DEPRESSION SCREENING AND TREATMENT FOR PEOPLE INITIATING HIV CARE IN MALAWI

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ABSTRACT

Melissa A Stockton: Depression Screening and Treatment for People Initiating HIV care in Malawi
(Under the direction of Brian W. Pence)

Depression is highly prevalent among people living with HIV in Malawi and elsewhere in sub-Saharan Africa (SSA). Beyond the morbidity produced by depression in its own right, depression is also an important barrier to early and consistent HIV care engagement and long-term viral suppression. Depression treatment has been linked to improved antiretroviral therapy (ART) adherence in observational studies, although evidence from interventions is mixed. To address the burden of depression among people living with HIV, the Malawi Ministry of Health implemented a pilot program that integrates depression screening and treatment into public HIV care at two clinics in Lilongwe, Malawi.

Using abstracted clinical data from patients enrolled in the program evaluation as well as in-depth interviews with patients and health care facility staff, this dissertation aims to 1) estimate the association between baseline depression and retention in HIV care and viral suppression; 2) evaluate the impact of depression treatment on retention in HIV care, viral suppression, and depression remission; and 3) explain the success or failure of the program implementation using a mixed-methods approach that focuses on fidelity, acceptability and sustainability.

Among the 1091 participants screened for depression prior to the launch of the treatment program included in Aim 1, the prevalence of depression was 27%. Those with depression had similar HIV care outcomes at 6 months to those without depression.

Among the participants with elevated depressive symptoms at ART initiation included in Aim 2, program exposure did not demonstrably affect most HIV or mental health outcomes, though the probability of currently being on ART at 6 months was significantly lower among the intervention group than the control group [RR 0.6(95%CI: 0.4-0.9)].

The mixed-methods process evaluation presented in Aim 3 found that fidelity to the program protocol was poor and the program was not delivered as intended. While antidepressants and problem-solving therapy appeared to be acceptable treatment options for patients, clinic staff and leadership found delivering this treatment challenging in light of constrained human resources and infrastructure. The program was ultimately not sustained. As designed and without substantial support to supervise the implementation of the program, continue to build and maintain the capacity of providers, integrate the program into the electronic medical records system and ensure the availability of counselors, it does not appear feasible to integrate this depression treatment program into HIV care in this setting.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ART	Antiretroviral therapy
EMR	Electronic medical record
HIV	Human immunodeficiency virus
HTC	HIV testing and counseling
MBC	Measurement-based care
MOH	Malawi Ministry of Health
NCD	Non-communicable disease
PHQ-9	Patient Health Questionnaire-9
SOAR-MH	SOAR-Mental Health
SSA	sub-Saharan Africa
WHO	World Health Organization

CHAPTER I: SPECIFIC AIMS

Depression is highly prevalent among people living with HIV in Malawi and elsewhere in sub-Saharan Africa (SSA). Depression affects 18-30% of patients receiving HIV care in Africa.[1] Beyond the morbidity produced by depression in its own right, depression is also an important barrier to another critical need for those living with HIV – early and consistent HIV care engagement and long-term viral suppression.[1-6] Depression treatment has been linked to improved antiretroviral therapy (ART) adherence in observational studies[7-9], although evidence from interventions is mixed.[10-15] Further evidence is needed about the association between depression and retention in care and the impact of depression treatment on mental health and HIV care outcomes in Malawi and the sub-Saharan region.

The SOAR-Mental Health (SOAR-MH) project provided a unique real-world opportunity to address this knowledge gap. As part of this project, the Malawi Ministry of Health piloted a program that integrates depression screening and treatment into real-world HIV care at two public clinics in Lilongwe, Malawi.[16] HIV care providers with no prior mental health training were trained in depression assessment, diagnosis, and treatment. All patients completed depression screening at ART initiation. Providers treated depressed patients with antidepressants or referred patients to lay health workers trained to offer problem-solving therapy. All patients were followed longitudinally to capture both mental health and HIV outcomes. The program was implemented in two phases; a screening-only "control" phase and an active "intervention" phase to permit evaluation of program impact. Data from this project provide an outstanding

opportunity both to: 1) assess the relationship of depression with HIV outcomes; 2) examine the impact of a depression treatment program on those same outcomes; and 3) evaluate the implementation of this depression treatment program in the context of real-world HIV services in a low-income country in SSA.

The main objectives of this dissertation are to evaluate the impact of the SOAR-MH depression treatment program on HIV care outcomes and depressive symptoms six months after ART initiation and to explain the implementation of the program. This dissertation should provide urgently needed and critical insight into depression management and HIV care engagement in Malawi. The aims of this dissertation are:

AIM 1: Estimate the association between depressive symptoms at ART initiation and HIV care retention and HIV RNA suppression at six months among patients newly initiating ART. We used clinical appointment and HIV RNA data collected from 852 patients without and 291 patients with elevated depressive symptoms who initiated care during the screening-only phase of the SOAR-MH project and examined potential modification by gender. We hypothesized that patients with elevated depressive symptoms at ART initiation would be less likely to be retained in care and less likely to be virally suppressed six months after ART initiation compared to patients without such symptoms.

AIM 2: Estimate the impact of the depression treatment program on 1) HIV care retention, 2) HIV RNA suppression, and 3) depression remission at six months among patients with depressive symptoms newly initiating ART. Using an intent-to-treat analysis approach, we compared 291 patients with elevated depressive symptoms during the screening-only phase of the SOAR-MH project to 212 patients with such symptoms during the project's treatment program phase and examined potential modification by gender. We hypothesized that

patients during the treatment program phase would be more likely to 1) be retained in HIV care, 2) be virally suppressed, and 3) achieve depression remission six months after ART initiation compared to patients during the screening-only phase.

AIM 3: Explain the success or failure of the program implementation using a mixed-methods approach. We used clinical data and in-depth interviews with patients, providers, and clinic leadership to describe and explain program implementation. We hypothesized that this mixed-methods approach would help contextualize findings from Aims 1 and 2 and that lessons learned from this experience would inform future efforts to implement and evaluate integrated depression treatment programs.

This dissertation was a unique opportunity to study real-world depression treatment and HIV care in a high-HIV-prevalence setting in SSA. The study employed an innovative approach, combining traditional epidemiologic methods with implementation science to better understand the effect of depression on HIV outcomes and the impact of an integrated model of HIV and depression treatment. This improved understanding is urgently needed and may improve retention in HIV care and psychological wellbeing – key determinants of HIV-related mortality.

CHAPTER II: BACKGROUND

The prevalence of HIV in Malawi is one of the highest in the world at nearly 10% of the adult population. In 2018, an estimated 9.2% of the adult population (aged 15-49) in Malawi was living with HIV – approximately one million Malawians.[17] That same year, 90% of people living with HIV in Malawi were aware of their status, 78% were on treatment, and 69% were being virally suppressed.[17] Furthermore, women are disproportionately burdened by HIV in Malawi, a disparity that is especially prominent among 25- to 29-year-olds, as the prevalence among women in this age group (14.1%) is three time higher than among men (4.8%).[18] Such a drastically high prevalence of HIV may play a role in the country's low life expectancy, stress the health care system, and impede economic development.[19]

Malawi has rapidly scaled up its HIV testing and treatment services over the past two decades. Malawi was one of the first countries in sub-Saharan Africa (SSA) to adopt a "public health approach" to HIV scale-up, as promoted by the World Health Organization (WHO) to encourage rapid antiretroviral therapy (ART) initiation.[20,21] The country was also an early adopter in 2011 of Option B+, a mother-to-child-transmission strategy in which all pregnant women living with HIV are provided with ART.[22] Malawi now pursues a test-and-treat strategy in which patients found to be infected with HIV are immediately initiated on ART that same day.[20,21] Malawi, like many other countries in the sub-Saharan region, is striving to meet the UNAIDS 90-90-90 goals (diagnosing 90% of all people living with HIV, providing ART to 90% of those diagnosed, and achieving viral suppression for 90% of those treated). Despite recent

improvements in ART service provision[23], substantial attrition across the HIV care continuum continues to impede successful HIV outcomes for people living with HIV.[21,24]

Early retention and continued engagement in HIV care in Malawi remains challenging. While great strides have been made towards controlling the HIV epidemic and engaging people living with HIV in care, only 76% of adults initiating ART are retained in care at 12 months, and only 65% are both retained in care and virally suppressed at 12 months.[25] In Malawi, early retention in care is particularly challenging: nearly a quarter of people are lost to care during the first year of treatment.[26-28] As such, early retention remains a major obstacle to achieving the UNAIDS 90-90-90 goals.[26-28] Despite these retention shortfalls, research on retention in HIV care in Malawi has largely focused on a single population: pregnant women receiving the Option B+ intervention. Reasons for early attrition are among the general population living with HIV are not entirely understood and not well-explored. However, barriers to retention in care may include human resource and institutional challenges, distance to the clinic, lack of support, stigma and fear of HIV status disclosure, and psychiatric illnesses such as depression.[24,29-31]

Depression is a major contributor to the global burden of disease and disability and is highly prevalent among people living with HIV in Malawi and elsewhere in SSA where mental health care is limited.[32,33] A growing body of research is beginning to document the scope of mental health challenges in the general Malawian population. In Malawian primary care settings, 28.8% of all patients have a common mental disorder, most commonly depression.[34] Only a few studies have estimated the prevalence of depression among populations living with HIV in Malawi and estimates vary: 19% among adolescents attending HIV clinics[35]; 16% among adults newly initiating ART and 9% among adults on ART for at least 6 months[36]; and 10% of antenatal women and 1% to 6% of postpartum women.[37] Little is known about differences in

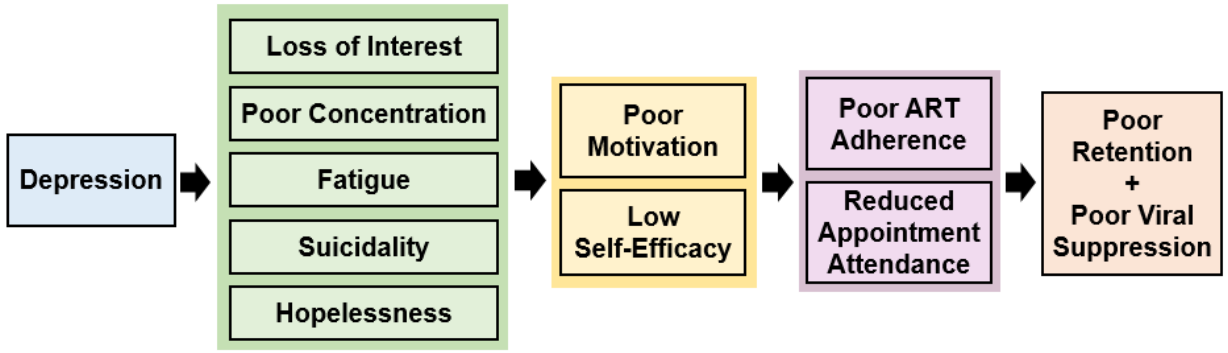
experiences with or prevalence of depression between men and women in SSA. A recent systematic review on the prevalence and factors associated with depression among people living with HIV in SSA found that being female was frequently associated with depression, but there was no consensus.[38] Worldwide, women generally have a higher prevalence of depression potential due to an array of social and biological factors.[39,40] However, qualitative research suggests that traditional masculine gender norms may impact the way men experience depression and engage with treatment.[41] Further research is needed to understand the magnitude of the burden of depression and unpack any gender differences in the sub-Saharan African region.

Depression is a critical barrier to HIV care engagement. Beyond the morbidity produced by depression in its own right, depression is also an important barrier to early and consistent HIV care engagement and long-term viral suppression.[1-6] A few studies conducted in SSA have found that depressed individuals are less likely to be linked to ART or start treatment.[42-44] For example, one study conducted in South Africa found that depressed individuals had a higher odds of waiting at least three months following an HIV diagnosis to initiate ART compared to their non-depressed counterparts.[42] Depression has been consistently associated with poor adherence to ART.[2,45] In SSA, and Malawi in particular, further evidence is needed to characterize the association between depression, HIV care engagement, and achievement of viral suppression.

The mechanisms through which depression undermines successful HIV care engagement are not fully clear; characteristics of depression including loss of interest, poor concentration, poor motivation, reduced self-efficacy, fatigue, hopelessness, and suicidality are all plausible factors which can impair adherence and appointment attendance.[2,4,46] A recent study evaluating the effect of depression treatment on ART adherence and HIV care appointment attendance in Uganda proposed a conceptual model for how depression may influence HIV care[47] (**Figure**

2.1). Drawing on social cognitive theory[48] and the information, motivation and behavioral skills (IMB) model of health behavior,[49] Wagner and colleagues argue depression may influence HIV care adherence through its effects on self-efficacy and motivation to adhere to treatment and attend clinic visits.[47] In order to address the burden of depression, prevent the disruption of these underlying determinants of HIV care engagement, and ultimately achieve the USAID 90-90-90 targets, evidence-based depression management approaches to improve early retention in HIV care are needed.

Figure 2.1. Conceptual framework



Conceptual Model Adapted from: Wagner et al. 2017 "Effects of Depression Alleviation on ART Adherence and HIV Clinic Attendance in Uganda, and the Mediating Roles of Self-Efficacy and Motivation"

A growing body of depression treatment programs and models of care have been developed for people living with HIV. A recent systematic review of depression interventions found that psychological and behavioral interventions were effective treatments for depression among people living with HIV.[50] A separate systematic review and meta-analysis of antidepressant medication among people living with HIV found medication to also be an effective means of managing depression.[51] Furthermore, depression treatment has been linked to improved ART adherence in observational studies[7-9], although evidence from interventions is mixed.[10-15] However, there are few evidence-based depression treatment programs for people living with HIV tailored for use in the sub-Saharan region. Among those, antidepressant and

psychological counseling interventions in Tanzania, Zimbabwe, Cameroon, and Uganda, among other countries, have demonstrated promising improvements in HIV and mental health outcomes.[52-58] Antidepressant interventions have employed measurement-based care (MBC) models of antidepressant management, often relying on tricyclic antidepressants such as amitriptyline[58,59] and imipramine,[60] which have demonstrated excellent safety and efficacy among people living with HIV. Problem-solving therapy, which centers around teaching patients how to identify triggers and effectively manage stressful life events by learning or reactivating problem-solving skills, has also been used in the region.[61] For example, a problem-solving therapy program called the "Friendship Bench" was effectively designed for use in Zimbabwe and proven to be a successful depression treatment option.[62] Further investment in depression treatment programs effective in low-resource settings is warranted.

Mental health care infrastructure and human resources are severely limited in Malawi; currently, the country contains only three operational mental health facilities, all of which are located in urban centers. Mental health care is considered a specialized service in Malawi and is offered almost exclusively at these facilities. As of 2018, there were only four fully trained psychiatrists in the country – approximately one psychiatrist for every 4.5 million Malawians. It is unlikely that it will be possible to increase the number of specialized mental health service providers as a means of appropriately meeting the mental health needs of the population. While the lack of national data demonstrating the magnitude of mental health problems has historically hampered efforts to secure resources for mental health care[16], movement over the last several years suggests this trend may be changing.

There is a growth of recognition, support, and investment in mental health by the Malawian government. The Malawi Ministry of Health (MOH) recently established their Non-

Communicable Disease (NCD) and Mental Health Unit and prioritized mental health treatment in their 2017-2022 Malawi Health Sector Strategic Plan.[63,64] The NCD and Mental Health Unit has since developed action plans to: 1) integrate mental health services into other general health services; 2) improve the capacity of general health care workers through training to diagnose and manage mental health conditions at different levels of care; and 3) raise awareness of mental health disorders and treatment among the general population through community health workers, teachers, religious leaders, peer educators, and the media.[65] As a result of these efforts, a pilot program aimed at building the mental health capacity of community health workers, encouraging community-level mental health promotion and detection, and integrating these community health worker activities into the primary care setting was successfully implemented in the Zomba District in southern Malawi from 2010 through 2014.[66-68] Despite these advances, there is an urgent need for further investment in mental health treatment programs to effectively realize the MOH's mental health goals and address the burden of depression among people living with HIV.

Task-shifting depression treatment programs have the potential to improve HIV care and mental health outcomes, in light of mental health resource limitations. Task-shifting describes a process of moving tasks to less specialized health workers as means of improving health care coverage by making more efficient use of available human resources.[69] Global guidance recommends task-shifting approaches as a means of providing mental health services in low-resource settings.[70] The integration of mental health services into existing primary and community health services in resource-limited settings has gained popularity in recent years.[71-73] In sub-Saharan Africa, task-shifting approaches are seen as an effective, economical, and practical means of managing depression.[71,74] While only a few such programs have been implemented in Africa,[56] the Malawi Ministry of Health piloted a task-shifting program, called

SOAR-Mental Health (SOAR-MH), that integrated depression screening and management into HIV care.[16] Evaluating the implementation and impact of task-shifting models of care on mental health and HIV care outcomes in Malawi may be key to improving comprehensive care for people living with HIV and provide insight into the potential for countrywide scale-up.

Significance

This dissertation advances understanding of depression, depression treatment, depression screening, and engagement in HIV care. This research quantified the association of depression with retention in HIV care and viral suppression (Aim 1) and evaluated the effect of depression treatment on HIV and depression outcomes (Aim 2). This research further examined program implementation and sustainability using both clinical and qualitative data (Aim 3).

Innovation

This was the first study conducted in Malawi to evaluate a program integrating depression treatment into HIV care, and findings can be used to directly inform Malawi's mental health treatment efforts. There is limited mental health infrastructure and few mental health specialists in Malawi, as is true in many other low- and middle-income countries.[16] The Malawi Ministry of Health piloted a program, called SOAR-Mental Health (SOAR-MH), that integrated depression screening and treatment into ART initiation at two public health clinics as a means to address the burden of depression and improve retention in care among people living with HIV.[16] This novel pilot program was the country's first depression treatment program for people living with HIV and one of the few in the sub-Saharan region to use a task-shifting model to provide both problem-solving therapy and antidepressant depression treatment.[52-56] This study is also the first to evaluate the impact of the program and investigate the potential benefits of this task-shifting depression care model. Findings from this study can be used to directly inform the

Malawi Ministry of Health's ongoing national strategic plans to: 1) integrate mental health services into other general health services; 2) improve the capacity of general health care workers to diagnose and manage mental health conditions at different levels of care; and 3) raise awareness of mental health among the general population.[65]

The study employed an innovative approach, combining traditional epidemiologic methods with implementation science. Implementation science is a relatively new discipline, particularly in low- and middle-income countries.[75] There is a clear need in the field of epidemiology to generate evidence-based practices, interventions, and policies that can readily (and rapidly) be adopted and integrated into routine care in public sector settings.[76,77] This study inherently lent itself to that purpose. We used traditional epidemiological techniques that are grounded in implementation science; specifically, our approach aimed to evaluate the effect of the SOAR-MH depression treatment on HIV outcomes and the feasibility of integrating depression treatment into existing public HIV services. SOAR-MH project was especially unique in that, while the evaluation staff worked on the ground to consent patients and collect data, none of the evaluation staff had any clinical responsibilities or influence on the provision of HIV or mental health care. As such, the study yielded high-quality, policy-relevant findings on depression and depression management integrated into HIV care – findings which are readily applicable to the implementation of integrated mental health services in non-specialist settings.

This study advances our understanding of the relationship between depression, depression treatment, and engagement in HIV care. The only other studies on depression in Malawi describe its prevalence, but fail to unpack the association between depression and HIV care outcomes.[35-37] While depression treatment has been linked to improved ART adherence in observational studies[7-9], evidence from interventions is mixed.[10-15] An improved understanding

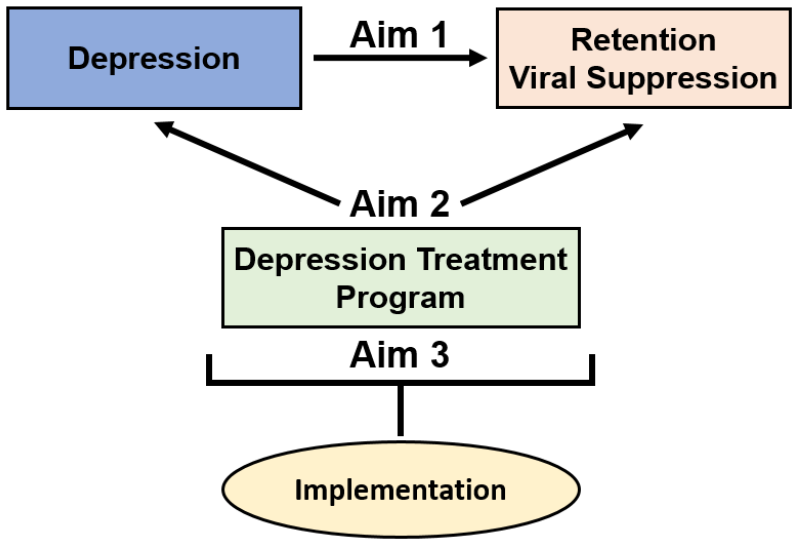
of depression treatment is urgently needed and may improve retention in HIV care, psychological wellbeing, and ultimately reduce mortality for people living with HIV. This study addressed this knowledge gap by generating evidence on the effect of depression on retention in HIV care and the potential impact of depression treatment on depression and mental health outcomes. Such evidence may be critical for allocating resources to optimize HIV and mental health treatment services in Malawi, sub-Saharan Africa, and other high-HIV-prevalence settings.

CHAPTER III: METHODS

Overview

The goals of this dissertation were to: estimate the association between depression at antiretroviral therapy (ART) initiation and retention in HIV care and viral suppression (Aim 1); evaluate the impact of a depression treatment on depression, retention in HIV care and viral suppression (Aim 2); and explain the implementation of the program (Aim 3; **Figure 3.1).**

Figure 3.1. Model for dissertation aims



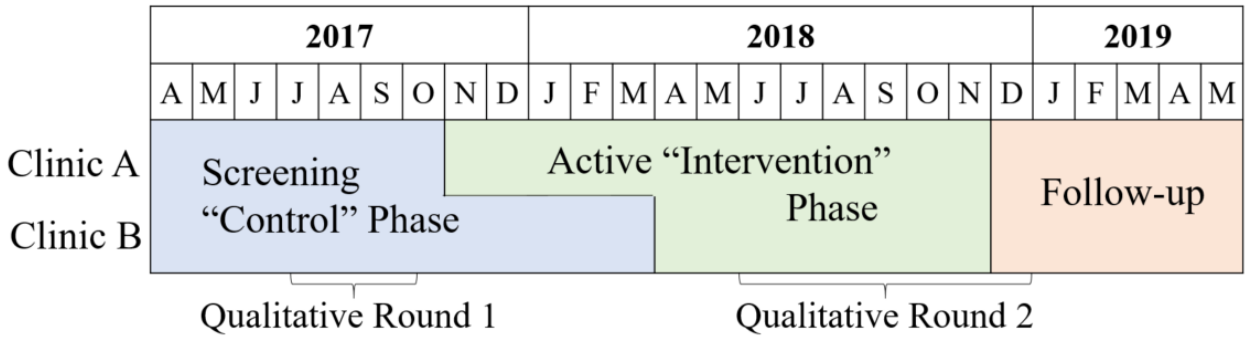
Parent Study

This study consisted of secondary analyses of existing data from the SOAR-MH evaluation study. SOAR-MH is a Malawi Ministry of Health pilot program that integrates depression screening and treatment into ART care at two clinics in Malawian capital of Lilongwe, where 10% of the population is HIV-positive.[78,79] These clinics, which offer health

care free of charge, are nested within two semi-urban primary-level health centers under Lilongwe District Health Management, in the Central Region of Malawi. One health center serves a catchment population of 63,783 adults and children while the other has a catchment population of 212,160 adults and children. However, anyone can receive health services at either facility, regardless of their residence. Both sites use electronic medical record (EMR) systems and host non-governmental partners that provide technical supervision and support, similar to what is seen at other public health facilities across the country.[16]

The program was implemented using a multiple baseline design in two phases: a screening-only "control" phase and a treatment "intervention" phase (**Figure 3.2**). In-depth interviews were conducted first during the screening phase (round 1) and then again after the launch of program (round 2).

Figure 3.2. Program implementation



During the screening phase, HIV care providers screened patients for depression and monitored their depressive symptoms using the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 is a widely used nine-item instrument that assesses the presence of nine symptoms of depression within the previous two weeks as specified by the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5).[80] The PHQ-9 was chosen because it focuses specifically on

depression, has been widely used and validated in many different settings[81], and works well both as a screening tool for depression as well as a longitudinal measure to monitor response to treatment. This tool has been validated for use in HIV-positive populations in other countries in the region.[82,83] Each of the nine items is scored as present from 0 (not at all) to 3 (nearly every day). A total score of 5-9 is considered indicative of mild depression, and a score of 10 or higher is considered indicative of moderate to severe depression (**Table 3.1**).[84]

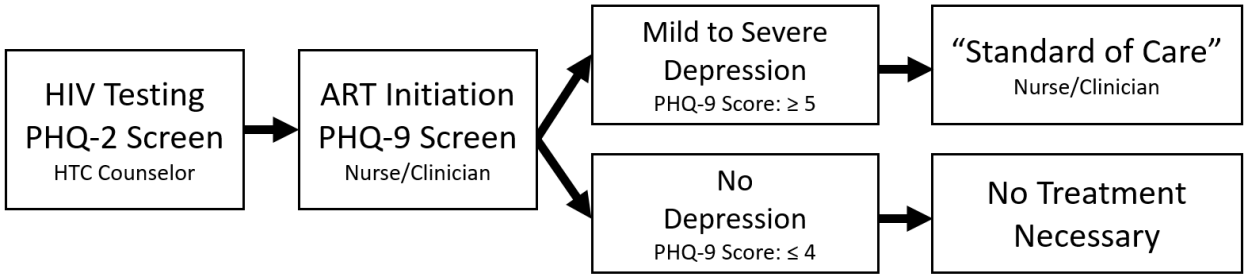
Table 3.1. PHQ-9 score interpretation and resulting treatment

Score	Depressive Symptoms	Screening Phase	Intervention Phase
0-4	No or minimal	No treatment	No treatment necessary
5-9	Mild	Clinician counseling or referral to psychiatric nurse or facility*	Problem-solving therapy
≥10	Moderate to severe	Clinician counseling or referral to psychiatric nurse or facility*	Antidepressants

Note: *Standard of care prior to the launch of the treatment program.

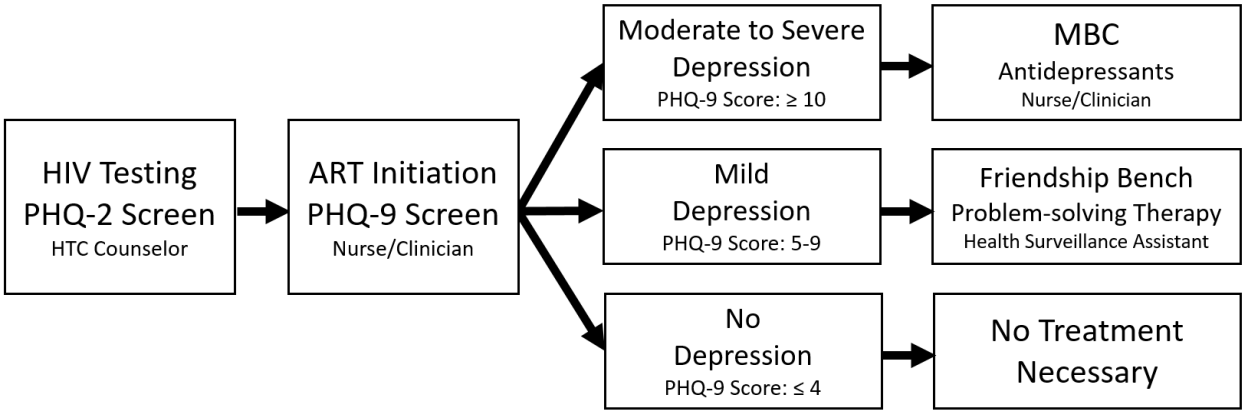
During the screening phase (**Figure 3.3**), the HTC counselors screened patients who test positive for HIV with the first two questions of the PHQ-9 – known as the Patient Health Questionnaire-2 (PHQ-2) – which capture depressed mood and anhedonia, the two core symptoms of depression. Only patients who scored above 0 on the PHQ-2 were then assessed for the presence of the remaining seven symptoms of the PHQ-9 by the ART nurse or clinician during ART initiation. ART providers managed patients identified with depression using existing "standard of care" pathways, which could include counseling by the clinician, referral to an on-site or off-site psychiatric nurse or other mental health specialist, or in acute cases, transport to the outpatient psychiatric unit at the nearby district hospital.

Figure 3.3. Depression screening during the screening "control" phase



During the intervention phase (**Figure 3.4**), patients continued to be screened with the PHQ-9, but with an important difference. At the launch of this intervention phase, HIV care providers received additional training in depression management using an algorithm-guided module that utilizes PHQ-9 scores. Clinic-based lay health workers received training on Friendship Bench problem-solving therapy, a type of cognitive-behavioral counseling. As part of this module, providers used a PHQ-9 score algorithm to 1) prescribe antidepressants and manage dosage changes using a measurement-based care (MBC) protocol or 2) refer patients for Friendship Bench problem-solving therapy. Specifically, providers treated moderate to severe cases of depression with amitriptyline or fluoxetine using MBC. MBC is a resource-efficient, task-sharing model for prescribing antidepressant management in non-psychiatric settings that has demonstrated safety, feasibility, and acceptability as part of HIV care when delivered by non-specialists in Africa.[58-60] Providers referred mild cases of depression to lay health workers. These lay health workers treated mild depression with Friendship Bench problem-solving therapy, a cognitive-behavioral counseling strategy originally developed in Zimbabwe that teaches patients how to identify triggers and effectively manage stressful life events by learning or reactivating problem-solving skills.[56] These patients continued to be monitored by providers at follow-up ART visits.

Figure 3.4. Depression screening during the treatment "intervention" phase



Study Population

To evaluate the program, clinical data was abstracted from consenting non-pregnant adults (age ≥ 18) who tested positive for HIV and initiated care at one of the program sites between April 2017 and November 2018 both with (PHQ-9 ≥ 5) and without (PHQ-9 <5) depressive symptoms (**Table 3.2**). Across both study phases (i.e., the screening-only "control" phase and the active "intervention" phase), the evaluation enrolled a total of 2067 patients.

Table 3.2. Study populations included in each aim

	Quantitative				**Qualitative**	
Phase Enrolled:	Screening		Treatment		Screening	Treatment
PHQ-9 Score*	≥ 5	< 5	≥ 5	< 5	n/a	n/a
Number of participants	290	852	212	724	24	26
Included in Aim 1	✓	✓				
Included in Aim 2	✓		✓			
Included in Aim 3		✓		✓		✓

Notes: *PHQ-9 ≥ 5 is indicative of elevated depressive symptoms. PHQ-9=Patient Health Questionnaire-9.

Only patients who completed depression screening at baseline were included in these analyses. Aims 1 (association between depression and successful HIV treatment retention) and 2

(depression treatment program evaluation) consisted of analyses of data from patients enrolled during the SOAR-MH program evaluation. Aim 3 (mixed-methods assessment of program implementation) used data from patients enrolled during the program evaluation as well as qualitative data from the second round of in-depth interviews with patients, Friendship Bench counselors, ART providers, and clinic leadership.

Data Collection and Abstraction

This study relied on the abstraction of routinely collected clinical data on depression screening and HIV care from consenting participants' ART clinical records over a 13-month period, starting at ART initiation. At the study sites, when a patient initiates ART, clinic staff create a paper medical chart (called an ART mastercard) and accompanying electronic medical record for the patient where HIV care data will be recorded.

Additionally, two rounds of in-depth interviews were conducted with patients and health care facility staff at both sites, the first round during the screening-only control phase and the second during the intervention phase. Prior to both rounds of data collection, evaluation staff met with administrators at both health centers and drew up a list of staff. The program coordinator or interviewer approached staff and leadership at each clinic to schedule interviews. The research assistants identified patients returning for ART services and invited these patients to participate. An effort was made to interview both men and women, as prior research has shown attitudes towards depression and the provision of mental health care may vary by gender in both providers and patients.[85-87]

The research team developed semi-structured interview guides to evaluate the implementation at different stages of the program. The first interview guide focused on experiences with the depression screening and care during the screening-only phase. The second

interview guide focused on experiences during the intervention phase, specifically with MBC or the Friendship Bench. Interviews were conducted in either Chichewa (the local language) or English, based on participants' preference, by two different Malawian women with backgrounds in qualitative research and HIV care services. All interviews were held at the respective clinics in a private location. The interviews were audio-recorded and transcribed as follows: The first round of qualitative interviews was directly translated and transcribed into English. The second round of qualitative interviews was transcribed in Chichewa and then translated into English. The research team reviewed transcripts as they became available and provided feedback to the interviewers throughout the data collection process to ensure quality.

Measures

This dissertation draws on abstracted clinical data from consenting participants. During the program evaluation, research assistants abstracted routinely collected clinic data on depression and HIV care from consenting participants' clinical records over a 13-month period, starting at ART initiation. Abstracted data included appointment dates, expected return dates, ART pills dispensed, PHQ-9 scores, and depression treatment provided. Additionally, data on age, sex, clinic, World Health Organization (WHO) disease stage[88], village of residence, ART medication prescribed, and presence of baseline suicidality were abstracted.

Depression at ART Initiation

Depression at ART initiation was measured with the PHQ-9. Elevated depressive symptoms suggesting a high risk of a depressive disorder was defined as a PHQ-9 score ≥5 at ART initiation.[89] We also considered a 3-level depressive severity measure (0-4, 5-9, and ≥10, corresponding to no depression, mild depression, and moderate to severe depression, respectively) and a continuous measure of depressive severity (range 0-27).

Retention in Care

The following metrics were used to measure retention in care:

Continuous engagement in care was defined as never being more that 14 days late to an appointment through six months in care.

Alive and in care at six months was defined as being on ART for at least some portion of the two months prior to the six-month anniversary of starting ART, in alignment with Malawi Ministry of Health reporting practices. According to the Malawi Guidelines for Clinical Management of HIV in Children and Adults, an ART patient is classified as a defaulter if they go two months without ART based on the pill provided at their most recent appointment.[90] Patients who are not known to have transferred, stopped ART, or died are classified as alive and on ART.

Currently on ART at six months was defined as currently having ART on hand at six months, i.e., attending an appointment prior to the six-month point and receiving a supply of ART that would last through the six-month point. For example, if a participant attended an appointment five and a half months after starting ART and received a 30-day supply of ART, they would have been considered currently on ART at six months. This indicator aligns closely with the PEPFAR definition of "currently on treatment."[91]

In care after six months was defined as attending at least one appointment where ART is provided after six months in care. This definition aligns more closely with the UNAIDS Global AIDS Monitoring 2019 Indicators by identifying participants known to be on ART at some point six months after initiation.[92]

HIV appointment attendance was defined as the proportion of scheduled HIV appointments attended within one week of the scheduled appointment date in the first six months of care.[93]

Consistent ART was defined as never going more than five days without ART in the first six months, calculated from the cumulative days' supply of ART dispensed at each appointment in the first six months and the time between appointments.

ART pill possession ratio was defined as the proportion of the first six months (183 days) since ART initiation with ART in hand, calculated from cumulative pills dispensed at each ART appointment through six months.[94]

Viral Suppression

We defined viral suppression as a viral load <1,000 copies/mL drawn at least five and a half months (166 days) after starting ART, following the 2018 Malawian ART guidelines. Viral load testing was performed at Bwaila Hospital in Lilongwe using collected plasma or dried blood spots and processed by Abbott m2000 RealTime HIV-1 assay instruments.[95]

Depression Remission

Depression remission was defined as a PHQ-9 score of less than 5 taken after at least five and a half months (166 days) in care, to allow for completion of the acute phase of treatment and maintenance of that response.[96]

Other Covariates

Potential confounders included in the Aims 1-2 analyses included age (in years), sex, clinic, World Health Organization (WHO) HIV clinical stage for HIV surveillance (I-IV)[88], village of residence, ART medication prescribed, and presence of baseline suicidality. Village of residence categorized individuals as residing in urban Lilongwe City, in rural Lilongwe District, or outside of Lilongwe District. Presence of suicidal thoughts was defined as any endorsement of the ninth question of the PHQ-9: "During the past two weeks, how many days have you been bothered by thoughts that you would be better off dead or of hurting yourself in some way?"

Data Analyses

All analyses were performed using STATA IC 14 or NVivo (Version 12).

Aim 1: Analysis

We completed unadjusted, tabular comparisons of HIV care outcomes by depressive severity. We used log-binomial models to estimate adjusted risk ratios comparing the probability of each binary HIV care outcome among those with depression compared to those without. For the continuous outcomes, we used ordinary least-squares linear regression models to estimate mean differences. Potential confounders were identified through directed acyclic graph (DAG) analysis.

To address missing outcome data for those who transferred to a non-study facility or who returned for care around six months but did not get a viral load, we used multiple imputation by chained equations (MICE) to fill missing values using logistic regression imputation methods[97].

Aim 2: Analysis

The main analysis followed an "intent-to-treat" approach, classifying participants according to the phase during which they initiated ART (i.e., to either the screening-only "control" group or the active "intervention" group) without regard to actual treatment received. We first completed unadjusted, tabular comparisons of HIV care and depression outcomes in the intervention group relative to the control group. We then used log-binomial models to estimate adjusted risk ratios comparing the probability of the primary outcome, i.e. retention with viral suppression, as well as the probability of other secondary HIV care outcomes in the intervention group compared to the control group. To separately evaluate the impact of the Friendship Bench therapy and the antidepressant treatment, we then stratified the main analysis by depressive severity at baseline (mild or moderate-to-severe depressive symptoms). Other secondary

analyses used a "treatment started" approach, comparing those who actually started Friendship Bench therapy or antidepressants to those who did not in both phases, and then an "as treated" approach, comparing those who received at least two Friendship Bench therapy sessions or two months of antidepressants to patients who did not in both phases, restricted to only those who attended at least their first follow-up visit.

To address missing outcome data due to transferring to a non-study site facility for HIV care, we used multiple imputation by chained equations (MICE) to fill missing values using logistic regression imputation methods. [97]

Aim 3: Analysis

Using clinically abstracted data, participants were classified by the phase during which they initiated ART treatment, i.e., to either the screening-only "control" or active "intervention" group. We completed tabular comparisons of participants' depression treatment data to describe the implementation of the program.

Only the second round of qualitative data was analyzed as part of this aim. After reading each of the transcripts, the doctoral candidate (MS) drafted a thematic codebook that addressed the study objectives and captured emerging themes evident from her initial review of the transcripts.[98,99] As such, many codes were developed *a priori*, given that the interview questions were linked to the program implementation, while others were developed *a posteriori*. MS then met with research team members who had simultaneously been reviewing the transcripts to review and finalize the codebook. Two coders (MS and an additional second coder) coded a subset of the same transcripts to ensure consistency in their use of the codes using NVivo (Version 12). Coding was treated as an iterative process and the coders met several times throughout to discuss the addition, definition, and appropriate use of the codes that emerged from

the data. Additionally, the coders wrote memos for the individual transcripts and on emerging themes. Upon completion of coding, MS executed queries in NVivo and both she and the second coder reviewed coded data related to the key aspects of program implementation: depression treatment initiation, depression treatment over time, program impact, and program sustainability. While synthesizing these findings, MS met with the research team to ensure accurate interpretation of the interviews.

CHAPTER IV: ASSOCIATION BETWEEN DEPRESSION AND HIV CARE ENGAGEMENT OUTCOMES AMONG PATIENTS NEWLY INITIATING ART IN LILONGWE, MALAWI

Introduction

The prevalence of HIV in sub-Saharan countries such as Malawi is among the highest in the world.[17,100] Like many other countries in the region, Malawi has adopted a "public health approach" to HIV scale-up in order to meet the UNAIDS 90-90-90 goals (diagnosing 90% of all people living with HIV, providing antiretroviral therapy [ART] to 90% of those diagnosed, and achieving viral suppression for 90% of those treated).[20,21,101] Great strides have been made towards achieving these goals and engaging people living with HIV in care across the region[102,103]; in 2018 in Malawi, 90% of those living with HIV were estimated to be aware of their status, 87% of those aware of their status were on treatment, and 89% of those on treatment were virally suppressed.[17] Despite recent improvements in ART service provision, both linkage to care and continued engagement in HIV care in sub-Saharan Africa (SSA) remain challenging[104,105]; improving retention in HIV care will be crucial to attaining the 90% on ART target in the sub-Saharan region.[104,106] The reasons for attrition among people living with HIV are not entirely understood, though barriers to retention in care may include human resource and institutional challenges, distance to the clinic, lack of support, stigma and fear of HIV status disclosure, and psychiatric illnesses such as depression.[24,29-31]

Depression is a major contributor to the burden of disease and disability and is highly prevalent among people living with HIV in Malawi and elsewhere in SSA, a region where mental health care is often limited.[32,33] Depression affects 18% to 30% of patients receiving HIV

care in Africa,[1] and estimates from Malawi range from 1% to 19%.[35-37,107] The high prevalence of depression among people living with HIV is thought to be due to coping with the HIV diagnosis, disease symptoms, bereavement, relationship crises, stigma and discrimination, co-existing poverty, ART side effects, fear of death, and infection-related inflammatory processes[108,109]. Depression can result in reduced quality of life, decreased economic productivity, social isolation, and cognitive decline.[108,109] Among people with HIV, depression has the potential to worsen HIV-related morbidity and mortality, particularly in low-resource settings.

Depression has been shown to be an important barrier to linkage to care, retention, ART adherence and ultimately long-term viral suppression across the globe.[1-6,110] A bourgeoning body of research in SSA is beginning to demonstrate that depressed individuals are less likely to be linked to ART care or start ART.[42-44] Further, depression is also associated with poor adherence to ART in SSA.[1,2,45] However, limited research has been conducted in SSA on the association between depression and consistent retention in HIV care and viral suppression. As such, further evidence is needed to characterize the association between depression, HIV care engagement, and achievement of viral suppression is the sub-Saharan region.

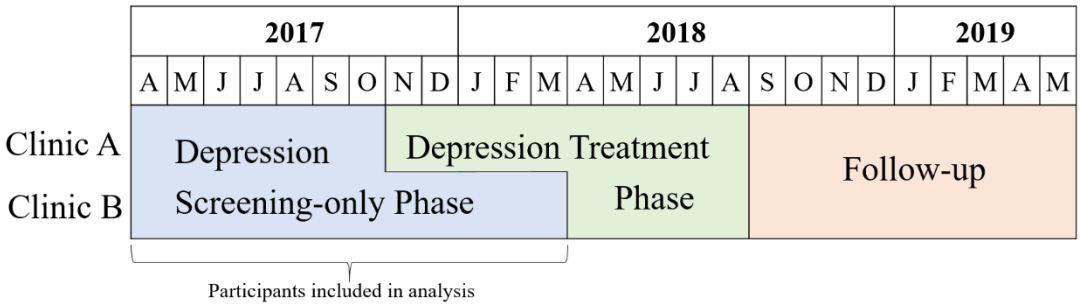
This analysis addresses this knowledge gap by generating evidence on the association of depression with two key HIV care outcomes: retention in HIV care and viral suppression. Compared to those without depressive symptoms, we hypothesized that those with elevated depressive symptoms at ART initiation would be less likely to be retained in HIV care and to be virally suppressed six months after ART initiation.

Methods

Study Design

This study is nested within the first phase of a pilot program that integrated depression screening and treatment into routine HIV primary care using existing staff at two public health clinics in Lilongwe, Malawi, that employed a staggered, multiple baseline design.[111] We implemented this program in two staggered phases – a depression screening-only phase and a depression treatment intervention phase (**Figure 4.1**). During the screening-only phase, HIV testing and counseling (HTC) counselors screened all patients newly diagnosed with HIV for depressed mood or anhedonia using the Patient Health Questionnaire-2 (PHQ-2), or the first two questions of the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 is a nine-item questionnaire that assesses the presence and frequency of the nine Diagnostic and Statistical Manual of Mental Disorders symptoms of major depression.[80] It has been widely used in the sub-Saharan region.[82,83,112] For patients who endorsed the PHQ-2, the ART clinician then administered the remaining seven PHQ-9 questions during ART initiation. A total score of 5-9 is considered indicative of mild depression and a total score of 10 or above is considered indicative of moderate-to-severe depression.[84] During the screening-only phase, patients who were identified with elevated depressive symptoms were managed by clinicians using existing care options within the Malawi primary care system. These options theoretically included counseling, antidepressants or referral to an on-site or off-site mental health specialist, or in acute cases, transport to the outpatient psychiatric unit at the nearby district hospital. However, in practice, counseling consisted of informal counseling by the ART provider and antidepressants were rarely prescribed (and when prescribed, only at sub-therapeutic doses).

Figure 4.1. Program implementation



Population

All non-pregnant adults (18 years or older) newly initiating ART at the study sites were eligible to be enrolled in the program evaluation. Research assistants approached such individuals awaiting ART initiation to invite them to participate in the study and nearly all (98%) provided informed consent. This analysis is restricted to consenting individuals who completed depression screening during the screening-only phase of the program, e.g., only those who initiated care between April 2017 and October 2017 at Clinic A and between April 2017 and March 2018 at Clinic B (**Figure 4.1**).

Data Collection and Abstraction

This study relied on the abstraction of routinely collected clinical data on depression screening and HIV care from consenting participants' ART clinical records over a 13-month period, starting at ART initiation. At the study sites, when a patient initiates ART, clinic staff create a paper medical chart (called an ART mastercard) and accompanying electronic medical record for the patient where HIV care data will be recorded. At each appointment, the clinicians schedule the next follow-up appointment and provide the patient with a supply of ART that will last until their next appointment. ART pills are provided in increments of 30. Generally, for the

first six months of care, newly initiating ART patients are scheduled to come monthly, though exceptions can be made and a larger supply of ART can be provided.

Measures

Depression at ART Initiation

Elevated depressive symptoms suggesting a high risk of a depressive disorder (hitherto described as "depression") was defined as a PHQ-9 score ≥5 at ART initiation, following the definition in the parent study[89]. We also consider a 3-level depressive severity measure (0-4, 5-9, and ≥10, corresponding to no, mild, and moderate to severe depression, respectively) and a continuous measure (range 0-27) of depressive severity.

Viral Suppression

We defined viral suppression as a viral load <1,000 copies/mL drawn at least five and a half months (166 days) after starting ART, following the 2018 Malawian ART guidelines. Viral load testing was performed at Bwaila Hospital in Lilongwe using collected plasma or dried blood spots and processed by Abbott m2000 RealTime HIV-1 assay instruments.[95]

Retention in HIV Care

We constructed several measures to capture retention in HIV care through six months in care. Some measures were constructed specifically for this analysis, while others were constructed in alignment with nationally and internationally recognized measures of retention.

Continuous engagement in care was defined as never being more that 14 days late to an appointment through 6 months in care.

Alive and in care at six months was defined as being on ART for at least some portion of the two months prior to the six-month anniversary of starting ART, in alignment with Malawi Ministry of Health reporting practices. According to the Malawi Guidelines for Clinical

Management of HIV in Children and Adults, an ART patient is classified as a defaulter if they go two months without ART based on the pill provided at their most recent appointment.[90] Patients who are not known to have transferred, stopped ART, or died are classified as alive and on ART.

Currently on ART at six months was defined as currently having ART on hand at six months, i.e. attending an appointment prior to the six-month point and receiving a supply of ART that would last through the six-month point. For example, if a participant attended an appointment five and a half months after starting ART and received a 30-day supply of ART, they would have been considered currently on ART at six months. This indicator aligns closely with the PEPFAR definition of "currently on treatment."[91]

In care after six months was defined as attending at least one appointment where ART is provided after six months in care. This definition aligns more closely with the UNAIDS Global AIDS Monitoring 2019 Indicators by identifying participants known to be on ART at some point six months after initiation.[92]

HIV appointment attendance was defined as the proportion of scheduled HIV appointments attended within one week of the scheduled appointment date in the first six months of care.[93]

Consistent ART was defined as never going more than five days without ART in the first six months, calculated from the cumulative days' supply of ART dispensed at each appointment in the first 6 months and the time between appointments.

ART pill possession ratio was defined as the proportion of the first six months (183 days) since ART initiation with ART in hand, calculated from cumulative pills dispensed at each ART appointment through six months.[94]

Retention + Viral Suppression

A combined outcome of continuous engagement in HIV care with viral suppression six months after starting ART was defined as meeting both of the following criteria: never being more than 14 days late to a scheduled HIV appointment through six months in care and having a viral load <1,000 copies/mL drawn at least five and a half months (166 days) after ART initiation.

Variables of Interest

Due to the data collection design of this study, only routinely collected clinical data was captured including age, sex, clinic, World Health Organization (WHO) HIV clinical stage for HIV surveillance (I-IV) [88], village of residence, and ART medication prescribed. Village of residence was used to categorize individuals as residing in urban Lilongwe City, in rural Lilongwe District, or outside of Lilongwe District. Baseline CD4 and viral load are not collected in the Malawi public health system as the policy encourages a "test and treat" strategy; individuals who test positive for HIV are initiated on ART irrespective of CD4 and viral load.

Analysis

We first completed unadjusted, tabular comparisons of HIV care outcomes by depressive severity (none, mild, and moderate to severe). We then used log-binomial models to estimate adjusted risk ratios comparing the probability of each binary HIV care outcome among those with depression compared to those without. For the continuous outcomes, we used ordinary least-squares linear regression models to estimate mean differences. Potential confounders were identified through directed acyclic graph (DAG) analysis.

To address missing outcome data for those who transferred to a non-study facility or who returned for care around six months but did not get a viral load, we used multiple imputation by chained equations (MICE) to fill missing values using logistic regression imputation methods.[97]

We imputed values based on the covariates included in the final model. We generated 15 imputed datasets to ensure the number of imputed datasets was at least as large as the percentage of incomplete information for the main outcome, "continuous engagement with viral suppression."[113] Finally, we confirmed that the number of imputed datasets was also larger than the parameter-specific fraction of missing information for all parameters included in the final model.[114]

All analyses were performed using STATA IC 14.

Ethical Review

The National Health Sciences Research Committee of Malawi (NHSRC) and the Biomedical Institutional Review Board (IRB) of the University of North Carolina at Chapel Hill approved the study protocol. All participants underwent a consent process during ART initiation and gave written informed consent to allow the abstraction of their clinical data.

Results

Participant Characteristics

Of 1091 participants screened, 601 (55%) screened negative on the PHQ-2; the full PHQ-9 was administered to the remaining 490 (**Table 4.1**). Of these, 291 (27% of those enrolled) endorsed symptoms consistent with our operational definition of depression (PHQ-9 score ≥5). Of these, 74% had mild depression (PHQ-9 scores 5-9) and 26% had moderate to severe depression (PHQ-9 scores ≥ 10). Just over half of all participants were female; those with depression were slightly more likely to be female than those without. The mean age of participants was 33.5 years and did not vary appreciably between participants with and without depression. Nearly all participants were classified as asymptomatic (Stage I) for HIV at ART

initiation and were initiated on a combination of tenofovir, lamivudine, and efavirenz (TDF/3TC/EFV).

Table 4.1. Participant characteristics (N=1091)

n (%) or mean (sd)	**Overall (N=1091)**	**Not Depressed (N=800)**	**Depressed (N=291)**
Baseline Depressive Severity			
Screen-negative (PHQ-2: 0)	601 (29%)	601 (75%)	N/A
Minimal (PHQ-9: 1-4)	199 (18%)	199 (25%)	N/A
Mild (PHQ-9: 5-9)	215 (20%)	N/A	215 (74%)
Moderate (PHQ-9: 10-19)	71 (7%)	N/A	71 (24%)
Severe (PHQ-9: 20-27)	5 (<1%)	N/A	5 (2%)
Sex			
Male	513 (47%)	387 (48%)	126 (43%)
Female	578 (53%)	413 (52%)	165 (57%)
Age	33.5 (9.6)	33.4 (9.4)	33.6 (10.1)
Residence*			
Urban Lilongwe	976 (93%)	717 (93%)	259 (93%)
Rural Lilongwe	54 (5%)	40 (5%)	17 (6%)
Outside Lilongwe District	17 (2%)	15 (2%)	2 (1%)
WHO Disease Stage			
I	1089 (>99%)	800 (100%)	289 (99%)
II-IV	2 (<1%)	0 (0%)	2 (1%)
Baseline ART prescription**			
TDF/3TC/EFV	1078 (99%)	790 (99%)	288 (99%)
Other	12 (1%)	9 (1%)	3 (1%)
Clinic			
Clinic A	435 (40%)	319 (40%)	116 (40%)
Clinic B	656 (60%)	481 (60%)	175 (60%)

Notes: *Missing n=44. **Missing n=1. ART=antiretroviral therapy. PHQ-2=Patient Health Questionnaire 2. PHQ-9=Patient Health Questionnaire-9. TDF/3TC/EFV=tenofovir, lamivudine, and efavirenz.

HIV Care Outcomes: Retention in Care and Viral Suppression

The HIV care outcomes measures did not vary appreciably between those without, with mild, and with moderate to severe depression (**Table 4.2**). Regardless of metric, retention in HIV care was generally low. Using the Malawi Ministry of Health ART patient classification, around 60% of participants would have been classified as alive and in care at 6 months. Around 50% were currently on ART at 6 months and around 40% attended an appointment after 6 months and maintained a consistent supply of ART through 6 months. While only 45% (N=454) of patients who had not transferred or died had viral loads drawn; nearly all of those were virally suppressed. Only around 23% of participants achieved both continuous engagement and viral suppression.

Table 4.2. HIV care outcomes, by depressive severity

Outcome	Total	Depression		
		None	Mild	Moderate to Severe
		% or Mean (SD)		
Retention Indicators	**N=1017**	**N=750**	**N=200**	**N=67**
Continuous engagement	30%	28%	34%	34%
Alive and in care	58%	57%	63%	58%
Currently on ART	48%	46%	53%	48%
In care after 6 months	43%	43%	43%	39%
Consistent ART	40%	40%	43%	42%
HIV appointment attendance (Range: 0-1)	0.5 (0.4)	0.5 (0.4)	0.6 (0.4)	0.5 (0.4)
ART pill possession (Range: 0.16-1),	0.7 (0.4)	0.7 (0.4)	0.7 (0.3)	0.7 (0.4)
Viral suppression	**N=454**	**N=339**	**N=88**	**N=27**
Viral suppression	93%	93%	94%	93%
Retention + Viral Suppression	**N=945**	**N=698**	**N=186**	**N=61**
Continuous engagement with viral suppression	23%	21%	28%	26%

Notes: This table does not include data on individuals who transferred within the first 6 months of care: Not Depressed n=48; Mild Depression n=15; Moderate to Severe Depression n= 9; Died within the first 6 months of care: Not Depressed n=2. Denominators vary due to viral loads not being drawn or not having or attending a scheduled appointment around 6 months. ART=antiretroviral therapy.

The final adjusted model controlled for clinic and sex. As a continuous variable, age introduced model instability and was removed from the final adjustment set as age did not appear to be associated with any of the outcomes or depression at baseline. WHO stage, ART medication, and area of residence did not vary enough to be considered potential confounders. Addressing missing data through multiple imputation did not appreciably change any of the results.

After adjustment, depression at ART initiation did not appear to be significantly associated with any of the HIV care outcomes (**Table 4.3**).

Table 4.3 Association of depression (PHQ-9≥5) at ART initiation with HIV care outcomes

Outcome	**Unadjusted**	**Adjusted**	**Imputation**
		RR (95% CI)	
Retention Indicators			
Continuous retention	1.21 (0.99-1.48)	1.15 (0.95-1.4)	1.16 (0.96-1.4)
Not a defaulter	1.08 (0.97-1.21)	1.08 (0.97-1.21)	1.09 (0.98-1.21)
Currently on ART	1.11 (0.97-1.28)	1.11 (0.97-1.27)	1.11 (0.97-1.27)
Retention in care	1.03 (0.91-1.16)	1.04 (0.93-1.17)	1.04 (0.93-1.17)
Consistent ART	1.06 (0.89-1.25)	1.05 (0.89-1.23)	1.05 (0.89-1.23)
Retention + Viral Suppression			
Continuous retention with viral suppression	1.27 (0.99-1.63)	1.21 (0.95-1.53)	1.18 (0.97-1.44)
		Mean Difference (95% CI)	
HIV appointment attendance (Range: 0-1)	0.03 (-0.02-0.08)	0.03 (-0.02-0.08)	0.06 (-0.00-0.12)
ART pill possession (Range: 0.16-1)	0.01 (-0.04-0.06)	0.01 (-0.04-0.06)	0.02 (-0.03-0.06)

Notes: ART=antiretroviral therapy. PHQ-9=Patient Health Questionnaire-9.

Discussion

While the prevalence of depression among this population of adults newly initiating ART was high at 27%, those with depression had similar HIV care outcomes at six months compared

to those without depression. Retention metrics were generally poor for both groups. However, among those sent for viral load testing, nearly all achieved viral suppression.

The influence of depression on retention in HIV care is complicated. Several recent reviews and meta-analyses have documented the association between depression and ART adherence[2,115], though the relationship between depression and engagement in HIV care or retention is less well understood. We hypothesized that depression could plausibly impair adherence and appointment attendance as depression often manifests through loss of interest, poor concentration, poor motivation, reduced self-efficacy, fatigue, hopelessness, and suicidality.[2,4,46] However, in our study population, depression was not associated with any of the retention indicators or viral suppression at six months. Several studies conducted in South Africa, Kenya, and Uganda examining the association between depression prior to HIV testing and linkage to care had mixed results.[44,116,117] In South Africa, where linkage to care was defined as obtaining a CD4 count within three months of a positive HIV test, one study found no difference between those with and without depression at testing[116] and one found that those with depression were less likely to be linked to care.[44] In Kenya and Uganda, greater depressive symptom severity was associated with greater likelihood of ART initiation during the study period among sero-converted partners of previously sero-discordant couples.[117] Studies of depression and retention in care conducted in Malawi and the Democratic Republic of the Congo found no difference between 12-month retention or viral suppression among pregnant women with and without depression at ART initiation.[37,118] One explanation for the differences in the literature relating depression and ART adherence versus relating depression and retention is that depression may not affect engagement in care in the same way it impacts ART adherence; different skills sets are required for adherence to daily ART versus maintaining monthly clinic

visits.[116] Further efforts to understand the relationship between depression and HIV will need to unpack the mechanisms through which depression impacts the different aspects of HIV care engagement.

Nonetheless, the lack of association between depression at ART initiation and any of the HIV outcomes in this study population is striking. Qualitative interviews with providers and patients conducted within the larger parent study during the screening phase of the program, suggest that individuals identified with depression during the screening phase possibly received additional counseling on accepting their HIV status, ART adherence, and managing their depression.[119] While these participants with depression did not receive evidence-based standardized depression treatment, it is possible that this additional attention may have acted as an informal intervention. As such, this additional attention may have had a positive impact on HIV care engagement for depressed patients included in this analysis relative to those without depression.

Locally adapted, valid depression diagnostic and management tools are vital for addressing the burden of depression among people living with HIV. The implementation team chose the PHQ-9 for use among people living with HIV because it focuses specifically on depression, has been widely used and validated in many different cultures (including among people living with HIV in SSA)[81-83], and works well both as a case identification tool as well as a longitudinal monitor of response to treatment. However, at the time, the PHQ-9 had yet to be validated in Malawi, though it has since undergone validation among a population of patients with diabetes.[120] Along that vein, cases of "depression" were identified with the PHQ-9 screening tool and not a diagnostic interview. It is plausible that some depressive symptoms were not actually features of a major depressive episode, but rather a manifestation of milder

syndromes, more likely to resolve spontaneously and not require an intervention. Furthermore, the PHQ-9 was originally developed to be self-administered, but was administered by providers due to low levels of literacy among the patient population. Given the overlap in symptomology between HIV and depression itself, HIV providers may have identified an inaccurate burden of depression among people living with HIV.[121] As this study relied on existing staff to screen patients for depression who were not incentivized to engage in the depression screening program, it is also possible that providers underdiagnosed cases of depression. While a small sub-study comparing the providers' administration of the PHQ-9 to that of trained research assistants did find that research assistants identified more cases of depression than providers, there was still high overall agreement between providers and research assistants.[122] Nevertheless, the accuracy of the PHQ-9 may have been compromised, given the mode of administration, i.e., administration by existing staff with varying degrees of commitment to the program as opposed to self-administered. Tools such as the PHQ-9 would benefit from further quantitative validation against a "gold standard" diagnostic instrument to confirm their utility as part of task-shifting programs in SSA, particularly among people living with HIV.

Finally, complexities in measuring engagement and retention in HIV further complicate the study of the role of depression in HIV care. Despite the importance of retention to successfully treating HIV, there is no recognized "gold standard" measure for retention in care.[93] A recent meta-analysis highlighted some of the challenges around comparing studies examining the association between mental health disorder diagnoses and retention in HIV care, noting that "retention in care" may be operationalized to include measures of visit constancy, kept visits, no-show rates, and gaps in care.[110] In this study, retention overall was very low; only 30% of all participants remained continuously engaged in care through six months and only 43% attended

an appointment after six months in care. Using Malawi's definition of retention, overall 58% of participants were considered alive and in care at six months, though this is still lower than Malawi's 2018 12-month retention estimates which found that 72% of adults who initiated ART were still in care at 12 months.[123] It is possible that we potentially underestimated retention in care due to "silent transfers," or individuals who decided to access care at a different location without formally transferring their records. In fact, the Malawi Ministry of Health assumes that actual retention is about 10% higher due to this misclassification of "silent transfers" as "defaulters" in clinic-based retention analysis, though a meta-analysis of low- and middle-income country studies suggests retention may be as much as 18% higher.[124] Recognizing that this misclassification could have influenced all of the HIV care engagement measures, the rate of silent transfer should not have varied between groups, so "silent transfers" should not have significantly biased comparisons between those with and without depression.[123] In this sense, "retention" in our study is tantamount to "retention at the specific clinic," and the data available may not yield a complete picture of engagement in care, limitations often faced by studies on retention in HIV care in SSA.[125,126] Innovative methods and approaches for measuring retention in care to manage these complexities are needed, particularly in low-resource settings.

Limitations

Due to the implementation science nature of this study, the covariates captured were limited to routinely collected clinical data. It is possible that the presented analyses were biased by unmeasured confounding factors. It is also possible that we overestimated viral suppression, as viral loads could only be drawn from patients who remained in care and a large proportion of patients who did return for care were never sent for viral load testing.

Conclusion

This study documented a high prevalence of depression among patients newly initiating ART and low retention in care at six months. However, the examined HIV care outcomes at six months were similar between those with and without depression. Further research is needed to understand the mechanisms through which depression may undermine different aspects of the HIV care continuum, from testing through sustained retention and ultimately viral suppression.

CHAPTER V: THE IMPACT OF AN INTEGRATED DEPRESSION AND HIV TREATMENT PROGRAM ON MENTAL HEALTH AND HIV CARE OUTCOMES AMONG PEOPLE NEWLY INITIATING ANTIRETROVIRAL THERAPY IN MALAWI

Introduction

The burden of depression among people living with HIV in Malawi is high, ranging from 1% to 19% [35,37,107,112], as in other sub-Saharan African countries.[1] Depression is associated with poor HIV care engagement and ultimately increased HIV-related mortality and morbidity.[1-6] The mechanisms through which depression undermines HIV care engagement are not fully clear. However, loss of interest, poor concentration, poor motivation, reduced self-efficacy, fatigue, hopelessness, and suicidality – key characteristics of depression – are all factors which can impair adherence and appointment attendance.[2,4,46] Fortunately, depression treatment programs have been developed that have the potential to improve both HIV care and mental health outcomes, with a small but growing number of interventions adapted for low- and middle-income countries.[7-9,53,127,128] In places such as Malawi, where nearly 10% of the adult population is living with HIV[129] and nearly a quarter of people living with HIV are lost to care in the first year of treatment[26-28], incorporating depression screening and treatment into HIV care may be key to improving engagement in care across the HIV care continuum.

There are limited resources for mental health care in Malawi, and a dearth of mental health infrastructure and specialists. Malawi treats mental healthcare as a specialized service, offered only by specialists in tertiary settings. There are only four psychiatrists and three functioning psychiatric hospitals in the country.[130] In such settings where it is unlikely that the number of specialists and infrastructure could grow rapidly enough to meet the demands of the

population, task-shifting programs – i.e., models of care that shift specialized services to non-specialists[69] – are a popular and often cost-effective strategy for providing mental health services.[71-73] Of the few depression treatment interventions developed for the sub-Saharan region, most employ a task-shifting model.[53-59]

Two notable task-shifting interventions include algorithm-based care for depression[58-60] and the Friendship Bench behavioral activation and problem-solving therapy.[56] Algorithm-based care is a resource-efficient, task-shifting model for prescribing antidepressant management in non-psychiatric settings. This model of care has demonstrated safety, feasibility, and acceptability when adapted for HIV care and delivered by general practice medical providers in Cameroon, Tanzania and Uganda.[58-60] Developed over many years of formative research in Zimbabwe, the Friendship Bench is patient-centered counseling that teaches patients how to identify triggers and effectively manage stressful life events by learning or reactivating problem-solving skills.[56,61] These programs as well as others have proven efficacy in improving depression outcomes, though evidence on improvements in HIV care outcomes has been mixed.[54,58-60,74,131,132] Further investment in understanding the feasibility of task-shifting program implementation and the effectiveness of these models of depression care is needed to meet the mental health care needs of people living with HIV.

The Malawi Ministry of Health (MOH) has recognized the importance of addressing the burden of depression among people living with HIV as a means of improving engagement in HIV care. The MOH has also prioritized the integration of mental health services into other general health services and the development of mental health capacity of general providers.[63-65] Expanding the growing nidus of investment in mental health care programming and capacity development, the MOH implemented a pilot program integrating depression management into

HIV care at two public clinics in Lilongwe, Malawi, using both algorithm-guided depression treatment and adapted Friendship Bench therapy.[95] Inspired by the key principles of implementation science, we use a multiple-baseline design to investigate the program's impact on HIV care and depression outcomes.

Methods

Objectives

The main objective of this study was to evaluate the program's impact on retention, viral suppression, and depression remission among patients with elevated depressive symptoms at antiretroviral therapy (ART) initiation after six months in care.

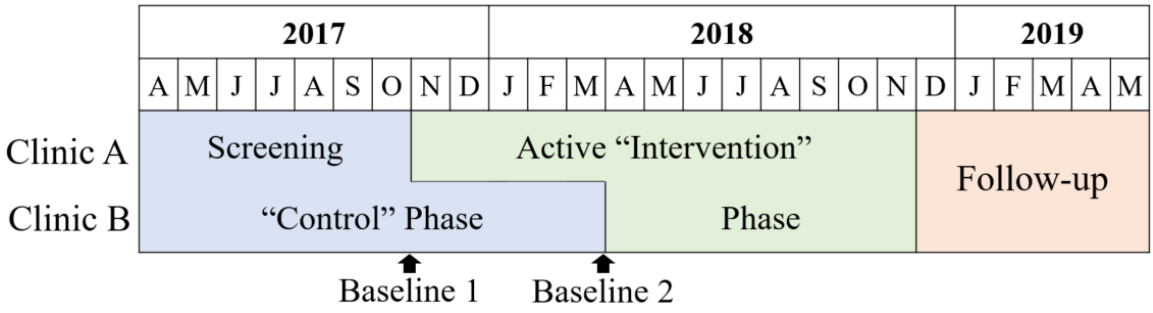
Study Design

This study employed a staggered multiple baseline (pre-post) design to evaluate a pilot program integrating depression screening and treatment into routine HIV primary care using existing staff at two public health clinics in Lilongwe, Malawi.[111] Multiple baseline studies use a time-series design that can be used for studies with multiple sites in which each site intentionally receives the intervention at a different time point.[111,133] This design can also provide evidence of causal relationships where randomization is not possible and provides stronger control for temporal trends.[111,133] As such, the program rolled out in two phases, a screening-only "control" phase and an active "intervention" phase. The screening control phase launched at both clinics in April 2017. However, the launch of the intervention phase was staggered, launching at Clinic A in November 2017 and at Clinic B in April 2018 **(Fig 5.1).** Additional information on the study design is available in the published protocol paper.[95]

Control Phase

During the control phase, providers screened patients for depression using the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9, a nine-item screening questionnaire that assesses the presence and frequency of the nine Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition symptoms of major depression.[80] It has been widely used in the region[82,83,112] and was recently validated in Malawi among patients with diabetes.[135] A total score of 5-9 is considered indicative of mild depressive symptoms and ≥10 is considered indicative of moderate to severe depressive symptoms.[84] Patients who endorsed the last question of the PHQ-9, which asks about thoughts of being better off dead or hurting oneself, completed a suicide risk assessment protocol (SRAP) with the providers. The SRAP guided providers' evaluation of whether such thoughts were passive or active. During the control phase, ART providers were re-oriented to existing options for depression care within the Malawi primary care system. These options theoretically include counseling and antidepressants, although in actuality counseling consists of informal counseling by ART providers and antidepressants are rarely prescribed. For patients with suicidality, providers were trained to respond based on the level of severity, ranging from a brief safety assessment to immediate transport to the outpatient psychiatric department at the district hospital.

Figure 5.1. Staggered multiple baseline study design



Intervention Phase

During the intervention phase, ART providers (nurses or clinicians) used PHQ-9 scores at ART initiation to triage patients by depressive severity. ART providers were trained to refer participants with mild depressive symptoms (PHQ-9 score 5-9) to clinic-based lay health workers or a project-employed counselor trained to provide an adapted problem-solving intervention called Friendship Bench therapy.[54,56] These counselors provided patient-centered counseling that guided patients through recognizing problems, identifying their own solutions, implementing those solutions, and assessing the outcome.[56,61] Patients referred to the Friendship Bench would ideally receive at least six counseling sessions. While these patients were encouraged to return weekly for Friendship Bench therapy, patients set their own appointments in line with the protocol's patient-centered approach. For participants with moderate to severe depressive symptoms (PHQ-9 score ≥10), ART providers were trained to prescribe antidepressants (fluoxetine or amitriptyline) with appropriate dosing and dose changes, using an algorithm-based care protocol. Under this protocol, providers used PHQ-9 scores and drug side effects to guide antidepressant prescription, titrating the antidepressant dose by monitoring depressive symptoms and antidepressants side effects at each clinic visit[58-60] (**Table 5.1**). Patients who started antidepressants were meant to be reevaluated monthly at their ART visits when they would be re-prescribed antidepressants for at least three months. Additional

Table 5.1. Depression treatment overview, by study phase

Score	Depressive Severity	Screening "Control" Phase	Active "Intervention" Phase
0-4	No or minimal	None	None
5-9	Mild	No formal depression treatment – could include informal clinician counseling or, rarely, antidepressant prescription	Friendship Bench
10-27	Moderate to severe		Antidepressants

information on the combined medication and counseling depression treatment program has previously been published.[130]

Study Population

From April 2017 through November 2018, all non-pregnant adults newly initiating ART at the study sites were eligible to be included in the program evaluation. Pregnant women were excluded as they typically test for HIV at a specific antenatal care clinic and continue to receive ART as part of their antenatal care. This analysis is restricted to participants who completed depression screening and had elevated depressive symptoms (PHQ-9 score ≥ 5) at ART initiation. Participants were placed in the "control" or "intervention" groups based on the phase during which they initiated ART.

Control group: Includes participants with elevated depressive symptoms who initiated ART at either clinic during the screening "control" phase (e.g. at Clinic A between April 2017 and November 2017 and at Clinic B between April 2017 and April 2018).

Intervention group: Includes participants with elevated depressive symptoms who initiated ART at either clinic after the launch of the treatment program during the active "intervention" phase (e.g. at Clinic A after November 2017 and at Clinic B after April 2018).

Data Collection

As an implementation science study, the primary objective was to assess the impact of an intervention that could readily (and rapidly) be adopted and integrated into routine care in the public sector setting.[76,77] Just as the program made use of existing clinical staff and systems, the evaluation was intentionally designed to influence and disrupt the provision of care as little as possible by collecting only data that was already routinely captured during clinical care and using research staff only to consent patients and abstract data. Specifically, we did not conduct

baseline interviews or schedule six-month follow-up interviews, which would have limited enrollment and potentially brought participants back into care, biasing our primary outcome measure of HIV care engagement. Research assistants at the study sites approached potential participants during ART initiation to invite them to allow their clinical data to be used in the program evaluation. Research assistants abstracted routinely collected clinic data on depression and HIV care from consenting participants' clinical records over a 13-month period, starting at ART initiation. Abstracted data included appointment dates, expected return dates, ART pills dispensed, PHQ-9 scores, and depression treatment provided. At ART initiation and each subsequent ART appointment, providers give patients a follow-up appointment date and a sufficient supply of ART. Generally, for the first six months of care, new ART patients receive a 30-day supply of ART and a return appointment date in 30 days at each appointment. Most often, patients need to attend monthly ART refill appointments for their first six months of care in order to maintain their ART supply. Additionally, we obtained electronic medical record data from the clinical sites to ensure the quality and completeness of the abstracted data.

Measures

Exposures

Adequate Friendship Bench therapy should consist of six sessions over the first six months in care and a standard course of antidepressants should consist of at least three consecutive months of antidepressant prescription with dosage adjustments as necessary. For analysis purposes, we have operationalized the intervention exposure as follows:

Intent-to-treat: Intervention group participants were considered "exposed" to the intervention if they initiated ART during the intervention phase. Control group participants were considered "unexposed" to the intervention if they initiated ART during the control phase.

Treatment started: The intervention group included participants who either had: 1) mild depressive symptoms at ART initiation who started Friendship Bench therapy at ART initiation or 2) moderate to severe depressive symptoms who were prescribed antidepressants at ART initiation. The control group participants did not start Friendship Bench therapy or antidepressants at ART initiation.

As treated: The intervention group included participants who attended at least their first follow-up appointment and either had: 1) mild depressive symptoms at ART initiation and at least two Friendship Bench therapy sessions over their first six months in care or 2) moderate to severe depressive symptoms at ART initiation and were prescribed at least two months of antidepressants over their first six months in care. The control group included participants who attended at least their first follow-up appointment, but did not have at least two Friendship Bench sessions or two months of antidepressant prescription over their first six months in care. Those participants who did not attend at least their first follow-up visit were excluded. While this definition was less stringent than the ideal course of treatment, this definition allowed for a more refined comparison of those who received early and consistent depression treatment compared to those who had not.

Outcomes

Retention was defined as never being more that 14 days late to an appointment through six months in care. Maintaining a consistent ART supply was defined as never more than five days without ART in the first six months, calculated from the cumulative days' supply of ART dispensed at each appointment in the first six months and the time between appointments. In alignment with the PEPFAR definition of "currently on treatment"[91], participants were currently on ART six months after ART initiation if they attended an appointment and received a supply of

ART that would last through the six-month mark. Viral suppression was defined as a viral load of less than 1,000 copies/mL drawn after at least five and a half months (166 days) in care. Depression remission was defined as a PHQ-9 score of less than five taken after at least five and a half months (166 days) in care, to allow for completion of the acute phase of treatment and maintenance of that response.[96] Additionally, we examined the proportion of scheduled HIV appointments attended within one week during the first six months of care and the ART pill possession ratio**,** the proportion of the first six months (183 days) since ART initiation with ART in hand, calculated from cumulative pills dispensed at each ART appointment through six months.

Covariates

Due to the implementation science nature of this study, we only abstracted routinely collected clinical data. Measured covariates included the healthcare facility where patients received ART (Clinic A or B), months since program launch at ART initiation, gender, age, baseline depressive severity at ART initiation (mild or moderate to severe), and baseline presence of suicidal thoughts at ART initiation. Presence of suicidal thoughts was defined as any endorsement of the ninth question of the PHQ-9: "During the past two weeks, how many days have you been bothered by thoughts that you would be better off dead or of hurting yourself in some way?"

Data Analysis

The main analysis followed an "intent-to-treat" approach, classifying participants according to screening "control" vs. active "intervention" phase (unexposed vs. exposed to the program) without regard to actual treatment received. Although patients identified with elevated depressive symptoms late in the control phase could theoretically have received depression care

from providers during the intervention phase during their first six months of care, in practical terms, depression treatment was only provided to patients newly entering care. Furthermore, we monitored crossover between groups. We first completed unadjusted, tabular comparisons of HIV care and depression outcomes in the intervention group relative to the control group. We then used log-binomial models to estimate adjusted risk ratios comparing the probability of the primary outcome, retention with viral suppression, as well as the probability of other secondary HIV care outcomes in the intervention group compared to the control group. Since the evaluation employed a staggered multiple baseline design, with the intervention launching at different dates at the two clinics, all models were adjusted for clinic and months since program launch to allow for the assessment of and potential correction for any secular trend in outcomes ("confounding by history"). While the study design should have produced comparable control and intervention groups, we did additionally consider controlling for measured covariates. To separately evaluate the impact of the Friendship Bench and the antidepressant treatment, we then stratified the primary analysis by depressive severity at baseline (mild or moderate to severe depressive symptoms). Other secondary analyses used a "treatment started" approach, comparing those who actually started Friendship Bench therapy or antidepressants to those that did not in both phases and then an "as treated" approach, comparing those who received at least two Friendship Bench therapy sessions or two months of antidepressants to patients who did not in both phases, restricted to only those who attended at least their first follow-up visit.

Outcome data for those who transferred or died in the first six months of care were treated as missing. To address missing outcome data, we used multiple imputation by chained equations (MICE) to fill missing values using logistic regression imputation methods.[97] We imputed values based on phase, healthcare facility, months since program launch at ART

initiation, age, sex, baseline depressive severity at ART initiation, and baseline presence of suicidality at ART initiation. We generated 18 imputed datasets to ensure the number of imputed datasets was at least as large as the percentage of incomplete information for the main outcome, "retention with viral suppression."[113] To verify that this was sufficient, we confirmed that the number of imputed datasets was also larger than the parameter-specific fraction of missing information for all parameters included in the final model.[114]

All analyses were performed using STATA IC 14.

Ethical Review

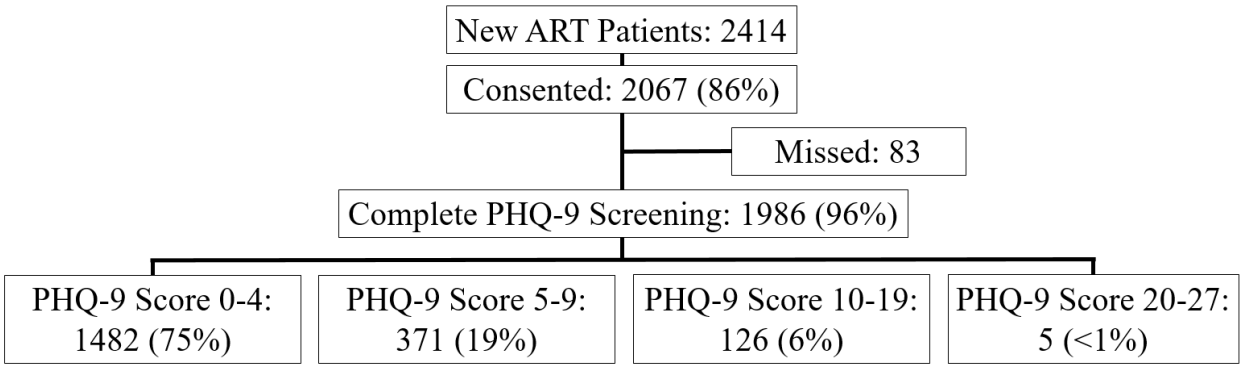
The National Health Sciences Research Committee of Malawi (NHSRC) and the Biomedical Institutional Review Board (IRB) of the University of North Carolina at Chapel Hill approved the study protocol. All participants gave written informed consent to allow the abstraction of their clinical data. The evaluation only used de-identified clinic data to ensure the protection of participants' identities and confidentiality. Patients with depression received depression care regardless of whether or not they provided consent for their data to be abstracted.

Results

Depression Screening

Over the course of the program, 2414 patients newly initiated ART (**Fig 5.2**). Of these new initiators, 2067 (86%) consented to allow their data to be abstracted to evaluate the program. Nearly all of those who consented (96%) were screened with the PHQ-9 appropriately. Among those who completed the PHQ-9 screening, the prevalence of mild depressive symptoms (PHQ-9 score 5-9) was 19% and the prevalence of moderate to severe depressive symptoms (PHQ-9 score ≥ 10) was 6%. Only those participants with elevated depressive symptoms (PHQ-9 score ≥ 5) are included in this analysis (N=502).

Figure 5.2. Evaluation enrollment



Participant Characteristics

Of the 501 consenting participants with elevated depressive symptoms, the control group consisted of the 290 who initiated ART during the control phase and the intervention group consisted of the 211 who initiated during the intervention phase (**Table 5.2**). As the program launched later at Clinic B, a larger proportion (75%) of the intervention group were from Clinic A. Otherwise, the two groups appear very similar. About 43% of participants were male. The average age of participants was 33.8 years. Nearly all participants were classified as asymptomatic (Stage I) for HIV at ART initiation, according to the World Health Organization's (WHO) HIV clinical stages for HIV surveillance [88]. At ART initiation, 74% of participants had mild depressive symptoms, only around 1% of participants had severe depressive symptoms and 21% of participants reported suicidality.

Depression Treatment Exposure

Initiating Depression Treatment

Among the control group, 89% of participants with mild depressive symptoms and 80% participants with moderate to severe depressive symptoms received some additional counseling

by ART clinicians ("standard depression care" during the control phase) (**Table 5.3)**. During this phase, only 18% (n=14) of those with moderate to severe depressive symptoms started amitriptyline during the control phase and most (n=11) started at a subtherapeutic dose of 25 mg.

Table 5.2 Participant characteristics (N=501)

n(%) or mean (sd)	**Overall**	**Control Group**	**Intervention Group**
Overall	501	290	211
Clinic			
Clinic A	276 (55%)	116 (40%)	160 (76%)
Clinic B	225 (45%)	174 (60%)	51 (24%)
Sex			
Male	214 (43%)	125 (43%)	89 (42%)
Female	287 (57%)	165 (57%)	122 (58%)
Age	33.8 (9.5)	33.6 (10.0)	34.0 (8.7)
WHO Disease Stage			
I	498 (99%)	288 (99%)	210 (>99%)
II-IV	3 (1%)	2 (1%)	1 (<1%)
Baseline Depressive Severity			
Mild (PHQ-9: 5-9)	370 (74%)	214 (74%)	156 (74%)
Moderate (PHQ-9: 10-19)	126 (25%)	71 (24%)	55 (26%)
Severe (PHQ-9: 20-27)	5 (1%)	5 (2%)	0 (0%)
Baseline Suicidality			
No thoughts	397 (79%)	228 (79%)	169 (80%)
Passive thoughts	53 (11%)	33 (11%)	20 (9%)
Active thoughts	46 (9%)	27 (9%)	19 (9%)
Not assessed with SRAP	5 (1%)	2 (1%)	3 (1%)

Notes: SRAP=Suicide Risk Assessment Protocol. PHQ-9=Patient Health Questoinnaire-9. WHO=World Health Organization.

Most of the intervention group started the appropriate treatment as defined by the intervention protocol during the intervention phase. During this phase, 86% of participants with mild

depressive symptoms started Friendship Bench therapy and nearly all (96%) participants with moderate to severe depressive symptoms started antidepressants. All of the participants with moderate to severe depressive symptoms who started antidepressants at ART initiation started at a minimal effective dose (operationally defined as a daily oral dose of either 20 mg of fluoxetine or 50 mg of amitriptyline).

Table 5.3. Depression treatment initiation

N (%)	Control Group	Intervention Group
Mild depressive symptoms (PHQ-9: 5-9)	214 (100%)	156 (100%)
Counseling by clinician	191 (89%)	15 (10%)
Friendship Bench therapy	-	134 (86%)
Antidepressant*	2 (1%)	2 (1%)
None**	21 (10%)	5 (3%)
Moderate to severe depressive symptoms (PHQ-9: ≥10)	76 (100%)	55 (100%)
Counseling by clinician	60 (79%)	2 (4%)
Friendship Bench therapy	-	0 (0%)
Antidepressant***	14 (18%)	53 (96%)
None	2 (3%)	0 (0%)

Notes: *Includes those who received both antidepressants and the Friendship Bench (n=2). **Those with missing baseline treatment plan (n=4) are treated as none. ***Includes those who received both antidepressants and counseling by clinician (n=8) or both antidepressants and the Friendship Bench (n=4).

Provision of Ongoing Depression Treatment

Few patients in the intervention group continued to receive ongoing depression treatment during the intervention phase after ART initiation. Only 42% of participants referred to the Friendship Bench attended three or more therapy sessions (**Table 5.4**). Of those who were prescribed antidepressants, less than a third of participants (n=17) received three or more months of antidepressant prescription. Only six of those participants received at least three consecutive

months of the same antidepressant. Inadequate sustained treatment was in part due to poor appointment attendance, medication stock-outs, and clinicians' failure to identify patients with elevated depressive symptoms at follow-up ART appointments. However, it did not appear that there was much crossover between groups. None of the control participants ever started Friendship Bench therapy and very few started antidepressants at ART initiation (n=16) or at a follow-up visit (n=6).

Table 5.4. Depression treatment over time

	Control Group	Intervention Group
Of those directed to Friendship Bench:*	-	140 (100%)
Number of sessions attended		
1	-	60 (43%)
2	-	21 (15%)
≥3	-	59 (42%)
Of those prescribed antidepressants:**	16 (100%)	55 (100%)
Number of months antidepressants provided		
1	13 (81%)	23 (42%)
2	2 (13%)	15 (27%)
≥3	1 (6%)	17 (31%)

Notes: * Includes those who were referred to the Friendship Bench and those who were both prescribed antidepressants and referred to the Friendship Bench. **Includes those who were prescribed antidepressants and those who were both prescribed antidepressants and were referred to the Friendship Bench.

Program Impact

Most HIV and mental health outcomes did not appear to differ between groups. (**Table 5.5**). Retention in both arms was poor; approximately a third of participants in both groups remained in care through six months. Just over half of the control group and just under half of the intervention group were currently on ART at six months. Close to 40% of participants in both the control and intervention phases maintained a consistent ART supply (never more than 5 days

without ART) through six months. Many participants had missing data for viral suppression and depression remission after 5.5 months; only 36% (n=181) of participants had viral load draw after 5.5 months and 26% of participants (n=132) had a measured PHQ-9 score. Among those with a measured viral load or PHQ-9 score after 5.5 months, respectively, viral suppression and depression remission were high (>91%) in both groups. Findings were similar when stratified by baseline depressive severity (mild or moderate to severe) and when using a "treatment started" and an "as treated" approach (**Appendix Tables 1-4)**.

Table 5.5. Program impact on HIV and depression outcomes

n (%) or mean (sd)	**Control**	**Intervention**
Retention: never >14 days through 6 months	91/266 (34%)	66/186 (35%)
HIV appointment attendance: average proportion of scheduled appointments attended through 6 months (Range: 0-1)	0.57 (0.39)	0.59 (0.38)
Currently on ART: attended appointment prior to 6 months with next scheduled appointment after 6 months	138/266 (52%)	87/186 (47%)
Consistent ART: never >5 days without ART through 6 months	112/266 (42%)	73/186 (39%)
ART pill possession: average proportion of days with ART through 6 months (Range: 0.16-1)	0.69 (0.35)	0.67 (0.37)
Viral suppression: VL < 1,000 copies/mL after 5.5 months, among those with a viral load	108/115 (94%)	60/66 (91%)
Depression remission: PHQ-9 score < 5 after 5.5 months, among those with a PHQ-9 score	87/93 (94%)	37/38 (97%)

Notes: This table does not include data on individuals who transferred within the first 6 months of care: Control Phase n=24; Intervention Phase n=25. Denominators vary due to viral loads not being drawn, the PHQ-9 not being administered, not having or attending a scheduled appointment around 6 months. ART=antiretroviral therapy. PHQ-9=Patient Health Questionnaire-9. VL=viral load.

To assess potential bias due to missing data from transferring or attending care without getting a 6-month viral load or PHQ-9 assessment, we compared baseline information between those with and without missing data. While a larger proportion of transfers were from Clinic A, missing data did not appear to be associated with any other measured baseline characteristics (**Appendix Tables 5-7**).

The final adjusted model controlled for clinic, months since program launch at ART initiation, sex and baseline depressive severity. Both age and baseline presence of suicidality introduced model instability. As age did not appear to be associated with any of the outcomes or program exposure, we ultimately removed it from the model. We only retained baseline depressive severity in the final adjustment set as baseline presence of suicidality was highly correlated with baseline depressive severity.

In the adjusted "intent-to-treat" analysis, program exposure did not demonstrably affect the primary outcome, retention with viral suppression at six months (**Table 5.6**). While no difference was evident for most of the secondary outcomes, the probability of currently being on ART at six months and the ART pill possession ratio was significantly lower among the intervention group than among the control group [RR 0.6(95%CI: 0.4-0.9) and Mean Difference -0.1(95%CI: -0.3-0), respectively]. Correction for missing data with multiple imputation did not have a significant impact on any of the outcomes. When stratified by baseline severity, only the probability of being on ART at six months was significantly lower during the intervention phase

Table 5.6. Effect of intervention on HIV care and depression outcomes

Outcome	**Adjusted***	**Imputation****
	RR or Mean Difference (95%CI)	
Retention: never >14 days through 6 months	1.1 (0.6-1.9)	1.1 (0.6-1.9)
HIV appointment attendance: average proportion of scheduled appointments attended through 6 months	0.0 (-0.1-0.2)	0.0 (-0.1-0.1)
Currently on ART: attended appointment prior to 6 months with next scheduled appointment after 6 months	**0.6 (0.4-0.9)**	**0.6 (0.4-0.9)**
Consistent ART: never >5 days without ART through 6 months	0.8 (0.5-1.2)	0.8 (0.5-1.3)
ART pill possession: average proportion of days with ART through 6 months (Range: 0.16-1)	-0.1 (-0.3-0.0)	-0.1 (-0.4-0.1)

Notes: *Adjusted for clinic, months since program launch (quadratic term), sex, and baseline depressive severity. **Further corrected for missing data via multiple imputation. ART=antiretroviral therapy.

than during the control phase [RR 0.33(95%CI: 0.13-0.83)] among those with moderate to severe depressive symptoms at baseline (**Appendix Table 8**). The "treatment started" and "as treated" approaches generally showed similar results (**Appendix Tables 9-10**).

Discussion

We investigated the impact of a program integrating depression management into HIV care initiation on six-month HIV care and depression outcomes. Clinic staff screened nearly all patients for depression, documenting the prevalence of mild and moderate to severe depressive symptoms among people newly initiating ART. During the intervention phase of the program, they successfully started the majority of the intervention group on the appropriate depression treatment. However, providing ongoing treatment proved more challenging, and few patients received a standard course of antidepressants or attended a sufficient number of Friendship Bench therapy sessions. Retention was very low in both the intervention and control groups. Nearly all participants who did remain in care and had a six-month viral load drawn and PHQ-9 assessment achieved viral suppression and depression remission. However, the evaluation did not yield evidence that the integrated depression treatment program improved six-month HIV care or depression outcomes among the intervention group compared to the control group.

The successful integration of depression screening allowed this evaluation to document the prevalence of depression among people newly initiating ART. A growing body of research is beginning to establish the magnitude of mental health disorders in Malawi. In Malawian primary care settings, a third of all patients have a common mental disorder, most commonly depression.[34] However, few studies have estimated the prevalence of depression among the general adult population of people living with HIV. We found that around a quarter of people newly initiating ART at the study sites had mild to severe depressive symptoms. This finding is

only slightly higher than estimates from various subpopulations (adolescents, pregnant women, adults receiving HIV care) of people living with HIV in Malawi[35,37,112] and supports other sub-Saharan regional estimates of depression prevalence.[1] Such evidence indicates a clear need for depression treatment among people living with HIV.

The integration of depression screening and treatment initiation at the time of ART initiation appeared feasible. During ART initiation, nearly all of the 2067 participants who consented to participate in the study were successfully screened for depression. Further, nearly all intervention participants started the treatment appropriate for their depressive severity at ART initiation. Factors that may have contributed to this success include the effective utilization of existing ART initiation processes and the creation of a collaborative training environment [130]. For example, after careful study of patient flow, we designed the initial PHQ-9 screening to be shared by the HTC counselors and the ART providers, distributing the additional work and time burden. We also ensured that every HIV provider received training in how to administer and interpret the PHQ-9, provide depression treatment, and manage depression symptoms over time – creating opportunities for iterative learning and ongoing support.[130] Another task-shifting study in Uganda found that both depression screening by lay workers and antidepressant treatment initiation by ART provider were feasible, a success the researchers attributed to ongoing training and appropriate mentorship.[60] As such, using non-psychiatric specialists to screen and triage cases of depressions appears possible in this sub-Saharan setting.

While effective integration into existing processes was key to the success of depression screening and treatment initiation, the aspects of existing infrastructure and supply management that the program was unable to effectively utilize hampered the provision of sustained depression treatment. Providers at the study sites typically rely on an electronic medical record (EMR)

system to provide ART, which did not incorporate PHQ-9 screening or depression treatment and thus did not alert providers to re-assess depressed patients returning for care. Despite developing a system of marking patients' health passports so that those needing depression treatment re-evaluation could be identified, providers struggled to re-identify depressed patients returning for ART care.[130] Very few studies on task-shifting models of care in the region have relied on existing staff (as opposed to study-employed staff) or assessed the provision of depression treatment over time. For example, the study evaluating different task-shifting strategies for depression treatment in Uganda only reported on depression treatment initiation[60], making comparisons challenging. Other implementation science studies will need to track and assess the provision of treatment over time.

Antidepressant stock-outs were also common and problematic. While the Malawi Ministry of Health has committed to making antidepressants freely available at health center pharmacies [65], ensuring their availability was complicated and required substantial coordination, often beyond the scope of work of the health center pharmacist. Other countries such as Mozambique with similar policies on the provision of antidepressants have also experienced challenges stocking these medications at the district or clinic level.[136] Another task-shifting depression program in Tanzania also experienced antidepressant stock-outs.[58] Greater engagement and investment of health sector stakeholders involved in the procurement, supply and distribution of drugs such as Malawi's Central Medical Stores is required to ensure antidepressant stocks are maintained to ensure the success and safety of depression treatment programs.

The clinics also found it challenging to provide proper Friendship Bench therapy, in part due to community health care workers' availability and in part due to patients' ability to return to

the clinic for therapy sessions, in light of financial, time, and transport barriers[119]. As the community health workers already had a very high workload and often traveled off-site to run various Ministry of Health initiatives, the one program-employed counselor at each site ultimately provided the majority of the therapy sessions. Community health workers are often already overloaded with work and are at risk of becoming additionally overburdened when drawn into task-sharing models of care[137,138], as was potentially the case at the study sites. Furthermore, while the original Friendship Bench protocol called for six weeks of weekly therapy sessions[56], patients were reluctant to make additional trips to the clinic primarily due to time and transportation barriers. This resulted in scheduling Friendship Bench sessions to coincide with the patients' monthly ART refill appointments. While attending weekly sessions appeared acceptable in the original Friendship Bench program[56], it is difficult to tell from other adaptations as they may have incentivized attending sessions with reimbursement.[139] These findings highlight the importance of implementation science research to establish the real-world feasibility of task-shifting depression care for people living with HIV.

As implemented, the program did not appear to improve HIV care or depression outcomes, as few patients received depression treatment as intended. Studies in the region have found that similar programs, albeit with higher fidelity to their treatment protocols, have been effective at treating depression.[74,131] In our study, nearly all participants achieved depression remission, regardless of depression treatment. As many of these other evaluations of depression treatment programs were quite small or did not include control arms[74,131], it is possible that depressive symptoms could have improved in the absence of depression treatment. However, it should be noted that we could have overestimated six-month depression remission if patients who did not remain in care were more likely to have persistent depressive symptoms. In regards

to the program's impact on HIV outcomes, the literature on linking depression treatment to improvements across the HIV care cascade is mixed.[7-15,53,139,140] A recent meta-analysis of depression treatment interventions for people living with HIV in sub-Saharan Africa also did not find that interventions improve viral suppression, though they did conclude that the programs with an ART adherence component had the greatest impact on HIV outcomes[131]. As it was impossible for the program to have a pure control group in which patients were denied depression treatment, it is possible that providers discussed the depression screening results with participants or provided brief additional ART adherence counseling. While even unstructured additional patient attention has the potential to impact engagement in care, it is no substitute for evidence-based depression treatment and adherence counseling interventions. Further research is needed to understand the factors that influenced adherence to the program protocol and to identify the more effective ways to implement depression treatment programs that will improve depression and HIV care outcomes.

Retention in care was remarkably low in both of the study phases; only a quarter of patients achieved retention and viral suppression at six months. Aligned with PEPFAR's less-stringent definition of being in care at six months (our "currently on ART" measure)[91], only half of patients were retained at six months. These estimates are much lower than national 12-month estimates from 2018, which found that 65% of adults who initiated ART were still in care at 12 months.[141] However, as our entire study population had elevated depressive symptoms, it possible that depression is responsible for this difference in retention. The program did not appear to improve HIV care engagement, even when using the "treatment started" or "as treated" approach, and in the main analysis the intervention group was significantly less likely to currently be on ART at six months than the control group. It is possible that this population faced

other barriers to care that were more relevant and difficult to overcome, such as human resource and institutional challenges, distance to the clinic, lack of support, and stigma and fear of HIV status disclosure.[24,29-31] Nonetheless, there is a distinct need for urgent action to improve early retention in care for people living with HIV and depression.

Limitations

The results should be considered in light of several limitations. Although the study's design was not guided by a formal implementation science framework, the study was designed in congruence with the key principles of implementation science, using methods that would promote the systematic uptake of evidence-based practices (e.g. the Friendship Bench and algorithm-based care) into routine care.[142,143] In line with the implementation science-inspired design of the study and our efforts not to unduly influence the provision of or engagement in care, all of the measures were drawn from routinely collected medical chart data. As we did not conduct baseline interviews or schedule six-month follow-up interviews, we captured limited information on potential confounders. A large proportion of patients did not have six-month viral loads or PHQ-9 scores due to either dropout or provider failure to refer patients for viral load testing or screen patients appropriately. Still, the multiple baseline design should have protected against confounding from unmeasured confounders by producing balanced characteristics across phases, as evident from similar characteristics of intervention and control groups seen in **Table 5.2**. Additionally, the program struggled to establish a sense of ownership among providers, develop capacity to manage depression treatment over time, and ensure the availability of antidepressants, which may have impacted providers' adherence to the depression treatment protocol.[130] As an extension of this challenge, ART providers administered the six-month PHQ-9, so part of the observed reduction in PHQ-9 scores could be due to less careful administration.

All of the HIV engagement measures may have been influenced by participants who sought care at another facility without formally transferring their records. These "silent transfers" would have been misclassified as being out of care. However, as the rate of silent transfers should not have varied between groups, this potential measurement error should not have introduced bias into the analyses.

Conclusion

This experience demonstrated that while it is feasible to integrate depression screening and treatment initiation into ART initiation, providing ongoing depression treatment over time is challenging; very few patients received ongoing depression treatment for many of the reasons discussed above. In this setting, it is clear that in order for such a program to be successful, additional resources are needed to support ongoing capacity building, ensure the availability of Friendship Bench counselors and antidepressants, encourage patient engagement in the full-course of treatment, and further integrate into the electronic medical records system. Additionally, further research is needed to explore the other factors that potentially govern both the implementation of and engagement with such a program. While the evaluation did not yield evidence that the program improved HIV care or depression outcomes in a real-world clinic setting, depression treatment in sub-Saharan Africa is efficacious for improving mental health and engagement in HIV care in more controlled research environments.[74] Further, this program targeted patients newly initiating ART, often at the highest risk for loss to care. Further research could explore whether other patient populations may benefit from depression treatment, such as those returning for care with elevated depressive symptoms or whether depression treatment for people living with HIV may be more effective if it includes a specific component supporting ART adherence or HIV care engagement. Moving the field of mental health care in low- and

middle-income countries forward, similar implementation science studies will be increasingly important as we strive to understand and test the best ways to implement evidence-based depression treatment protocols for this vulnerable population.

CHAPTER VI: MIXED-METHODS PROCESS EVALUATION OF THE IMPLEMENTATION OF A PILOT DEPRESSION TREATMENT PROGRAM

Introduction

The burden of depression is high among people living with HIV, particularly in sub-Saharan Africa (SSA).[1] Beyond the morbidity produced in its own right, depression hinders engagement in HIV care and antiretroviral therapy (ART) adherence, which ultimately predict HIV clinical morbidity and mortality.[1-6] Despite the deleterious impact of untreated depression among people living with HIV, investment in mental healthcare is lacking across the globe and especially in resource-limited settings such as in SSA.[144] Fortunately, interventions to address the burden of depression among people living with HIV are being developed[50,51], with several directed specifically for SSA or other settings with limited psychiatric infrastructure and human resources.[52-58]

To address the burden of depression among people living with HIV, the Malawi Ministry of Health (MOH) implemented a pilot task-shifting program that integrated depression management into ART care initiation at two clinics in Lilongwe, Malawi.[95,130] As part of this program, existing clinic-based staff provided two evidence-based depression treatment interventions, including measurement-based care (MBC) antidepressant prescription[58-60] and the Friendship Bench problem-solving therapy.[56,61] Despite the proven safety and efficacy of these treatment models, the initial program evaluation found that the treatment program did not improve retention, viral suppression or depression remission.[89]

The ultimate impact of health innovations depends not only on the effectiveness of the intervention, but also on its reach in the population and the extent to which interventions are properly adopted, implemented and maintained over time.[145] In this manuscript, we first describe how the program was designed. We then present a mixed-methods process evaluation investigating the extent to which our implementation strategy was delivered with fidelity, deemed acceptable by providers and patients, and sustained after the conclusion of the program evaluation. This mixed-method investigation allows us to contextualize our previous findings, share insights from the implementation experience, and comment on the feasibility of our implementation strategy.

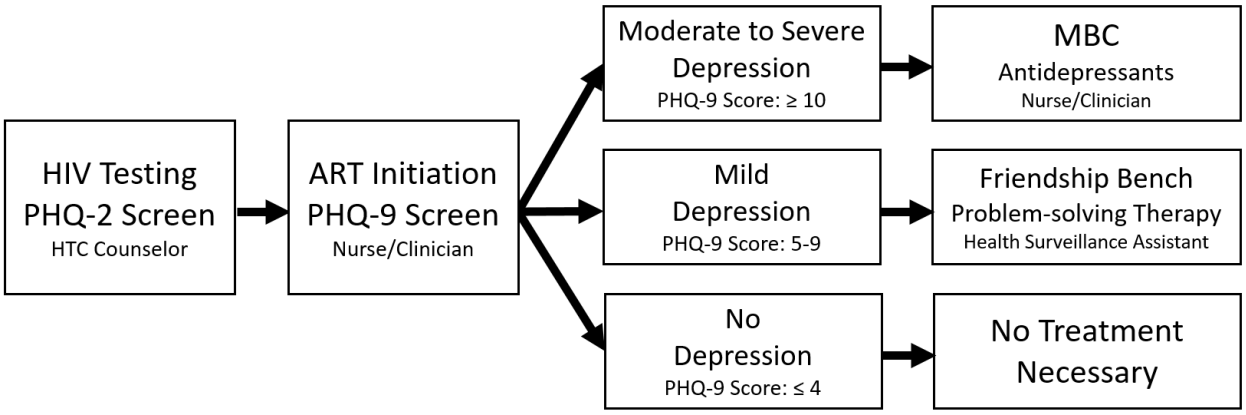
Program Overview

The pilot program integrated depression screening at treatment into ART initiation at two, semi-urban, primary level health facilities in Lilongwe, Malawi. These public facilities provide services free of charge and encompass an ART clinic, similar to a department. Only one facility employs a psychiatric nurse who does not regularly offer specialized psychiatric services. Private mental health care specialists irregularly offer mental health clinic days at the facilities. Otherwise, patients can be referred to the psychiatric department at the district hospital. Further details on the health facilities available in previous publications.[130]

HIV testing and counseling (HTC) counselors and ART providers were trained to screen patients newly initiating ART for depression using the Patient Health Questionnaire-9 (PHQ-9), a nine-item depression screening questionnaire that has been widely used in the region.[82,83,112,134,135] HTC counselors were to screen patients who tested positive for HIV with the first two questions of the PHQ-9 [called the Patient Health Questionnaire-2 (PHQ-2)] that screen for depressed mood and anhedonia. ART providers were to complete the remaining seven

questions of the PHQ-9 with any patients who reported either of the symptoms captured by the PHQ-2. ART providers were instructed on how to provide depression treatment to patients based on their depressive severity **(Figure 6.1)**.

Figure 6.1. Depression management during the intervention phase



ART providers were trained to treat moderate to severe cases of depression (PHQ-9 score ≥10) with antidepressants (amitriptyline or fluoxetine) using measurement-based care (MBC) (**Figure 6.1**). MBC is a resource-efficient, task-sharing model for prescribing antidepressant management in non-psychiatric settings that has demonstrated safety, feasibility, and acceptability when adapted for HIV care and delivered by non-specialists in Cameroon, Tanzania and Uganda.[58-60] The pharmacies at the health facilities were instructed to stock amitriptyline and fluoxetine, two antidepressants that are considered "essential medicines" under Malawi's Essential Health Package and are meant to be freely available for patients at health facilities.[63,64] ART providers were instructed to discuss the available antidepressants with the patient and jointly decide on the best option for the patient. When patients returned for ART care, ART providers were then meant to reassess patients' depressive symptoms, evaluate their response to the depression treatment and prescribe antidepressants as necessary. The study staff hung posters in the ART clinic rooms that provided an overview of the MBC protocol and detailed how to use

PHQ-9 scores and side-effect tolerability to guide changes in dosage or type of antidepressant. A standard course of antidepressants should consist of at least three consecutive months of antidepressant prescription with dosage adjustments as necessary.

ART providers were trained to refer cases of mild depression (PHQ-9 score 5-9) to clinic-based community health workers [called Health Surveillance Assistants (HSAs)] who were trained to provide Friendship Bench problem-solving therapy (**Figure 6.1**) Friendship Bench therapy is an adapted form of problem-solving therapy or patient-centered counseling that was developed in Zimbabwe and teaches patients how to identify triggers and effectively manage stressful life events by learning or reactivating problem solving skills.[56,61] Patients referred to the Friendship Bench were to receive at least six counseling sessions, with adequate treatment comprising at least six sessions within the first six months. While Friendship Bench counselors were meant to encourage patients to return weekly for Friendship Bench therapy, patients were asked to set their own appointments in line with the protocol's patient-centered approach. The study also employed one Friendship Bench counselor at each site, to provide back-up support the HSAs trained in the Friendship Bench protocol. Additionally, the study built covered shelters at both sites as a dedicated space for the Friendship Bench therapy.

Throughout the program implementation, the study coordinator held bi-monthly meetings at each site to support clinic staff and leadership deliver the program. However, the study staff were otherwise not meant to assist in the provision of daily clinical care and were only meant to consent patients and abstract their clinical data. Prior to the conclusion of the program evaluation, the study coordinator worked with the health facility staff and leadership to transition ownership of the program entirely to the health facilities. As such, the HIV providers were to

continue screening and treating patients as before after the study ended. Previous publications can provide further details on the on the program design[95], implementation[130],and impact.[89]

Methods

Clinical Data

After the launch of the intervention, all non-pregnant adults newly initiating ART were exposed to the depression screening and treatment program and eligible to participate in the program evaluation. Between April 2017 and November 2018, study staff approached potential participants during the ART initiation process to invite them to allow their clinical data to be used in the program evaluation. Study staff abstracted sociodemographic information as well as data on depression and HIV care from consenting participants' clinical records over a 13-month period, starting at ART initiation. Again, further details on enrollment in the program evaluation, clinical data abstraction and the measures captured have been previously published.[89,95] Only participants with elevated depressive symptoms (PHQ-9 $\geq$ 5) at ART initiation are included in this mixed-methods process evaluation. All analyses were performed using STATA IC 14.

Qualitative Data

In-depth interviews were conducted over after the launch of the intervention between June and December 2018 with the following objectives: 1) explore providers' and patients' attitudes towards and experiences with the depression treatment intervention; 2) understand barriers and facilitators to integrating depression treatment into HIV care; and 3) prepare for the long-term sustainability of the program after the conclusion of the program evaluation. The qualitative interviews were conducted with a convenience sample of patients with depression at ART initiation who were referred to the Friendship Bench or prescribed antidepressants, ART providers, Friendship Bench counselors, and clinic leadership. Prior to data collection, study staff

met with the administrators at both health centers and drew up a list of staff. The study coordinator or interviewer approached staff and leadership at the clinic to schedule interviews. The study staff identified patients returning for ART services and invited these patients to participate. An effort was made to interview a range of men and women as prior research has shown attitudes towards depression and the provision mental health care may vary by the gender of both providers and patients.[85-87] The research team developed semi-structured interview guides based on the study objectives. Interviews were conducted in either Chichewa (the local language) or English, based on participants' preference, by a Malawian woman with a background in qualitative research and HIV care services. All interviews were held at the respective health facility in a private location. The interviews were audio-recorded, translated and transcribed to English. The research team reviewed transcripts as they became available, and provided feedback to the interviewer throughout the data collection process to ensure quality.

After reading each of the transcripts, the author (MS) drafted a thematic codebook that would address the study objectives and capture emerging themes evident from her initial review of the transcripts [98,99]. As such, many codes were developed *a priori*, given that the interview questions were linked to the program implementation, while others were developed *a posteriori*. MS then met with research team members who had simultaneously been reviewing the transcripts to review and finalize the codebook. Two coders coded a subset of the same transcripts from each round to ensure consistency in their use of the codes using NVivo (Version 12). Coding was treated as an iterative process and the coders met several times throughout to discuss the addition, definition, and appropriate use of the codes that emerged from the data. Additionally, the coders wrote memos for the individual transcripts and on emerging themes. Upon completion of coding, MS executed queries in NVivo and both she and the second coder

(CM) reviewed coded data related to the key aspects of program implementation, depression treatment initiation, depression treatment over time, acceptability, and sustainability. While synthesizing these findings, MS met with the study team to ensure accurate interpretation of the interviews.

Implementation outcomes

We defined these implementation outcomes in line with Proctor and colleagues' conceptualization of implementation science research outcomes and Caroll and colleagues' framework for implementation fidelity.[146,147] Fidelity is the degree to which this program was implemented as intended or adherence to the program protocol. Acceptability is the perception among stakeholders and consumers, in this case health facility staff, leadership and patients, that the program is agreeable or satisfactory based on their knowledge, experience, and comfort with the program's content and complexity. Sustainability is defined as the extent to which the program is maintained within the health facilities' ongoing operations after the conclusion of the program evaluation. We assess each of these outcomes in the following manner:

Fidelity

We examined adherence to the program protocol in terms of content, coverage, frequency, and duration[147] by using clinical data to determine whether patients initiated the correct depression treatment (content) based on their depressive severity (coverage) and whether these patients continued to attend Friendship Bench therapy sessions or receive antidepressants (frequency) over their first six months in care (duration). Data from the qualitative interviews explain and contextualize the quantitative fidelity measures.

Acceptability

We used data from the qualitative interviews to explore participants' views towards delivering the program and its impact on patient outcomes. We specifically considered providers' comfort with the depression treatment options, their opinions about the complexity of the program, and various structural impediments to program delivery. Additionally, patients' and providers' experiences with the program's effect on patient health outcomes were also reviewed.

Sustainability

We examined screening rates soon after the study stopped enrolling participants in the program evaluation (from February to May 2019) and then again in December 2019. We also used discussions with clinic staff and leadership about maintaining the program in the future to help understand these findings.

Ethical Considerations

We sought and obtained approval from both the Malawi MOH's National Health Science Research Committee (NHSRC) institutional review board (IRB) and the Biomedical IRB of the University of North Carolina at Chapel Hill. All participants who agreed to participate in the study provided informed consent. Qualitative study participants were given a travel reimbursement equivalent of and 10USD (7,000MK). The study team collected no identifying information and maintained unlinked consent forms, abstracted clinical data, and transcripts.

Results

We first describe the characteristics of the study participants and then assess fidelity, acceptability and sustainability. Fidelity is examined in regards to depression treatment initiation and engagement over time for both the MBC protocols and Friendship Bench protocols. Of note, there are some themes presented in the fidelity section that speak to participants' comfort with the program and its overall complexity that are pertinent to assessing acceptability.

Participant Characteristics

Of the 936 patients who enrolled in the program after the launch of the intervention, 211 were depressed at ART initiation (**Table 6.1**). A total of 14 patients participated in in-depth

Table 6.1. Participant characteristics

	Intervention (N=211)	**Intervention* (N=14)**	**Screening (N=11)**
Sex			
Female	89	6	7
Male	122	8	5
Age**	34.0 (19-65)	36.1(23-47)	34.2 (26-46)
Health Facility			
Clinic A	116	14	6
Clinic B	174	0	6
Marital Status			
Married	n/a	6	n/a
Single	n/a	0	n/a
Separated	n/a	7	n/a
Employment			
Employed	n/a	12	n/a
Self-employed	n/a	0	n/a
Unemployed	n/a	1	n/a
Position			
ART Provider	n/a	n/a	6
Friendship Bench Counselor	n/a	n/a	4
Leadership	n/a	n/a	2
Professional Experience			
Years at clinic	n/a	n/a	4.9 (0.7-11)
Years as clinician	n/a	n/a	8.7 (4-15)

Notes: *Marital status and employment missing (n=1). **Age missing (n=3) and excludes leadership. ART=antiretroviral therapy.

interviews. Of these 14 patients, 11 were prescribed antidepressants and three started Friendship Bench therapy at ART initiation. As a small number of participants had depression at Clinic B,

all of the interviewed patients were from Clinic A. A total of 12 clinic staff participated in the qualitative interviews.

Fidelity

MBC

The clinical data demonstrates that ART providers successfully prescribed antidepressants at a therapeutic dose to nearly all (96%) cases of moderate to severe depression, achieving high fidelity to the MBC protocol (**Table 6.3**). Based on the qualitative interviews,

Table 6.3. Depression treatment initiation

	Mild Depression (PHQ-9 score 5-9)*	**Moderate to severe Depression (PHQ-9 score ≥10)**
	N=156	**N=55**
Counseling by ART provider	15 (10%)	2 (4%)
Friendship Bench	134 (86%)	0 (0%)
Antidepressant (AD)	0 (0%)	41 (75%)
w/counseling by ART provider	0 (0%)	8 (15%)
w/Friendship Bench	2 (1%)	4 (7%)
None*	5 (3%)	0 (0%)
Of those who start AD	**N=2**	**N=53**
Type		
Amitriptyline	1 (50%)	37 (70%)
Fluoxetine	1 (50%)	16 (30%)
Dose		
Sub-therapeutic dose	0 (0%)	0 (0%)
Therapeutic dose	2 (100%)	53 (100%)

Notes: *Includes 4 patients with missing baseline treatment. ART=antiretroviral therapy. PHQ-9=Patient Health Questionnaire-9.

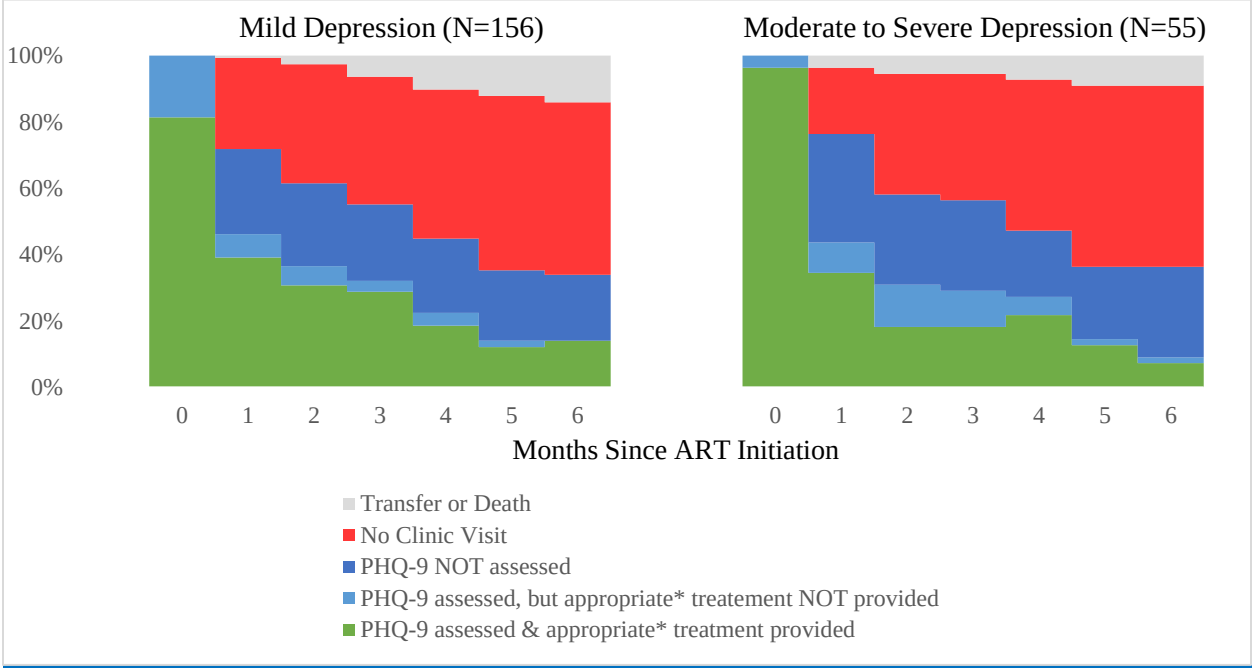
ART providers appeared knowledgeable of the depression treatment protocol and how to appropriately triage patients based on their PHQ-9 scores. The interviews further suggested that providers deviated from guidance to discuss the antidepressant options with patients and jointly decide on the best antidepressant. It seemed that providers were most comfortable prescribing amitriptyline and that the decision around which antidepressant to prescribe was almost entirely governed by what was in stock. As heard from one ART provider: *"We just prescribe the antidepressants that are in stock at that time, but the first choice is amitriptyline. If amitriptyline is not available, then we give that patient the other antidepressant."* While it was not entirely clear why ART providers were more comfortable with amitriptyline, leadership and ART providers felt that providers were more familiar with amitriptyline and that it was easier for patients to take. Patients take amitriptyline daily, while they initially take fluoxetine every other day and have to physically cut the pills in half.

However, the provision of MBC over time was challenging. This may be in part due to waning retention over the first 6 months of care. (**Figure 6.2**). Built using clinical data, Figure 6.2 shows that by the first follow-up appointment (month 1) only around three quarters of participants attended an ART appointment and by month only around a third of participants attended an ART appointment. Among those who did come to follow-up HIV care appointments, providers often failed to reassess these patients with the PHQ-9, which would have guided depression management, or to continue to provide appropriate depression treatment to those who were rescreened.

The qualitative interviews help explain why it was difficult to identify depressed patients returning for care and reassess those patients for depression. ART providers felt both identifying patients with depression and reassessing with the PHQ-9 took a lot of time and significantly

added to their workload, especially in light of the general shortage of staff and high patient case load. For context, study staff timed the administration of the PHQ-9 and ART providers took about a minute per question.

Figure 6.2. Depression treatment engagement, by phase and depressive severity



Notes: *Appropriate treatment is operationalized as attending a Friendship Bench session, or having completed 6 Friendship Bench sessions for those with mild depression during; or being prescribed antidepressants among those with moderate to severe depression.

That said, clinic leadership admitted, "*[ART providers] said they get tired and they don't even ask the PHQ because they know that 'this will take much of my time.' But if we had more personnel more people seeing patients that would have been better.*" This statement reveals how the added burden of the intervention negatively impacted both attitudes towards the program as well as adherence to the program protocol. Identifying patients was also difficult because the program was not integrated into the electronic medical records system. Providers had to look for stickers on the patients' health passports that signified they had previously been diagnosed with depression. If providers noticed the sticker, they would then have to manually search for the

patients' file, reassess the patient with the PHQ-9, and then provide appropriate treatment. It was difficult for providers to determine when a patient no longer needed to be assessed or had completed their depression treatment. One ART provider ventured that "*there wouldn't be a problem if depression questions were in the electronic system."* As an extension of these issues, ART providers often had a poor attitude towards the program. This phenomenon was summarized by clinic leadership, "*The workload [is problematic] when you are alone in the ART room and you need to screen those people with the green sticker, so sometimes people may be annoyed, [thinking] 'I should screen this one, but this will delay me,*" a sentiment echoed by other interviewed ART providers. As a result, ART providers often relied on the program evaluation staff to identify patients with depression returning for care and the accuracy of the follow-up PHQ-9 assessments may have been compromised.

Few of those with moderate to severe depression received antidepressants continuously for the recommended minimum three months based on analysis of the clinical data. (**Table 6.4**) Only six participants received at least three consecutive months of the same antidepressant. Switching the type of antidepressant prescribed was common; of the 30 individuals who were prescribed antidepressants at least twice, 40% (n=12) changed antidepressants at least once. Providers also failed to increase the dose of antidepressants for any of the patients when indicated by persistent elevated symptoms.

The qualitative interviews provided insight into the barriers to achieving the recommended duration of antidepressant prescription. The main challenge was rooted in identifying patients returning for care, as previously described above. While prescribing antidepressants did add to ART providers' workload, providers were much more concerned about the time it took to identify and rescreen patients. When asked specifically about the added

workload of prescribing antidepressant, one ART provider responded *"now we are supposed to check each and every file. If the patient's file has the sticker [marking a depressed patient's file] it means you have to ask the questions.... the issue is just the time to ask the PHQ only, the time to ask the PHQ is what trouble us."*

Table 6.4. Provision of antidepressants to patients with moderate to severe depression at baseline, by phase

	Intervention (N=55)
Months of AD prescription	
0	2 (4%)
1	23 (42%)
2	14 (25%)
3	7 (13%)
≥4	9 (16%)

Additionally, antidepressant stock-outs were common, as noted by an ART provider: *"It's very rare where by you have both [antidepressants] available…, sometimes you find that the one [antidepressant the patient started taking] also is not available so we switch them."* These reports from the clinics show that switches in antidepressant prescription were not due to side effects or to the antidepressants not having the desired effect, but necessitated by stock-outs. Ensuring that staff were properly trained on the MBC protocol was also challenging, due to high staff turnover and/or rotation through clinic departments and staff availability to attend the original trainings or the supervision sessions. Clinic leadership spoke to these needs:

> *The training was just a one day one, so most people were not familiar with the dosages so they need to be reminded here and there. Of course there are debriefing meetings that are done on Thursdays, but still not everybody was attending that review meeting. So prescribing is difficult just because people forget the dosage of the medication.*

This feedback speaks to the complexity of MBC and a need for ongoing support and training. From a patient perspective, actually taking antidepressants appeared largely acceptable. While some providers were concerned about the added pill burden, patients mostly found the antidepressants tolerable; patients did not complain of many side effects nor did they report any challenges to antidepressant adherence.

Friendship Bench

Clinic staff were only moderately successful at initiating cases of mild depression on Friendship Bench therapy. According to the clinical data, while 86% of participants with mild depression correctly started the Friendship Bench therapy that same day, the study-employed Friendship Bench counselor provided over half of the initial Friendship Bench therapy sessions (**Table 6.3**). As noted by one ART provider, *"Most of the times they [Friendship Bench counselors] are in the field, so we refer them to the [study-employed counselor],"* suggesting that the clinic-based Friendship Bench providers were often unavailable and that the clinics often relied heavily on the program-employed Friendship Bench counselor.

The clinical data revealed that few participants with mild depression at ART initiation during the intervention phase received consistent Friendship Bench therapy over the course of their first six months in care (**Table 6.5).** The original Friendship Bench therapy protocol was designed to be administered over the course of six consecutive weekly sessions. None of the patients completed this ideal "full course" in their first two months of care. Only 13 patients completed at least six Friendship Bench sessions within their first six months of care. The study-employed Friendship Bench counselor provided over half of the follow-up Friendship Bench therapy sessions.

The qualitative interviews help explain the challenges to achieving the recommended number of Friendship Bench sessions. Both patients and providers reported that scheduling weekly Friendship Bench sessions was almost impossible as the cost of transport was prohibitive, alongside expected long wait times at the clinic and the opportunity cost of having to take off work. Instead, patients often chose to schedule their Friendship Bench appointments

Table 6.5. Provision of Friendship Bench therapy to patients with mild depression at baseline during the intervention phase (N=156)

	Within the first: 2 months	6 months
Friendship Bench sessions attended		
0	20 (13%)	20 (13%)
1	64 (41%)	59 (38%)
2	32 (21%)	19 (12%)
3	37 (24%)	13 (8%)
≥4	3 (2%)	45 (29%)

monthly in conjunction with their ART appointments. As described by one Friendship Bench counselor, *"Some [challenges] are transport...we [Friendship Bench counselors] give dates and ART give their dates. …So the person weighs the cost…Many are prioritizing coming for [ART] medications rather than just coming for the Friendship Bench*." Beyond highlighting the complexities of attending follow-up Friendship Bench sessions in light of constrained resources, this quote also hints at a disconnect between the ART and depression care for patients on Friendship Bench therapy.

The same staffing challenges that impeded initiating Friendship Bench therapy were also raised. The Friendship Bench counselors were not always available due to their competing responsibilities as community health workers and the Friendship Bench counselors felt their

workload had substantially increased. While the Friendship Bench counselors strove to share the added workload, the clinics often relied heavily on the program-employed Friendship Bench counselor, previously described. Friendship Bench counselors felt the provision of the Friendship Bench therapy was hampered by the sheer number of patients who defaulted or failed to attend follow-up sessions. They were frustrated by their inability to adequately trace patients in light of phone numbers not working, difficulties locating patients' residences, and limited funds for airtime or transport.

The qualitative interviews also suggest patient discomfort may have played a role in poor continued engagement in Friendship Bench therapy. Interviewed Friendship Bench counselors believed it was important to develop rapport with patients and create an environment where patients felt comfortable speaking openly and that their privacy would be respected and maintained. Patients echoed this sentiment, both as a concern and as something they appreciated about the Friendship Bench therapy. As an extension of this, clinic staff and leadership raised concerns about the availability of confidential spaces. One Friendship Bench counselor noted that other patients were often nearby the Friendship Bench shelters and *"when the client sees that, they feel that when we tell them that what we are going to discuss is confidential, we cheat on them because people are passing by."* This suggests that the open, outdoor nature of these shelters may not be conducive to provision of depression counseling in this setting.

Acceptability

The qualitative interviews show that nearly all patients, staff and leadership believed both MBC and the Friendship Bench helped improve patients' mental health, relieve their depressive symptoms, and prevent risk of suicide. In contrast, the previously published quantitative evaluation found that the treatment program did not demonstrably improve retention in HIV care,

viral suppression, or depression remission six months after ART initiation.[89] In the qualitative interviews, ART providers cited patients' reduced PHQ-9 scores as proof of the effectiveness of both antidepressants and the Friendship Bench. The Friendship Bench counselors attributed the program's perceived success to its focus on teaching patients to identify their own problems and solutions. Some patients described the specific ways their respective depression treatment helped them. For example, patients believed treatment allowed them to calm their thoughts, eat and sleep regularly, or, as heard from one patient taking antidepressants, *"I am able to talk normally and I do not have any anxiety. I am now able to chat with my friends, just like the way life should be."* While this patient believed taking antidepressants helped manage their anxiety and depression, other patients did demonstrate a lack of understanding of depression, their respective depression treatment, and its intended purpose and effect. Patients expressed a reverence for the medical field, often stating that they believed their treatment worked simply because the doctors told them it would. Finally, both Friendship Bench counselors and ART providers recognized that depressed patients may struggle to accept their HIV diagnosis and consistently take their ARTs. For example, a Friendship Bench counselor described how *"because of the counseling session, it helped the people...and now they are taking the medications consistently…this person is coming to collect drugs and their outlook [*towards their*] status has changed,"* as did an ART provider, *"Taking antidepressants have helped our friends with depression … to take their ARVs adherently because when they are depressed they don't even take the ARVs."* These descriptions demonstrate that clinic staff perceive that depression treatment supports ART adherence and engagement in HIV care.

Sustainability

The clinical data demonstrates the program was not sustained. After enrollment into the program evaluation ended, the rate of screening dropped sharply (**Table 6.6**). By December 2019, six months after the study staff had complete data abstraction, ART providers had completely stopped screening patients newly initiating ART.

Table 6.6. Screening rates

	PHQ-2 Screening*	**Complete PHQ-9 Screening****
Program Enrollment Period (Apr. 2017-Nov. 2018)	91.8%	90.5%
Brief Follow-up Period (Feb. 2019-May 2019)	25.1%	58.8%

Notes: *Among all new ART initiators. **Among those who endorse the PHQ-2. PHQ-2=Patient Health Questionnaire-2. PHQ-9=Patient Health Questionnaire-9.

These quantitative findings are partially in contrast with staff attitudes towards sustainability identified in the qualitative interviews. The staff generally expressed a belief that they would continue to screen and manage depression after the study staff left the facilities. As heard from one ART provider, *"It will continue, because it's our job us as health workers to assist those people, because if we don't assist, then who will? It's like most people will not be taking the ARVs."* In fact, only two ART providers directly expressed any skepticism towards the sustainability of the program, *"because there are people who are supporting [us] but if they can move out, it is when the true picture of their [providers'] attitude can be seen."* These ART providers acknowledged that the clinics receive a lot of support from the study staff and that challenges to sustainability may become evident after they leave. However, clinic staff and leadership did suggest certain resources would be key to supporting the sustainability of the program. These included increasing the number of trained staff, particularly Friendship Bench

providers; refresher trainings and opportunities for continued learning; ongoing supervision; maintaining the stock of antidepressants; and space for providing screening and counseling.

Discussion

In this mixed-methods process evaluation of a program integrating depression screening and treatment into routine HIV care in Malawi, we found relatively poor fidelity in delivering the program as intended, variable views towards the program's acceptability, and a lack of sustainability after the conclusion of the program evaluation. After the launch of the intervention, HIV providers appeared able to triage patients with depression at ART initiation and start cases of moderate to severe depression on the appropriate dose of antidepressants. While most cases of mild depression started Friendship Bench therapy at ART initiation, most of those initial Friendship Bench sessions were provided by the study-employed counselor as opposed to the ART providers. Over time, both ART providers and Friendship Bench counselors struggled to provide continued depression treatment. ART providers struggled to identify and reassess depressed patients returning for ART, which hampered provision of antidepressants. Staff and space availability hindered the provision of Friendship Bench therapy and the cost of transport prohibited many patients from attending weekly appointments. The quantitative program evaluation did not find that program exposure improved HIV care or depression outcomes.[89] Contrasting with these quantitative findings, patients, clinic staff and leadership generally found the depression treatment helpful, suggesting that both antidepressants and the Friendship Bench therapy may be acceptable depression treatment options for patients in this setting. The program was not sustained after the evaluation concluded, potentially due to limited staff, training, infrastructure, and supply of antidepressants.

The clinics failed to deliver Friendship Bench therapy with fidelity to the program protocol, particularly in regards to the low frequency of attended sessions over the six-month duration of follow-up.[147] The original Friendship Bench therapy protocol ideally called for six weekly therapy sessions, though patients were meant to set their own follow-up appointment dates. Similar to our findings, various evaluations of the original Friendship Bench therapy program in Zimbabwe suggest low patient engagement may not be uncommon. The pilot evaluation found that only 30% of participants completed six sessions in the first six weeks[56], the randomized control trail found around 40% completed six sessions over a six month period,[54] and a mixed-methods longitudinal study over a five-year period found nearly half of patients only attended one session, with only around 6% receiving four or more sessions.[148] We found that scheduling weekly appointments was challenging for patients, often due to the prohibitive cost of transport and spending time at the clinic. Patient follow-up was also difficult for providers, in light of limited resources and challenges contacting patients. The mixed-methods evaluation of the Friendship Bench in Zimbabwe also noted the lower-than-expected appointment attendance and follow-up challenges, which were attributed to the lack of incentives for Friendship Bench counselors to follow up with patients.[54] While the Friendship Bench is a promising approach to providing evidence-based psychosocial therapy, further investigation of how best to engage patients over time is needed.

Providers managed to start the right patients on the correct dose of antidepressants, but fidelity to the MBC protocol over time was hampered by stock-outs, ART providers' level of comfort, difficulties identifying depressed patients, lack of integration into the electronic medical records system, and negative attitudes. These challenges are unsurprising as the providers are already overburdened and were expected to engage with the depression treatment program

without additional incentives. A literature review on health systems facilitators and barriers to integration of HIV and chronic disease services found that successful integration programs have adequate, appropriately skilled, incentivized healthcare workers; supportive institutional structures; dedicated resources; strong leadership and political will or support for the program.[149] However, ensuring such a comprehensively supportive environment is particularly challenging in resource-limited settings. Furthermore, very few studies have been conducted on task-shifting programs that use algorithm-guided protocols for antidepressant prescription in the region, and those that have been conducted often do not rely on existing staff or incentivize the staff involved in the research.[58,59] Further research that seeks to evaluate and compare integrated models of care for the provision of antidepressants is urgently needed to ensure the mental health needs of people living with HIV are met.[71]

Designing implementation science studies to evaluate programs that can readily (and rapidly) be adopted and integrated into routine care in the public sector is challenging.[76,77] In an effort to assess such a depression treatment intervention, our program was intentionally designed to rely almost entirely on existing clinical staff and systems. Similarly, the evaluation was deliberately designed to influence the provision of care as little as possible. However, it is clear that the program-employed Friendship Bench counselors provided a significant proportion of the therapy sessions, suggesting this aspect of the program may not have truly been integrated or effectively task-shifted to existing community health workers. Further, the study staff likely significantly supported both patients and providers involved in the program. The evaluation coordinator spent a substantial amount of time supervising and engaging clinic staff and assisting in supply-chain management to ensure the availability of antidepressants. The evaluation staff may have acted as "expert peers" by helping patients navigate clinical care, likely as a result of

engaging patients in the consent process.[130] Further, evaluation staff helped providers identify depressed patients returning for care, thus artificially inflating the number of patients that would have been reassessed or would receive ongoing depression treatment. The lack of sustained implementation after the completion of the evaluation further suggests that the dedicated study staff on the ground were integral to the program implementation. Implementation science studies that are both supporting program implementation and evaluating the program may need to take into account how the relationship between the evaluating institution and the study site may affect the study itself.

Several key recommendations have emerged from this experience. As implemented, integrating depression treatment into HIV care in resource-limited settings was not feasible and the clinics would have benefitted from substantially more support. This mixed-method evaluation has identified the following potential facilitators:

- *The presence of a salaried, on-site coordinator or champion employed by the Ministry of Health would have increased the likelihood of more faithful implementation.* Such an individual would have been well-positioned to foster clinic ownership of the program and provide the ongoing supervision and training that is needed to effectively build and sustain mental healthcare capacity.
- *HTC counselors could administer the entire PHQ-9 at ART initiation.* This would partially address the added burden of administering the PHQ-9 at ART initiation placed on ART providers, who are still well-positioned to interpret the results and provide appropriate treatment.

- *Integration into the electronic medical records system is critical.* This integration would help ensure that screening was completed and that returning patients were re-assessed.
- *Finally, successful implementation requires a dedicated, clinic-based Friendship Bench counselor.* Task-shifting to an already overburdened cadre of community health workers was an ineffective means of providing depression services.

Limitations

Findings from this mixed-method process evaluation should be considered in light of limitations due to the program and evaluation design. First, neither the program nor the evaluation design were guided by a formal implementation science framework. However, both were designed in congruence with the key principles of implementation science, using methods that would promote the systematic uptake of evidence-based practices (e.g. the Friendship Bench and algorithm-based care) into routine care.[142,143] Further, we have drawn from various implementation science frameworks for this process evaluation to help ground this mixed-methods approach in implementation science theory.[145,147] A convenience sample of health care facility staff and patients from the program sites participated in the interviews. Notably, patients invited to participate in the interviews had to still be engaging with HIV care, and may have had very different opinions about the depression treatment program than those who did not continue to seek care at the program sites. Thus, the attitudes captured here may not be generalizable to all of the patients exposed to the screening and treatment program. Further, as the main objective of the study was to evaluate a program at the sites where participants worked or received care, it is possible that participants' responses were subject to social desirability bias. As evident from one participant being asked to explain how they believe antidepressants had helped them: *"I do not*

know whether my response to this question is right. I do not know, I am just repeating over and over again. You should correct me sometimes." However, the use of mixed-methods approaches is particularly useful for evaluating implementation outcomes.[145] In this process evaluation, the experiences and opinions captured in the qualitative interviews help contextualize and provide nuanced information about the reasons behind the program's shortcomings.

Conclusion

This depression treatment program was not delivered as intended, as fidelity to the program protocol was poor. While antidepressants and problem-solving therapy appeared to be acceptable treatment options for patients, clinic staff and leadership found delivering this treatment challenging in light of constrained human resources and infrastructure. These challenges may be responsible for the program's lack of impact on retention, viral suppression, and depression remission.[89] The program was not ultimately sustained after the conclusion of the formal evaluation. Without substantial support to supervise the implementation of the program, continue to build and maintain the capacity of providers, integrate the program in the electronic medical records system, and ensure the availability of Friendship Bench counselors, integrating such a depression treatment program into HIV care in this setting may not be feasible. This process evaluation helps explain why this implementation strategy did not work and provides valuable insight into how it could be improved. Taking these findings forward, further research is needed to test enhanced implementation strategies for integrating evidence-based mental health interventions into existing healthcare systems, particularly in low-resource settings.

CHAPTER VII: CONCLUSIONS

Summary of Findings

In light of research suggesting that depression undermines engagement in HIV care and that treating depression can improve depression and HIV outcomes, the Malawi Ministry of Health (MOH) integrated depression management into HIV care at two clinics in Lilongwe, Malawi. This pilot task-shifting program, called SOAR-Mental Health (SOAR-MH), moved psychiatric screening and management responsibilities to non-specialists. The program was implemented in two phases, a screening-only control phase and an intervention treatment phase. During the control phase, adult patients newly initiating antiretroviral therapy (ART) were screened for depression, but those with depression were managed following the existing standard of care which primarily consisted of brief supportive counseling by the HIV medical provider and thus did not receive evidence-based depression treatment. During the intervention phase, Friendship Bench problem-solving therapy or algorithm-guided antidepressant treatment was offered to patients with elevated depressive symptoms based on their depressive severity.

Aim 1 of this dissertation investigated whether HIV care engagement differed for those with and without depression in the absence of evidence-based depression treatment. This first aim only included participants who initiated care during the screening-only phase of SOAR-MH and compared retention in HIV care and viral suppression at six months between those with and without depression at baseline. The prevalence of depression among this population was 27%. We ultimately found that HIV care outcomes did not vary between those with and without depression at baseline.

Aim 2 of this dissertation evaluated the impact of the depression treatment program on HIV care and depression outcomes at six months. This second aim only included participants with depression at ART initiation and compared retention in HIV care, viral suppression, and depression remission between those who initiated during the screening-only control phase (who were unexposed to the program) and those who initiated during the intervention phase (who were exposed to the program). While almost all of the patients who initiated during the intervention phase started the appropriate depression treatment, we ultimately found that few participants in the intervention group received consistent depression treatment over their first six months in care. Further, program exposure did not demonstrably affect most HIV or mental health outcomes, though the probability of currently being on ART at six months was significantly lower among the intervention group than the control group [RR 0.6(95%CI: 0.4-0.9)].

Aim 3 of this dissertation examined the implementation of the SOAR-MH treatment program by focusing on implementation fidelity, acceptability, and sustainability. Using a mixed-methods approach, we used clinical data to describe the implementation of the program and qualitative interviews with clinic staff and patients to contextualize and explain these findings. There were many challenges to implementing this task-shifting depression program as intended. Using existing HIV testing and counseling (HTC) workers and ART providers to identify patients with depression at ART initiation appeared feasible. However, fidelity to the program protocol was poor. While antidepressants and problem-solving therapy appeared to be acceptable treatment options for patients, clinic staff and leadership found delivering these treatment options challenging in light of constrained human resources and infrastructure. The program was not sustained.

Strengths and Limitations

The results presented in this dissertation should be considered in light of several limitations. Due to the implementation science nature of this study, the covariates captured were limited to routinely collected clinical data. In order to design a study that would promote the systematic uptake of evidence-based practices into routine care, the study team strove to limit the evaluation's influence on the provision of or engagement in care. As such, all of the measures were drawn from routinely collected medical chart data. We did not conduct baseline interviews or schedule six-month follow-up interviews, and we captured limited information on potential confounders. While the multiple baseline design used in the Aim 2 analysis should have protected against confounding from unmeasured confounders by producing balanced characteristics across phases, it is possible that the presented analyses were biased by unmeasured confounding factors.

A large proportion of patients did not have data on six-month viral loads or PHQ-9 scores, due to either dropout or provider failure to refer patients for viral load testing or to screen patients appropriately. As such, it is possible that we overestimated depression remission and viral suppression as six-month PHQ-9s and viral loads could only be established for patients who remained in care. Further exacerbating these issues, it is possible that part of the observed reduction in PHQ-9 scores could be due to less careful administration of the PHQ-9 at six months. Additionally, a large proportion of patients who did return for care at six months were never sent for viral load testing.

All of the HIV engagement measures may have been influenced by participants who sought care at another facility without formally transferring their records. These "silent transfers" would have been misclassified as being out of care. However, as the rate of silent transfers

should not have varied between groups, this potential measurement error should not have introduced substantial bias into either of the Aim 1 or Aim 2 analyses.

It is also possible that providers inaccurately identified cases of depression using the PHQ-9. The PHQ-9 is not a diagnostic tool, but a questionnaire that assesses the presence of the nine core symptoms of depression and has yet to be validated among people living with HIV in Malawi. However, the PHQ-9 was specifically chosen for use in this program because it has been widely used and validated among people living with HIV in SSA[81-83], works well both as a case identification tool as well as a longitudinal monitor of response to treatment, and has been validated among a Malawian population of people living with diabetes.[120] Again, it is possible that the ART providers incorrectly administered the PHQ-9 to patients. However, capacity-building meetings and check-ins were held throughout the program implementation to support providers and to help ensure they understood how to use and interpret the tool. Furthermore, we did a small sub-study comparing the providers' administration of the PHQ-9 to that of trained research assistants. While we found that research assistants identified more cases of depression than providers, there was still high overall agreement between providers and research assistants.[122]

There are also some limitations unique to the qualitative analysis presented in Aim 3. A convenience sample of health care facility staff and patients from the program sites participated in the interviews. Notably, patients invited to participate in the interviews had to still be engaging with HIV care, and may have had very different opinions about the depression treatment program than those who did not continue to seek care at the program sites. Thus, the attitudes captured here may not be generalizable to all of the patients exposed to the screening and treatment program. Further, as the main objective of the study was to evaluate a program at

the sites where participants worked or received care, it is possible that participants' responses were subject to social desirability bias. Nonetheless, the experiences and opinions captured in the interviews help contextualize and provide useful insights explaining some of the program's value and shortcomings.

Interpretation and Implications of Findings

The Malawi MOH integrated a depression treatment program offering Friendship Bench problem-solving therapy and algorithm-guided antidepressant treatment into ART initiation at two clinics in Lilongwe, Malawi. The impetus for implementing this program was that research has documented a high prevalence of depression among people living with HIV in Malawi and has found that depression can undermine engagement in HIV care.[1-6] While studies have shown the efficacy of various evidence-based treatment protocols for using Friendship Bench therapy and antidepressants to manage depression symptoms in low-income settings, the best methods for providing psychiatric services in such settings are not often clear.[56,58-61] As such, the evaluation of this program was designed to test whether this implementation method was an effective means of providing depression services for people initiating ART and improving HIV care and depression outcomes.

In parallel with understanding and evaluating the implementation of this program, this dissertation accomplished three goals. First, it investigated the questions guiding the premise or motivation for implementing this program. Namely, is there a high prevalence of depression among people newly initiating ART and is depression at ART initiation associated with reduced retention in HIV care? Second, it evaluated the implementation of the program and its impact on HIV care and depression outcomes. Third, it examined the implementation of the program in an effort to explain the program's failure to improve patient outcomes.

The prevalence of depression among patients newly starting ART was quite high – around a quarter of those enrolled who completed the PHQ-9 screening reported mild to severe depressive symptoms. This finding is in line with previous research conducted in Malawi which found a prevalence of depression ranging between 1% and 19% among various subpopulations (adolescents, pregnant women, adults receiving HIV care) of people living with HIV [35,37,107,112], and supports other sub-Saharan regional estimates of depression prevalence.[1] Such evidence confirms a high burden of depression among people living with HIV and does indicate a clear need for depression treatment among people living with HIV.

However, depression at ART initiation was not associated with any of the retention metrics for HIV care engagement and viral suppression at six months. Key to interpreting this finding is recognizing that these retention metrics were all dictated by appointment attendance. While the association between depression and reduced ART adherence is relatively well-established[2,115], the effect of depression on overall engagement in HIV care is less understood and few studies have investigated this specific aspect of the depression-HIV care engagement relationship. Several studies conducted in the region examining the association between depression prior to HIV testing and linkage to care had mixed results, as previously described.[44,116,117] Research into the effect of depression on HIV care engagement suggests that depression manifests through loss of interest, poor concentration, poor motivation, reduced self-efficacy, fatigue, hopelessness, and suicidality.[2,4,46] While these mechanisms may directly impact daily ART adherence, they may have less of an effect on monthly clinic attendance. As such, it is not evident that untreated depression is driving reduced retention among people newly initiating ART in this setting.

The program evaluation found that while nearly all patients were correctly screened for depression and, following the launch of the treatment phase, depressed patients initiated the appropriate treatment, the continued provision of depression treatment was nonetheless challenging. Both clinical and qualitative data were used to describe and explain the following key aspects of the program implementation across both phases in the Aim 2 and Aim 3 analyses: depression screening, depression treatment initiation, and depression treatment engagement over time.

Integrating depression screening and depression treatment initiation into HIV care appeared feasible at the clinic sites. Nearly all patients who initiated ART during the program evaluation were completely screened for depression. ART providers also managed to appropriately triage cases of depression and start patients on the appropriate depression treatment during the intervention phase. Another task-shifting study in Uganda found that both depression screening by lay workers and antidepressant treatment initiation by ART providers were feasible, a success the researchers attributed to ongoing training and appropriate mentorship.[60] Factors that may have contributed to this success in our study include efforts to ensure that every HIV provider received training in how to administer and interpret the PHQ-9; the effective utilization of existing ART initiation processes; and the creation of a collaborative training environment.[130] However, as a caveat to this success, it is evident from the interviews with clinic staff that the research assistants may have played a role in escorting patients from HTC to ART initiation and ensuring that the ART providers actually completed the PHQ-9 when necessary patients. Furthermore, the program-employed Friendship Bench counselor provided over half of the initial Friendship Bench therapy sessions, often because the existing clinic-based Friendship Bench counselors were unavailable. Nevertheless, these findings suggest that using public-sector, non-

psychiatric specialists to screen patients newly initiating ART for depression and initiate depressed patients on appropriate treatment is possible in this low-resource SSA setting.

The clinic staff struggled to provide continuous depression treatment over time in light of human resource constraints, an inability to effectively integrate depression management into existing clinic infrastructure, and supply chain management inadequacies. Very few patients received ongoing depression treatment. The difficulties of providing ongoing depression treatment seemed to largely stem from challenges in re-identifying depressed patients returning for care, persistent stock-outs of antidepressants, the lack of availability of Friendship Bench therapy counselors, and the inability of patients to return for Friendship Bench therapy sessions.

ART providers struggled to re-identify patients returning for care for several reasons. First, these providers often relied on the electronic medical record (EMR) to provide ART, but the EMR did not include a depression screening module. Despite efforts to mark patients' physical files, this often resulted in patients not being reassessed with the PHQ-9 at their follow-up visits or substantial reliance on the research assistants to help providers identify patients and ensure they were rescreened. Second, the interviews with providers revealed that some providers felt overburdened and were frustrated with the time it took to identify patients and administer the entire PHQ-9, suggesting some unwillingness to implement the program.

As an extension of this challenge, when patients on antidepressants were not re-identified at follow-up visits, providers were then unable to assess these patients' response to the antidepressants or further prescribe depression medication. Exacerbating this challenge, medication stock-outs were common. While amitriptyline and fluoxetine are both considered essential medicines in Malawi and are meant to be stocked at public-sector pharmacies, ensuring their availability proved complicated and required substantial coordination. Other countries in

the region with similar essential medicine policies have also experienced challenges stocking these medications at the district or clinic level.[136] Similarly, another task-shifting depression program in Tanzania also experienced anti-depressant stock-outs.[58] Ensuring the stock of antidepressants is maintained would have required greater engagement and investment of health sector stakeholders involved in the procurement, supply, and distribution of psychiatric medications.

The provision of and engagement with the Friendship Bench therapy over time was also challenging. The original Friendship Bench therapy protocol ideally called for six weekly therapy sessions, though patients were meant to set their own follow-up appointment dates in congruence with the Friendship Bench patient-centered approach. In our setting, almost none of the participants chose to attend weekly sessions and very few participants managed to receive six sessions within their first six months in care. Interviews with patients and providers revealed that patients found the cost of transport prohibitive, alongside expected long wait times at the clinic and the high opportunity cost of having to take off work. Additionally, the clinic-employed Friendship Bench therapy counselors were often unavailable due to their competing responsibilities as community health workers. As a result, the program-employed Friendship Bench counselor provided many of the Friendship Bench therapy sessions. A mixed-methods evaluation of the Friendship Bench in Zimbabwe also noted the lower-than-expected appointment attendance and follow-up challenges, but that evaluation did not identify patient-driven barriers to appointment attendance.[54] While the Friendship Bench is a promising approach to providing evidence-based psychosocial therapy, further investigation of how best to engage patients over time is needed as the model is adapted for implementation in varying settings.

The lack of other studies on task-shifting models of care in the region – in particular, studies which have relied on existing staff (as opposed to study-employed staff) or assessed the provision of depression treatment over time – make drawing comparisons to this study particularly challenging. This gap in available research demonstrates a clear need to investigate the provision of and engagement in depression treatment over time in real-world, low-resource settings.

The program evaluation ultimately found that exposure to the program as implemented was not associated with improved HIV care or depression outcomes. These findings persisted even when using the "treatment started" or "as treated" approach, and in the main analysis the intervention group was significantly less likely to currently be on ART at six months than the control group. Other studies conducted in the region have found that similar programs can effectively treat depression, though these programs often had higher fidelity to their treatment protocols over time.[74,131] However, research linking depression treatment to improvements across the HIV care cascade is mixed.[7-15,53,139,140] Nevertheless, the interviews with clinic leadership, providers, and patients all indicate that depression treatment could be valuable and important for patients with elevated depressive symptoms. While the evaluation did not yield evidence that the program improved HIV care or depression outcomes in a real-world clinic setting, depression treatment in sub-Saharan Africa is efficacious for improving mental health and engagement in HIV care in more controlled research environments.[74] As such, one could conclude this implementation strategy failed to deliver effective treatment and that further support and investment would be needed to ensure depressed patients receive sustained evidence-based treatment.

Other explanations for the main findings in the Aim 1 and Aim 2 analyses may lie in the study design itself. As it would have been unethical to entirely withhold depression treatment from patients during the screening-only control phase, ART providers were at liberty to address patients' depression *ad hoc*. The qualitative interviews used in Aim 3 analysis suggest that individuals identified with depression during the control phase possibly received additional supportive counseling on accepting their HIV status, ART adherence, and managing their depression. While this supportive counseling is not evidence-based depression treatment, patients still could have benefited from this additional attention. In fact, a recent meta-analysis of depression treatment interventions for people living with HIV in sub-Saharan Africa concluded that the programs with an ART adherence component had the greatest impact on HIV outcomes.[131] As a result, depressed patients may have been more likely to remain engaged in care through six months compared to their non-depressed counterparts during the control phase (Aim 1) as well as compared to their depressed counterparts who were exposed to evidence-based treatment during the intervention phase (Aim 2).

While depression at ART initiation was not associated with retention in HIV care at six months and depression treatment did not improve, it is worth noting that retention among the study population was astoundingly low. It is possible that we potentially underestimated retention in care due to "silent transfers," or individuals who decided to access care at a different location without formally transferring their records. In fact, the Malawi MOH assumes that actual retention is likely 10% higher due to this misclassification of "silent transfers" as "defaulters" in clinic-based retention analysis, as ART registries are not yet nationally linked.[90] However, a meta-analysis of low- and middle-income country studies suggests retention may be as much as 18% higher.[124] Still, it is likely that this population faced other barriers to care that

were more relevant and difficult to overcome, such as human resource and institutional challenges, distance to the clinic, lack of support, and stigma and fear of HIV status disclosure.[24,29-31] There is a distinct need for urgent action to improve both mental health and early retention in care for people living with HIV and depression and to develop innovative methods for measuring the complexities of retention in care in low-resource settings.

Future Directions

Findings from this dissertation suggest a need for future research is several key areas. Further investigation is warranted into: 1) the key factors impeding sustained engagement in HIV care in Malawi; 2) the mechanisms through which depression treatment undermines engagement in HIV care; and 3) how to best provide psychiatric services to people living with HIV and the general public in Malawi and other low-resource settings.

Retention in HIV care at six months among the study population was quite low. Attrition across the HIV care cascade will worsen patient health outcomes, hamper epidemic control, and present a major obstacle to achieving the UNAIDS 90-90-90 goals.[26-28] While depression at ART initiation was not associated with retention in HIV care at six months and depression treatment similarly did not improve retention in HIV care, research has shown that other factors such as human resource and institutional challenges, distance to the clinic, lack of support, stigma and fear of HIV status disclosure, as well as psychiatric illness may constitute barriers to HIV care engagement.[24,29-31] In order to improve retention in HIV care, future research will need to unpack and understand the factors that constitute the most salient barriers to HIV care engagement.

The impact of depression on engagement in HIV care is complicated. Research has shown that depression may manifest through loss of interest, poor concentration, poor motivation, reduced self-efficacy, fatigue, hopelessness, and suicidality.[2,4,46] These factors could

all plausibly undermine patients' ability to take daily medication and attend monthly appointments, the two key aspects of successful retention in HIV care. However, while we hypothesized that untreated depression would undermine retention in HIV care and that treating depression would lead to improved retention in HIV care, we ultimately found neither of these associations among our study population. As research on the associations between depression, depression treatment, and various HIV care outcomes remains mixed[2,7-15,44,53,115-117,139,140], further efforts to understand the relationship between depression and HIV will need to specifically unpack the mechanisms through which depression impacts the different aspects of HIV care engagement.

Designing implementation science studies to evaluate programs that can readily (and rapidly) be adopted and integrated into routine care in the public sector is challenging.76,77 Despite our best efforts, it was difficult to prevent the program evaluation from influencing the provision of depression treatment at the clinics. As a result, the clinic staff relied heavily on the research assistants. Furthermore, we are limited in our ability to truly know what the program would have looked like in the absence of outside support. The program evaluation identified many challenges to integrating depression treatment into HIV care at the study sites and found that the program, as implemented, did not improve HIV care or depression outcomes. As such, other depression implementation strategies will need to be identified in order to address the high burden of depression among this vulnerable population. Further implementation science research is needed to understand how best to integrate mental health care into existing healthcare systems for people living with HIV and the general public in Malawi and other low-resource settings.

Conclusions

This dissertation evaluated a program that integrated depression screening and treatment into ART initiation at two clinics in Malawi. In the absence of evidence-based depression treatment, depression at ART initiation was not associated with any of the HIV care retention metrics at six months. Among those with depression at ART initiation, exposure to the treatment program was also not associated with improved depression remission or any of the HIV care retention metrics. There were many challenges to implementing this depression treatment program. The provision of continuous depression treatment over time was particularly difficult. As implemented, this depression treatment program ultimately did not appear feasible or sustainable without additional support. Future research is needed to better understand the mechanisms through which depression and depression treatment affect the various aspects of HIV care engagement and to develop improved means of providing mental health services in low-resource settings.

APPENDIX

Appendix Table 1. Program impact on HIV and depression outcomes, among those with mild depressive symptoms (N=370)

n (%) or mean (sd)	**Screening Phase: Control**	**Active Phase: Intervention**
Retention: never >14 days through 6 months	68/199 (34%)	49/136 (36%)
HIV appointment attendance: average proportion of scheduled appointments attended through 6 months (Range: 0-1)	0.6 (0.4)	0.6 (0.4)
Currently on ART: attended appointment prior to 6 months with next scheduled appointment after 6 months	106/199 (53%)	66/136 (49%)
Consistent ART: never >5 days without ART through 6 months	85/199 (43%)	55/136 (40%)
ART pill possession: average proportion of days with ART through 6 months (Range: 0.16-1)	0.7 (0.4)	0.7 (0.4)
Viral suppression: VL < 1,000 copies/mL after 5.5 months, among those with a viral load	83/88 (94%)	45/49 (92%)
Depression remission: PHQ-9 score < 5 after 5.5 months, among those with a PHQ-9 score	63/67 (94%)	27/28 (96%)

Notes: This table does not include data on individuals who transferred within the first 6 months of care: Control Phase n=15; Intervention Phase n=20. Denominators vary due to viral loads not being drawn, the PHQ-9 not being administered, and not having or attending a scheduled appointment around 6 months. ART=antiretroviral therapy. PHQ-9=Patient Health Questionnaire-9. VL=viral load.

Appendix Table 2. Program impact on HIV and depression outcomes, among those with moderate to severe depressive symptoms (N=131)

n (%) or mean (sd)	**Screening Phase: Control**	**Active Phase: Intervention**
Retention: never >14 days through 6 months	23/67 (34%)	17/50 (34%)
HIV appointment attendance: average proportion of scheduled appointments attended through 6 months (Range: 0-1)	0.5 (0.4)	0.6 (0.4)
Currently on ART: attended appointment prior to 6 months with next scheduled appointment after 6 months	32/67 (48%)	21/50 (42%)
Consistent ART: never >5 days without ART through 6 months	27/67 (40%)	18/50 (36%)
ART pill possession: average proportion of days with ART through 6 months (Range: 0.16-1)	0.7 (0.4)	0.7 (0.4)
Viral suppression: VL < 1,000 copies/mL after 5.5 months, among those with a viral load	25/27 (93%)	15/17 (88%)
Depression remission: PHQ-9 score < 5 after 5.5 months, among those with a PHQ-9 score	24/26 (92%)	10/10 (100%)

Notes: This table does not include data on individuals who transferred within the first 6 months of care: Control Phase n=9; Intervention Phase n=5. Denominators vary due to viral loads not being drawn, the PHQ-9 not being administered, and not having or attending a scheduled appointment around 6 months. ART=antiretroviral therapy. PHQ-9=Patient Health Questionnaire-9. VL=viral load.

Appendix Table 3. Program impact on HIV and depression outcomes, "treatment started" approach* (N=502)

n(%) or mean(sd)	**Untreated**	**Started Treatment**
Retention: never >14 days through 6 months	88/269 (33%)	69/183 (38%)
HIV appointment attendance: average proportion of scheduled appointments attended through 6 months (Range: 0-1)	0.6 (0)	0.6 (0)
Currently on ART: attended appointment prior to 6 months with next scheduled appointment after 6 months	135/269 (50%)	90/183 (49%)
Consistent ART: never >5 days without ART through 6 months	108/269 (40%)	77/183 (42%)
ART pill possession: average proportion of days with ART through 6 months (Range: 0.16-1)	0.7 (0.4)	0.7 (0.4)
Viral suppression: VL < 1,000 copies/mL after 5.5 months, among those with a viral load	103/109 (94%)	65/72 (90%)
Depression remission: PHQ-9 score < 5 after 5.5 months, among those with a PHQ-9 score	82/87 (94%)	42/44 (95%)

Notes: *"Treatment started" approach compares patients who started the Friendship Bench or antidepressants to patients who did not start either. This table does not include data on individuals who transferred within the first 6 months of care: Untreated n=27; Started Treatment n=22. Denominators vary due to viral loads not being drawn, the PHQ-9 not being administered, and not having or attending a scheduled appointment around 6 months. ART=antiretroviral therapy. PHQ-9=Patient Health Questionnaire-9.

Appendix Table 4. Program impact on HIV and depression outcomes, "As treated" approach* (N=355)

n (%) or mean (sd)	**Inadequate**	**Adequate**
Retention: never >14 days through 6 months	125/268 (47%)	32/54 (59%)
HIV appointment attendance: average proportion of scheduled appointments attended through 6 months (Range: 0-1)	0.8 (0)	0.8 (0)
Currently on ART: attended appointment prior to 6 months with next scheduled appointment after 6 months	168/268 (62%)	38/54 (70%)
Consistent ART: never >5 days without ART through 6 months	137/268 (51%)	32/54 (59%)
ART pill possession: average proportion of days with ART through 6 months (Range: 0.16-1)	0.8 (0.3)	0.9 (0.2)
Viral suppression: VL < 1,000 copies/mL after 5.5 months, among those with a viral load	126/134 (95%)	25/29 (86%)
Depression remission: PHQ-9 score < 5 after 5.5 months, among those with a PHQ-9 score	96/103 (93%)	22/22 (100%)

Notes: *"As treated" approach compares patients who received at least two Friendship Bench therapy sessions or their first two months antidepressants to patients who did not, restricted to those who attended at least their first follow-up visit. This table does not include data on individuals who transferred within the first 6 months of care: Inadequate n=25; Adequate n=9. Denominators vary due to viral loads not being drawn, the PHQ-9 not being administered, not having or attending a scheduled appointment around 6 months. ART=antiretroviral therapy. PHQ-9=Patient Health Questionnaire-9. VL=viral load.

Appendix Table 5. Participant characteristics, by transfer (N=501)

n (%) or mean (sd)	**Overall**	**Did Not Transfer**	**Transferred**
Overall	501	452	49
Clinic			
Clinic A	276 (55%)	239 (53%)	37 (76%)
Clinic B	225 (45%)	213 (47%)	12 (24%)
Sex			
Male	214 (43%)	193 (43%)	21 (43%)
Female	287 (57%)	259 (57%)	28 (57%)
Age	33.8 (9.5)	33.9 (9.5)	33.2 (8.9)
Baseline Depression Severity			
Mild (PHQ-9: 5-9)	370 (74%)	335 (74%)	35 (71%)
Moderate to severe (PHQ-9: 10-27)	131 (26%)	117 (26%)	14 (29%)
Baseline Suicidality			
No thoughts	397 (79%)	354 (78%)	43 (88%)
Suicidal thoughts	104 (21%)	98 (22%)	6 (12%)

Note: PHQ-9=Patient Health Questionnaire-9.

Appendix Table 6. Participant characteristics, by viral load data (N=255)

n (%) or mean (sd)	**Overall**	**Viral Load Data**	**Attended, but no Viral Load Data**
Overall	255	181	74
Clinic			
Clinic A	148 (59%)	109 (60%)	39 (53%)
Clinic B	107 (41%)	72 (40%)	35 (47%)
Sex			
Male	110 (43%)	70 (39%)	40 (54%)
Female	145 (57%)	111 (61%)	34 (46%)
Age	33.8 (9.5)	35.3 (9.8)	34.9 (9.2)
Baseline Depression Severity			
Mild (PHQ-9: 5-9)	189 (74%)	137 (76%)	52 (70%)
Moderate to severe (PHQ-9: 10-27)	66 (26%)	44 (24%)	22 (30%)
Baseline Suicidality			
No thoughts	195 (76%)	133 (73%)	62 (84%)
Suicidal thoughts	60 (24%)	48 (27%)	12 (16%)

Note: PHQ-9=Patient Health Questionnaire-9.

Appendix Table 7. Participant characteristics, by 6-month PHQ-9 data (N=241)

n (%) or mean (sd)	**Overall**	**PHQ-9**	**Attended, but no PHQ-9**
Overall	241	131	110
Clinic			
Clinic A	143 (59%)	80 (61%)	63 (57%)
Clinic B	98 (41%)	51 (39%)	47 (42%)
Sex			
Male	104 (43%)	53 (40%)	51 (46%)
Female	137 (57%)	78 (60%)	589(54%)
Age	33.8 (9.5)	35.2 (10.2)	35.2 (8.9)
Baseline Depression Severity			
Mild (PHQ-9: 5-9)	178 (74%)	95 (73%)	83 (75%)
Moderate to severe (PHQ-9: 10-27)	63 (26%)	36 (27%)	27 (25%)
Baseline Suicidality			
No thoughts	185 (77%)	96 (73%)	89 (81%)
Suicidal thoughts	56 (23%)	35 (27%)	21 (19%)

Note: PHQ-9=Patient Health Questionnaire-9.

Appendix Table 8. Association between depression treatment and HIV care and depression outcomes, by depressive severity at baseline

	Mild	Moderate to Severe
	aRR or Mean Difference (95%CI)	
Retention: never >14 days through 6 months	1.2 (0.6-2.3)	0.8 (0.3-2.4)
HIV appointment attendance: average proportion of scheduled appointments attended through 6 months	0.0 (-0.1-0.2)	-0.1 (-0.4-0.2)
Currently on ART: attended appointment prior to 6 months with next scheduled appointment after 6 months	0.7 (0.5-1.1)	**0.3 (0.1-0.8)**
Consistent ART: never >5 days without ART through 6 months	0.8 (0.5-1.4)	
ART pill possession: average proportion of days with ART through 6 months	-0.1 (-0.3-0.0)	-0.2 (-0.5-0.1)

Notes: Adjusted for clinic, months since program launch (quadratic term), and sex. ART=antiretroviral therapy.

Appendix Table 9. Association between depression treatment and HIV care and depression outcomes, "treatment started" approach*

Outcome	**Adjusted****	**Imputation*****
	RR or Mean Difference (95%CI)	
Retention: never >14 days through 6 months	1.4 (0.9-2.1)	1.4 (0.9-2.1)
HIV appointment attendance: average proportion of scheduled appointments attended through 6 months	0.1 (0.0-0.2)	0.0 (-0.1-0.1)
Currently on ART: attended appointment prior to 6 months with next scheduled appointment after 6 months	1.0 (0.8-1.3)	1.0 (0.8-1.3)
Consistent ART: never >5 days without ART through 6 months	1.2 (0.8-1.7)	1.2 (0.8-1.7)
ART pill possession: average proportion of days with ART through 6 months	0.1 (-0.1-0.1)	0.0 (-0.1-0.1)

Notes: *"Treatment started" approach compares patients who started the Friendship Bench or antidepressants to patients who did not start either. **Adjusted for clinic, months since program launch (quadratic term), sex, and baseline depressive severity. ***Pooled estimates from imputed datasets. ART=antiretroviral therapy.

Appendix Table 10. Association between depression treatment and HIV care and depression outcomes, "as treated" approach*

Outcome	**Adjusted****	**Imputation*****
	RR or Mean Difference (95%CI)	
Retention: never >14 days through 6 months	1.3 (1.0-1.9)	1.4 (1.0-2.0)
HIV appointment attendance: average proportion of scheduled appointments attended through 6 months	0.1 (0.0-0.1)	**0.3 (0.2-0.4)**
Currently on ART: attended appointment prior to 6 months with next scheduled appointment after 6 months	1.1 (0.9-1.4)	1.2 (0.9-1.5)
Consistent ART: never >5 days without ART through 6 months	1.1 (0.8-1.5)	1.1 (0.8-1.6)
ART pill possession: average proportion of days with ART through 6 months	0.1 (0.0-0.2)	0.1 (0.0-0.1)

Notes: *"As treated" approach compares patients who received at least two Friendship Bench therapy sessions or their first two months antidepressants to patients who did not, restricted to only those who attended at least their first follow-up visit. **Adjusted for clinic, months since program launch (quadratic term), sex, and baseline depressive severity. ***Pooled estimates from imputed datasets. ART=antiretroviral therapy.

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