-544.
116. Amico KR, Bekker L-G. Global PrEP roll-out: recommendations for programmatic success. *Lancet HIV*. 2019;6(2):E137-E140.
117. Goparaju L, Praschan NC, Warren-Jeanpiere L, Experton LS, Young MA, Kassaye S. Stigma, Partners, Providers and Costs: Potential Barriers to PrEP Uptake among US Women. *J AIDS Clin Res*. 2017;8(9).
118. Walsh JL. Applying the Information-Motivation-Behavioral Skills Model to Understand PrEP Intentions and Use Among Men Who Have Sex with Men. *AIDS Behav*. 2018 (e-pub). doi:10.1007/s10461-018-2371-3
119. Peng P, Su S, Fairley CK, et al. A Global Estimate of the Acceptability of Pre-exposure Prophylaxis for HIV Among Men Who have Sex with Men: A Systematic Review and Meta-analysis. *AIDS Behav*. 2018;22(4):1063-1074.
120. Haire BG. Preexposure prophylaxis-related stigma: strategies to improve uptake and adherence - a narrative review. *HIVAIDS*. 2015;7:241-249.
121. Atujuna M, Newman PA, Wallace M, et al. Contexts of vulnerability and the acceptability of new biomedical HIV prevention technologies among key populations in South Africa: A qualitative study. *PLoS One*. 2018;13(2):e0191251.
122. Mustanski B, Ryan DT, Hayford C, Phillips G, Newcomb ME, Smith JD. Geographic and Individual Associations with PrEP Stigma: Results from the RADAR Cohort of Diverse Young Men Who have Sex with Men and Transgender Women. *AIDS Behav*. 2018;22(9):3044-3056.

123. Grace D, Jollimore J, MacPherson P, Strang MJP, Tan DHS. The Pre-Exposure Prophylaxis-Stigma Paradox: Learning from Canada's First Wave of PrEP Users. *AIDS Patient Care STDs*. 2018;32(1):24-30.
124. Balkus JE, Brown E, Palanee T, et al. An Empiric HIV Risk Scoring Tool to Predict HIV-1 Acquisition in African Women. *J Acquir Immune Defic Syndr*. 2016;72(3):333-343.
125. Castillo-Mancilla JR, Zheng J-H, Rower JE, et al. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. *AIDS Res Hum Retroviruses*. 2013;29(2):384-390.
126. Montgomery ET, van der Straten A, Stadler J, et al. Male Partner Influence on Women's HIV Prevention Trial Participation and Use of Pre-exposure Prophylaxis: the Importance of "Understanding." *AIDS Behav*. 2015;19(5):784-793.
127. Idoko J, Folayan MO, Dadem NY, Kolawole GO, Anenih J, Alhassan E. "Why should I take drugs for your infection?": outcomes of formative research on the use of HIV pre-exposure prophylaxis in Nigeria. *BMC Public Health*. 2015;15:349.
128. Franks J, Hirsch-Moverman Y, Loquere AS, et al. Sex, PrEP, and Stigma: Experiences with HIV Pre-exposure Prophylaxis Among New York City MSM Participating in the HPTN 067/ADAPT Study. *AIDS Behav*. 2018;22(4):1139-1149.
129. Bekker L-G, Rebe K, Venter F, et al. Southern African guidelines on the safe use of pre-exposure prophylaxis in persons at risk of acquiring HIV-1 infection. *South Afr J Hiv Med*. 2016;17(1).
130. Hodges-Mameletzis I, Dalal S, Msimanga-Radebe B, Rodolph M, Baggaley R. Going global: the adoption of the World Health Organization's enabling recommendation on oral pre-exposure prophylaxis for HIV. *Sex Health*. 2018;15(6):489-500.
131. Schwartz K, Ferrigno B, Vining S, et al. PrEP Communications Accelerator: a digital demand creation tool for sub-Saharan Africa. *Sex Health*. 2018;15(6):570-577.
132. Pintye J, Kinuthia J, Roberts DA, et al. Integration of PrEP Services Into Routine Antenatal and Postnatal Care: Experiences From an Implementation Program in Western Kenya. *J Acquir Immune Defic Syndr*. 2018;79(5):590-595.
133. Rosenberg NE, Bhushan NL, Vansia D, et al. Comparing Youth-Friendly Health Services to the Standard of Care Through "Girl Power-Malawi": A Quasi-Experimental Cohort Study. *J Acquir Immune Defic Syndr*. 2018;79(4):458.
134. Travill D, Bekker L-G, Delaney-Moretlwe S, et al. Sexual behavior and PrEP uptake among young African women in a demonstration project about PrEP delivery. Presented at the: International AIDS Society Conference (IAS 2018); July 23, 2018; Amsterdam, the Netherlands.
135. Mall S, Middelkoop K, Mark D, Wood R, Bekker L-G. Changing patterns in HIV/AIDS stigma and uptake of voluntary counselling and testing services: the results of two consecutive community surveys conducted in the Western Cape, South Africa. *AIDS Care*. 2013;25(2):194-201.

136. Prinsloo CD, Greeff M, Kruger A, Khumalo IP. HIV stigma experiences and stigmatisation before and after a HIV stigma-reduction community “hub” intervention. *Afr J AIDS Res.* 2017;16(3):203-213.
137. Bauermeister JA, Muessig KE, LeGrand S, et al. HIV and Sexuality Stigma Reduction Through Engagement in Online Forums: Results from the HealthMPowerment Intervention. *AIDS Behav.* 2019;23(3):742-752.
138. Miles M, Huberman A, Saldana J. *Qualitative Data Analysis: A Methods Sourcebook.* London, United Kingdom: SAGE Publications; 2013.
139. Schwartz J, Grimm J. PrEP on Twitter: Information, Barriers, and Stigma. *Health Commun.* 2017;32(4):509-516.
140. Magno L, Dourado I, Suttan Coats C, et al. Knowledge and willingness to use pre-exposure prophylaxis among men who have sex with men in Northeastern Brazil. *Glob Public Health.* 2019 (e-pub). doi:10.1080/17441692.2019.1571090
141. Girometti N, McCormack S, Devitt E, et al. Evolution of a pre-exposure prophylaxis (PrEP) service in a community-located sexual health clinic: concise report of the PrEPxpress. *Sex Health.* 2018;15(6):598-600.
142. Biello KB, Marrow E, Mimiaga MJ, Sullivan P, Hightow-Weidman L, Mayer KH. A Mobile-Based App (MyChoices) to Increase Uptake of HIV Testing and Pre-Exposure Prophylaxis by Young Men Who Have Sex With Men: Protocol for a Pilot Randomized Controlled Trial. *JMIR Res Protoc.* 2019;8(1). doi:10.2196/10694
143. Sullivan PS, Driggers R, Stekler JD, et al. Usability and Acceptability of a Mobile Comprehensive HIV Prevention App for Men Who Have Sex With Men: A Pilot Study. *JMIR MHealth UHealth.* 2017;5(3).
144. Tung EL, Thomas A, Eichner A, Shalit P. Implementation of a community pharmacy-based pre-exposure prophylaxis service: a novel model for pre-exposure prophylaxis care. *Sex Health.* 2018;15(6):556-561.
145. Simoni JM, Huh D, Frick PA, et al. Peer support and pager messaging to promote antiretroviral modifying therapy in Seattle: a randomized controlled trial. *J Acquir Immune Defic Syndr.* 2009;52(4):465-473.
146. Mittal M, Thevenet-Morrison K, Landau J, et al. An Integrated HIV Risk Reduction Intervention for Women with a History of Intimate Partner Violence: Pilot Test Results. *AIDS Behav.* 2017;21(8):2219-2232.
147. Sikkema KJ, Neufeld SA, Hansen NB, et al. Integrating HIV prevention into services for abused women in South Africa. *AIDS Behav.* 2010;14(2):431-439.
148. Delany-Moretlwe S. Engaging young women in sub-Saharan Africa. Presented at the: Conference on Retroviruses and Opportunistic Infections 2019 (CROI); March 4, 2019; Seattle, WA, USA.

149. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003;289(23):3095-3105.
150. Ballenger JC, Davidson JR, Lecrubier Y, et al. Consensus statement on transcultural issues in depression and anxiety from the International Consensus Group on Depression and Anxiety. *J Clin Psychiatry*. 2001;62 Suppl 13:47-55.
151. Nydoo P, Naicker T, Moodley J. Depressive scores in newly diagnosed HIV-infected and HIV-uninfected pregnant women. *South Afr J Psychiatry*. 2017;23:a1085.
152. Parcesepe AM, Mugglin C, Nalugoda F, et al. Screening and management of mental health and substance use disorders in HIV treatment settings in low- and middle-income countries within the global IeDEA consortium. *J Int Aids Soc*. 2018;21(3):e25101.
153. Wagner GJ, Ngo V, Glick P, Obuku EA, Musisi S, Akena D. INtegration of DEPression Treatment into HIV Care in Uganda (INDEPTH-Uganda): study protocol for a randomized controlled trial. *Trials*. 2014;15:248.
154. Chibanda D, Verhey R, Gibson LJ, et al. Validation of screening tools for depression and anxiety disorders in a primary care population with high HIV prevalence in Zimbabwe. *J Affect Disord*. 2016;198:50-55.
155. Sidebottom AC, Harrison PA, Godecker A, Kim H. Validation of the Patient Health Questionnaire (PHQ)-9 for prenatal depression screening. *Arch Womens Ment Health*. 2012;15(5):367-374.
156. Omoro S a. O, Fann JR, Weymuller EA, Macharia IM, Yueh B. Swahili translation and validation of the Patient Health Questionnaire-9 depression scale in the Kenyan head and neck cancer patient population. *Int J Psychiatry Med*. 2006;36(3):367-381.
157. Kirmayer LJ. Cultural variations in the clinical presentation of depression and anxiety: implications for diagnosis and treatment. *J Clin Psychiatry*. 2001;62 Suppl 13:22-28; discussion 29-30.
158. Haroz EE, Ritchey M, Bass JK, et al. How is depression experienced around the world? A systematic review of qualitative literature. *Soc Sci Med*. 2017;183:151-162.
159. Kalichman SC, Rompa D, Cage M. Distinguishing between overlapping somatic symptoms of depression and HIV disease in people living with HIV-AIDS. *J Nerv Ment Dis*. 2000;188(10):662-670.
160. Heffron R, Ngure K, Quame-Amaglo J, et al. Successful use of safer conception strategies resulting in high pregnancy rates and no HIV transmissions among Kenyan HIV discordant couples. Oral Presentation Session SY07.01 presented at the: HIV Research for Prevention (HIVR4P) 2018; October 21, 2018; Madrid, Spain.
161. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613.

162. Levin K, Willis GB, Forsyth BH, et al. Using Cognitive Interviews to Evaluate the Spanish-Language Translation of Dietary Questionnaire. *Surv Res Methods*. 2009;3(1):13-25.
163. Murphy M, Hollinghurst S, Salisbury C. Qualitative assessment of the primary care outcomes questionnaire: a cognitive interview study. *BMC Health Serv Res*. 2018;18.
164. Malpass A, Dowrick C, Gilbody S, et al. Usefulness of PHQ-9 in primary care to determine meaningful symptoms of low mood: a qualitative study. *Br J Gen Pract*. 2016;66(643):e78-84.
165. Robinson J, Khan N, Fusco L, Malpass A, Lewis G, Dowrick C. Why are there discrepancies between depressed patients' Global Rating of Change and scores on the Patient Health Questionnaire depression module? A qualitative study of primary care in England. *BMJ Open*. 2017;7(4):e014519.
166. Gelaye B, Williams MA, Lemma S, et al. Validity of the Patient Health Questionnaire-9 for Depression Screening and Diagnosis in East Africa. *Psychiatry Res*. 2013;210(2).
167. Kohrt BA, Luitel NP, Acharya P, Jordans MJD. Detection of depression in low resource settings: validation of the Patient Health Questionnaire (PHQ-9) and cultural concepts of distress in Nepal. *BMC Psychiatry*. 2016;16:58.
168. Simoni JM, Safren SA, Manhart LE, et al. Challenges in addressing depression in HIV research: assessment, cultural context, and methods. *AIDS Behav*. 2011;15(2):376-388.
169. Egbe CO, Dakum PS, Ekong E, Kohrt BA, Minto JG, Ticao CJ. Depression, suicidality, and alcohol use disorder among people living with HIV/AIDS in Nigeria. *BMC Public Health*. 2017;17(1):542.
170. Thoughts of Death and Suicide Reported by Cancer Patients Who Endorsed the "Suicidal Thoughts" Item of the PHQ-9 During Routine Screening for Depression. *Psychosomatics*. 2011;52(5):424-427.
171. Mugisha J, Hjelmeland H, Kinyanda E, Knizek BL. Religious views on suicide among the Baganda, Uganda: a qualitative study. *Death Stud*. 2013;37(4):343-361.
172. Osafo J, Knizek BL, Akotia CS, Hjelmeland H. Influence of religious factors on attitudes towards suicidal behaviour in Ghana. *J Relig Health*. 2013;52(2):488-504.
173. Osafo J, Knizek BL, Akotia CS, Hjelmeland H. Attitudes of psychologists and nurses toward suicide and suicide prevention in Ghana: a qualitative study. *Int J Nurs Stud*. 2012;49(6):691-700.
174. Keugoung B, Kongnyu ET, Meli J, Criel B. Profile of suicide in rural Cameroon: are health systems doing enough? *Trop Med Int Health*. 2013;18(8):985-992.
175. Koenig HG, Pappas P, Holsinger T, Bachar JR. Assessing diagnostic approaches to depression in medically ill older adults: how reliably can mental health professionals make judgments about the cause of symptoms? *J Am Geriatr Soc*. 1995;43(5):472-478.

176. Koenig HG, George LK, Peterson BL, Pieper CF. Depression in medically ill hospitalized older adults: prevalence, characteristics, and course of symptoms according to six diagnostic schemes. *Am J Psychiatry*. 1997;154(10):1376-1383.
177. Cockram A, Judd FK, Mijch A, Norman T. The evaluation of depression in inpatients with HIV disease. *Aust N Z J Psychiatry*. 1999;33(3):344-352.
178. Kathol RG, Mutgi A, Williams J, Clamon G, Noyes R. Diagnosis of major depression in cancer patients according to four sets of criteria. *Am J Psychiatry*. 1990;147(8):1021-1024.
179. Shidhaye R, Mendenhall E, Sumathipala K, Sumathipala A, Patel V. Association of somatoform disorders with anxiety and depression in women in low and middle income countries: a systematic review. *Int Rev Psychiatry*. 2013;25(1):65-76.
180. Santos IS, Tavares BF, Munhoz TN, et al. Patient Health Questionnaire-9 versus Edinburgh Postnatal Depression Scale in screening for major depressive episodes: a cross-sectional population-based study. *BMC Res Notes*. 2017;10(1):57.
181. Zhong Q, Gelaye B, Rondon M, et al. Comparative performance of Patient Health Questionnaire-9 and Edinburgh Postnatal Depression Scale for screening antepartum depression. *J Affect Disord*. 2014;162:1-7.
182. Ab L, Ez A, Sm C. Screening for depression in pregnant women with HIV infection. *J Reprod Med*. 2008;53(5):352-356.
183. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct*. 2008;213(1-2):93-118.
184. Slavich GM, Irwin MR. From Stress to Inflammation and Major Depressive Disorder: A Social Signal Transduction Theory of Depression. *Psychol Bull*. 2014;140(3):774-815.
185. Forbes EE, Dahl RE. Research Review: altered reward function in adolescent depression: what, when and how? *J Child Psychol Psychiatry*. 2012;53(1):3-15.
186. Van Rode V, Rotsaert M, Delhay M. Loneliness and adolescence: clinical implications and outlook. Literature review. *Rev Med Brux*. 2015;36(5):415-420.
187. Witvliet M, Brendgen M, van Lier PAC, Koot HM, Vitaro F. Early adolescent depressive symptoms: prediction from clique isolation, loneliness, and perceived social acceptance. *J Abnorm Child Psychol*. 2010;38(8):1045-1056.
188. Nicolosi A, Moreira ED, Villa M, Glasser DB. A population study of the association between sexual function, sexual satisfaction and depressive symptoms in men. *J Affect Disord*. 2004;82(2):235-243. doi:10.1016/j.jad.2003.12.008
189. Chen H, Li X, Li B, Huang A. Negative trust and depression among female sex workers in Western China: The mediating role of thwarted belongingness. *Psychiatry Res*. 2017;256:448-452.

190. Baeten JM, Heffron R, Kidoguchi L, et al. Integrated Delivery of Antiretroviral Treatment and Pre-exposure Prophylaxis to HIV-1-Serodiscordant Couples: A Prospective Implementation Study in Kenya and Uganda. *PLoS Med.* 2016;13(8):e1002099.
191. Celum CL, Delany-Moretlwe S, Hosek SG, et al. Risk behavior, perception, and reasons for PrEP among young African women in HPTN 082. Presented at the: Conference on Retroviruses and Opportunistic Infections 2018 (CROI); March 4, 2018; Boston, Massachusetts.
192. Nglazi MD, van Schaik N, Kranzer K, Lawn SD, Wood R, Bekker L-G. An incentivized HIV counseling and testing program targeting hard-to-reach unemployed men in Cape Town, South Africa. *J Acquir Immune Defic Syndr.* 2012;59(3):e28-34.
193. Marcus JL, Levine K, Grasso C, et al. HIV Preexposure Prophylaxis as a Gateway to Primary Care. *Am J Public Health.* 2018;108(10):1418-1420.
194. Johnson LR, Mayanja MK, Bangirana P, Kizito S. Contrasting concepts of depression in Uganda: implications for service delivery in a multicultural context. *Am J Orthopsychiatry.* 2009;79(2):275-289.
195. Patel V, Abas M, Broadhead J, Todd C, Reeler A. Depression in developing countries: lessons from Zimbabwe. *BMJ.* 2001;322(7284):482-484.
196. Rochat TJ, Tomlinson M, Bärnighausen T, Newell M-L, Stein A. The prevalence and clinical presentation of antenatal depression in rural South Africa. *J Affect Disord.* 2011;135(1-3):362-373.
197. Wittkowski A, Gardner PL, Bunton P, Edge D. Culturally determined risk factors for postnatal depression in Sub-Saharan Africa: a mixed method systematic review. *J Affect Disord.* 2014;163:115-124.
198. Kaiser BN, Haroz EE, Kohrt BA, Bolton PA, Bass JK, Hinton DE. "Thinking too much": A systematic review of a common idiom of distress. *Soc Sci Med.* 2015;147:170-183.
199. Karasz A. Cultural differences in conceptual models of depression. *Soc Sci Med.* 2005;60(7):1625-1635.
200. Saxena S, Thornicroft G, Knapp M, Whiteford H. Resources for mental health: scarcity, inequity, and inefficiency. *The Lancet.* 2007;370(9590):878-889.
201. Burgess RA. Supporting mental health in South African HIV-affected communities: primary health care professionals' understandings and responses. *Health Policy Plan.* 2015;30(7):917-927.
202. Barry MC, Threats M, Blackburn NA, et al. "Stay strong! keep ya head up! move on! it gets better!!!!": resilience processes in the healthMpowerment online intervention of young black gay, bisexual and other men who have sex with men. *AIDS Care.* 2018;30(sup5):S27-S38.
203. Patel V, Saxena S, Lund C, et al. The Lancet Commission on global mental health and sustainable development. *The Lancet.* 2018;392(10157):1553-1598.

204. Whiteford HA, Degenhardt L, Rehm J, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *The Lancet*. 2013;382(9904):1575-1586.
205. *WHO Implementation Tool for Pre-Exposure Prophylaxis (PrEP) of HIV Infection. Module 12: Adolescents and Young Adults*. Geneva, Switzerland: World Health Organization; 2018.
206. van Ginneken N, Tharyan P, Lewin S, et al. Non-specialist health worker interventions for the care of mental, neurological and substance-abuse disorders in low- and middle-income countries. In: The Cochrane Collaboration, ed. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2013.
207. Dua T, Barbui C, Clark N, et al. Evidence-based guidelines for mental, neurological, and substance use disorders in low- and middle-income countries: summary of WHO recommendations. *PLoS Med*. 2011;8(11):e1001122.
208. Collins PY, Insel TR, Chockalingam A, Daar A, Maddox YT. Grand Challenges in Global Mental Health: Integration in Research, Policy, and Practice. *PLoS Med*. 2013;10(4).
209. Andersen LS, Magidson JF, O'Cleirigh C, et al. A pilot study of a nurse-delivered cognitive behavioral therapy intervention (Ziphamandla) for adherence and depression in HIV in South Africa. *J Health Psychol*. 2018;23(6):776-787.
210. Rahman A, Malik A, Sikander S, Roberts C, Creed F. Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomised controlled trial. *The Lancet*. 2008;372(9642):902-909.
211. Chibanda D. Reducing the treatment gap for mental, neurological and substance use disorders in Africa: lessons from the Friendship Bench in Zimbabwe. *Epidemiol Psychiatr Sci*. 2017;26(4):342-347.
212. Abas M, Nyamayaro P, Bere T, et al. Feasibility and Acceptability of a Task-Shifted Intervention to Enhance Adherence to HIV Medication and Improve Depression in People Living with HIV in Zimbabwe, a Low Income Country in Sub-Saharan Africa. *AIDS Behav*. 2018;22(1):86-101.
213. Gouse H, Robbins RN, Mellins CA, et al. Empowering Lay-Counsellors with Technology: Masivukeni, a Standardized Multimedia Counselling Support Tool to Deliver ART Counselling. *AIDS Behav*. 2018;22(10):3345-3356.
214. Robbins RN, Mellins CA, Leu C-S, et al. Enhancing Lay Counselor Capacity to Improve Patient Outcomes with Multimedia Technology. *AIDS Behav*. 2015;19 Suppl 2:163-176.
215. Wagenaar BH, Stergachis A, Rao D, et al. The availability of essential medicines for mental healthcare in Sofala, Mozambique. *Glob Health Action*. 2015;8(1):27942.
216. Thome J, Marenah E, Moraru D, Höppner J, Nyan O. Availability of psychiatric medication in an urban area of The Gambia/West Africa. *World J Biol Psychiatry*. 2011;12(sup1):114-117.

217. Gaynes BN, Pence BW, Atashili J, et al. Changes in HIV Outcomes Following Depression Care in a Resource-Limited Setting: Results from a Pilot Study in Bamenda, Cameroon. *PloS One*. 2015;10(10):e0140001.
218. Greene GJ, Swann G, Fought AJ, et al. Preferences for Long-Acting Pre-exposure Prophylaxis (PrEP), Daily Oral PrEP, or Condoms for HIV Prevention Among U.S. Men Who Have Sex with Men. *AIDS Behav*. 2017;21(5):1336-1349.
219. Minnis AM, Browne EN, Boeri M, et al. Young women's stated preferences for biomedical HIV prevention: results of a discrete choice experiment in Kenya and South Africa. *J Acquir Immune Defic Syndr*. 2019;80(4):394-403.

VITA

Jennifer Velloza completed her PhD in the Department of Epidemiology at the University of Washington in May 2019. Her research, teaching, and mentoring focuses on advancing the field of global mental health and the intersection with HIV prevention specifically for adolescent girls and young women. Prior to completing her doctorate degree, she received her BA in Neuroscience & Behavior from Columbia University and her MPH in Health Behavior from the University of North Carolina at Chapel Hill. Through her time at the University of Washington and her previous roles at FHI 360, Doctors Without Borders, and Duke University, she has worked on several NIH-funded studies to: 1) understand the potential effect of psychosocial factors including depression, trauma, and substance use on HIV risk; 2) integrate mobile health (“mHealth”) solutions into mental health, reproductive health, and HIV care; and 3) implement combined mental health and HIV prevention interventions for women in sub-Saharan Africa. For the four studies included in this dissertation, Ms. Velloza has been actively involved in the data collection, management, and analysis. In addition, she served as the Data Manager on the Safer Conception Intervention for Partners (SCIP) study and led database development, ran regular monitoring reports, and conducted statistical analyses for the primary study manuscripts. She was also involved in protocol development and qualitative data collection and analysis trainings for the HPTN 082 study. Ms. Velloza collaborates extensively with colleagues in Kenya, South Africa, and Zimbabwe. She utilizes a range of interdisciplinary methods including clinical epidemiology, behavioral science, causal inference, implementation science, and qualitative approaches to answer her research questions of interest.