HIV AND DEPRESSION IN A PRIMARY CARE CLINIC IN JOHANNESBURG, SOUTH AFRICA

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology.

Chapel Hill
2014

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ABSTRACT

RUSHINA CHOLERA: HIV and depression in a primary care clinic in Johannesburg, South Africa
(Under the direction of William C. Miller)

As rapidly expanding HIV care and treatment programs are implemented in sub-Saharan Africa, maintaining engagement in HIV care is proving to be a significant operational challenge. Depression is highly prevalent among HIV-infected people in sub-Saharan Africa and predicts a range of poor HIV-related clinical outcomes including faster disease progression and increased morbidity and mortality. Depression is strongly associated with non-adherence to anti-retroviral treatment (ART), and may also impact engagement in HIV care. Recognizing and treating depression among HIV-infected patients seeking care in primary health care settings, where most HIV testing and treatment takes place, could increase access to mental health services and may help to target patients at risk for negative outcomes.

An observational study was conducted between September 2012 and April 2013 among 1683 randomly selected adult patients undergoing routine, opt-out HIV counseling and testing (HCT) at Witkoppen Health and Welfare Center (WHWC), a high-HIV burden primary care clinic in Johannesburg, South Africa. Patients were screened for depression immediately prior to HCT using the Patient Health Questionnaire-9 (PHQ-9), a 9-item brief screening tool administered by lay health workers. A subset of 400 patients was included in a blinded diagnostic validation study of the PHQ-9 (Aim 1). Sensitivity and specificity of the

PHQ-9 were calculated with the Mini International Neuropsychiatric Interview (MINI) as the reference standard, and receiver operating characteristic (ROC) curve analyses were performed. Patients who tested positive for HIV were followed and linkage to care, defined as returning to WHWC within 3 months to obtain a CD4 count result, was assessed (Aim 2). Among patients who collected a CD4 count, ART initiation within 3 months was assessed. Multivariable Poisson regression with a robust variance estimator was used to assess the association between depression and linkage to care or ART initiation.

Nearly all patients completed depression screening and 82% (n=1386) subsequently tested for HIV. Of the patients who tested for HIV and were of unknown HIV status prior to testing, 26% (n=340) were found to be HIV-infected. Nearly a quarter of all patients (22%) were depressed. Similar to other studies, depression was more common among patients who tested positive for HIV compared to those who tested negative for HIV (30.3% versus 19.7%, $p<0.0001$).

In the validation sample included in Aim 1, the prevalence of depression was 11.8% and one-third of participants tested positive for HIV. Using the standard cut-off score of ≥ 10, the PHQ-9 demonstrated a sensitivity of 78.7% (95% CI: 64.3-89.3) and specificity of 83.4% (95% CI: 79.1-87.2) for identifying major depressive disorder. The area under the ROC curve was 0.88 (95% CI: 0.83-0.92). Test characteristics did not vary by HIV status or language and in sensitivity analyses, reference test bias associated with the MINI appeared unlikely. The PHQ-9 was easily implemented by lay health workers. The instrument performed reasonably well and may be a useful depression screening tool in high HIV-burden sub-Saharan African primary health care settings.

Of the HIV-infected patients included in Aim 2, 30% were depressed. The proportion who linked to care was 80% among depressed patients and 73% among patients who were not depressed (Risk ratio: 1.08; 95% confidence interval: 0.96, 1.23). Of the participants who linked to care, 81% initiated ART within 3 months in both depressed and not depressed groups (Risk ratio: 0.99; 95% confidence interval: 0.86, 1.15). Conducting this study in a clinic-based population may have selected for patients who are high-utilizers of health care and unlikely to be at high risk for loss to HIV care. These unexpected results highlight the importance of population selection and the timing of HIV testing relative to depression screening when studying the complex relationship between depression and engagement in HIV care.

ACKNOWLEDGEMENTS

I am so grateful for the support and guidance provided by my advisor and mentor, Bill Miller. Since I interviewed for the MD/PhD program with Bill in 2006, he has encouraged my development as a researcher, and my progression from basic scientist to epidemiologist. Bill's perspective and insight have been indispensable, particularly during the data collection phase of this dissertation. The many times when it seemed that my dissertation might fall apart, and in fact when it did fall apart, Bill's calm, solution-oriented approach always helped me to see the big picture. His example as a teacher, writer, and mentor has been invaluable. I am also so thankful for the mentorship and guidance provided by my other committee members- Audrey Pettifor, Brad Gaynes, Brian Pence, and Catherine MacPhail. Each of them has been unfailingly supportive and flexible as I've progressed through this program.

This work was only possible with the help of several generous funding sources. I received a year of pre-doctoral support from the UNC Clinical Translational Science Award-T32 Program (TL1) during my first year of graduate school. I subsequently received a training grant award from the National Institute of Mental Health (F30 MH096664) which funded two years of pre-doctoral work, and will provide continued funding support over the next two years. I was only able to hire study staff for data collection with generous support from the Triangle Community Foundation Gertrude B. Elion Award. I was also able to extend my study in South Africa through support from a Fogarty Pre-doctoral Global Health

Fellowship from the Fogarty International Center of the National Institutes of Health (R25TW009340).

I am also thankful to Dr. Annelies Van Rie for kindly facilitating my introduction to Dr. Jean Bassett at WHWC- without Annelies' help I would have had a very different dissertation. The administrators and staff at WHWC were so flexible, kind, and creative in helping me to make this study happen. I am especially grateful to Dr. Jean Bassett, Dr. Nandi Qangule, and Shelley Bernhardt for the many hours they spent helping me with study design and implementation at WHWC. I would also like to thank Happiness Ndobe, Mpho Mbulaheni, and Nonhlanhla Msimango for their dedicated hard work in recruiting and interviewing patients, conducting chart reviews, and entering data-- and laughing and singing the whole way through. They really kept the study going and gave me great peace of mind while I was traveling back and forth with one foot in North Carolina and the other in Johannesburg. I am also indebted to the many patients at WHWC who gave their time and clinical information through their participation in this study.

Nancy Colvin, Carmen Woody, Alison Regan, and Carol Heroin deserve special thanks for the amazing work they do to make sure we all get to the finish line. Their patience and support has been invaluable throughout this program. The MD/PhD program at UNC, particularly Dr. Gene Orringer, Dr. David Siderovski, Dr. Kim Rathmell, and Dr. Mohanish Deshmukh have provided dedicated leadership and support, for which I am grateful.

I have so much gratitude for my parents, who have been a source of love and unwavering encouragement. I thank them for always believing in me. And finally, but most importantly, I can't fully express my gratitude for the enduring love, generosity, and kindness of my partner, Christopher Deery.

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AIDS	Acquired Immune Deficiency Syndrome
aRR	Adjusted Risk Ratio
ART	Antiretroviral Treatment
AUC	Area under the Curve
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
GAD	Generalized Anxiety Disorder
HCT	HIV Counseling and Testing
HIV	Human Immunodeficiency Virus
IQR	Interquartile Range
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MINI	Mini International Neuropsychiatric Interview
PHC	Primary Health Care
PHQ-9	Patient Health Questionnaire-9
PTSD	Post-Traumatic Stress Disorder
RCT	Randomized Control Trial
REDCap	Research Electronic Data Capture
ROC	Receiver Operating Characteristic
RR	Risk Ratio
SCID	Structured Clinical Interview for DSM Disorders
TE	TherapyEdge

UNC	The University of North Carolina
WHWC	Witkoppen Health and Welfare Center
WHO	World Health Organization
YLD	Years Lived with Disability

CHAPTER I: INTRODUCTION

Depression is common among HIV-infected people.[1] In sub-Saharan Africa, the prevalence of mental illness, particularly depression, among HIV-infected people is several times greater than prevalence in the general population. [2-7] Depression can occur throughout the course of HIV acquisition and infection-- underlying depression can influence behaviors that increase the risk of acquiring HIV, adjusting to a chronic, life-threating disease can induce psychological distress, and the clinical sequelae of the virus itself can mirror and exacerbate symptoms of mental illness.[8] Psychiatric conditions, especially depression, are associated with risky HIV transmission behaviors, decreased uptake of antiretroviral treatment (ART), non-adherence to ART, and poor clinical outcomes such as immunologic decline and early mortality.[1, 8-10] Psychosocial factors such as social support and adaptive coping styles can mitigate mental health symptoms among HIV-infected people and may be important areas for intervention in settings where psychiatric treatment is not readily available.[11, 12]

Depression in HIV-infected patients can be successfully treated with a range of existing evidence-based pharmacologic or psychological regimens [12-15]. However, while depression screening and treatment services have been integrated into both primary healthcare settings and HIV programs in high-income countries, access to these services remain rare in sub-Saharan Africa where two-thirds of the world's HIV-infected patients reside[16]. The reasons for this include a limited understanding of the prevalence and

correlates of depression in sub-Saharan Africa as well as a scarcity of mental health care personnel in already overburdened health systems.[17] As large-scale HIV care and treatment programs are rapidly deployed in sub-Saharan African resource-poor settings, operational challenges such as delayed linkage to care, poor retention in care, and late initiation of ART are proving to be a significant threat to their success. [18-20] These critical actions are known to be influenced by depressive symptoms, and highlight the need for comprehensive interventions that address depression comorbidity among HIV-infected patients.

The ongoing expansion of HIV counseling and testing (HCT) programs as well as the rapid roll-out of ART in South Africa provides unique opportunities for the integration of longitudinal mental health services with HIV care.[3, 20] Such integration would allow for the early detection and treatment of depression and the identification of HIV-infected patients who are at risk for negative clinical outcomes. To accommodate the enormous expansion of HIV services in South Africa, a large proportion of these programs have been shifted to outpatient primary care clinics where patients can receive the full spectrum of HIV testing and treatment services longitudinally. Therefore, incorporation of standardized mental health services in these settings is particularly important. We conducted a series of studies to improve the current understanding of depression and HIV in a South African primary healthcare clinic. Specifically, we addressed the following two aims:

Aim 1: To validate the Patient Health Questionnaire-9 (PHQ-9), a brief screening tool for depression, at a primary healthcare clinic in Johannesburg, South Africa.

A first step in addressing depression among HIV-infected patients is the establishment of standardized methods for identifying depression among patients who already accessing health care services. In order for depression screening to be integrated into healthcare systems in sub-Saharan Africa, validated, rapid screening tools are needed that can be administered by lay-workers.[3, 21]

For this aim we validated the PHQ-9 depression screening tool compared to the Mini-International Neuropsychiatric Interview (MINI), an internationally validated psychiatric diagnostic tool.[3] Approximately 400 patients undergoing HCT at a high volume primary healthcare clinic in Johannesburg, South Africa were screened for depression by a lay health worker using the PHQ-9. Patients then completed the MINI with a trained interviewer prior to HIV testing. We determined the test characteristics of the PHQ-9 relative to the MINI.

Aim 2: To describe the association between underlying depression and engagement in care among newly diagnosed HIV-infected adults in Johannesburg, South Africa.

Hypothesis: We hypothesized that HIV-infected patients with underlying depressive symptoms would be less likely to engage in care compared to their counterparts who did not exhibit depressive symptoms.

The relationship between depression and adherence to ART has been extensively documented in sub-Saharan Africa but there is limited understanding of psychiatric symptoms preceding HIV diagnosis and how such symptoms might affect engagement in care.[9, 20] For this aim, approximately 1700 patients undergoing HCT at a high-volume

primary healthcare clinic in Johannesburg, South Africa were screened for depression using the PHQ-9. Among the patients who tested positive for HIV after depression screening, we obtained clinic data on linkage to care, defined as obtaining a CD4 count within 3 months. Among patients who linked to care we obtained data initiation of ART. The relationship between depression and engagement in HIV care was examined.

CHAPTER II: BACKGROUND AND SIGNIFICANCE

Depression is prevalent among HIV-infected people.[1, 3, 8]

In high-income countries mental illnesses, particularly mood and anxiety disorders, are recognized as a common comorbidity of HIV infection and a predictor of negative clinical outcomes in this population.[9] In the United States, the prevalence of major depressive disorder (MDD) among HIV-infected adults ranges from approximately 20-37%, and is at least two to five-fold greater than the prevalence of MDD in the general population of adults.[8, 15, 22]

In sub-Saharan African settings, where the majority of the world's HIV-infected population resides, depression is increasingly recognized as common among HIV-infected people. [3, 5, 7, 20, 23-27] The reported prevalence of depression in HIV-infected sub-Saharan African adults ranges from 8-60%. [3, 5, 7, 20, 23, 28-30] A recent systematic review of depression, alcohol use, and ART adherence in sub-Saharan Africa reported a pooled prevalence estimate of depression symptoms of 31.2% (95% CI: 22.5-38.2%) among HIV-infected adults.[27] The large variability in these prevalence estimates is likely a result of variations in study design including 1) a range of study settings from hospital-based, urban HIV clinics to rural, community based antiretroviral treatment (ART) programs, 2) the use of different screening instruments and application of cut-off scores which have not been validated in sub-Saharan African settings and, 3) widely varying study populations that include participants at various stages of disease progression, such as newly diagnosed HIV-

infected patients, people initiating ART, ART-experienced patients, or a combination of these different population groups.

Depression is both a risk factor and a consequence of HIV infection.

Risk factors for HIV include poverty, transactional sex, substance abuse, and a history of trauma[8]. People experiencing these factors often disproportionally come from disenfranchised and socially disadvantaged populations, and are at high risk for psychological distress before ever acquiring HIV.[31-35] Additionally, underlying mental disorders including depression and substance abuse can influence high-risk behaviors such as sexual concurrency or unprotected sex that increase the risk of HIV transmission[36].

After diagnosis with HIV, emotional and physical adjustment to a chronic, life-threating disease can induce or worsen psychological distress in patients. Such distress can also be influenced by psychosocial factors such as stigma, social support, and coping mechanisms. [1, 12, 37] Depression is closely tied to physical health among HIV-infected patients- people successfully treated with ART demonstrated reduced rates of major and minor depression compared to patients who are not treated. [38] It is also plausible however that the side-effects of ART could lead to depression in some patients. From a biological perspective, the neurological sequelae of HIV can induce HIV-associated dementia (HAD) or otherwise imitate and exacerbate symptoms of depression.[8, 39, 40]

Mental illness can also vary over time relative to the course of HIV infection. For example, depression could be present prior to HIV infection and resolve after diagnosis, depression could occur immediately after HIV diagnosis, or depression could arise only during late-stage HIV infection. Patients can also have repeated episodes of depression,

necessitating careful monitoring. At each stage of the HIV infection process, mental health illness has the potential to negatively impact a patient's eventual clinical outcome.

Directionality of the complex relationship between HIV and mental health varies, and depends on the particular combination of factors in each situation. Separation of the multiple subsets of population and longitudinal study of each population will be required to further understand causality between HIV and depression.

HIV-infected people with comorbid depression have poor clinical outcomes.[41-43]

Clinically, HIV-infected patients experiencing depression have higher viral loads, faster disease progression, and a greater risk of HIV-associated morbidity and mortality. [44-46] In resource-rich settings, psychiatric disorders have also been associated with a number of negative health care utilization behaviors including delayed initiation of ART, an increased number of missed clinic visits, and especially reduced adherence to ART.[8, 9, 41, 44, 47, 48]

Systematic reviews and meta-analyses have confirmed a strong association between depression and ART non-adherence, and emphasized the need for interventions to reduce the severity of even mild, subclinical depressive symptoms among HIV-infected people.[9, 48] It is thought that ART non-adherence at least partially explains the relationship between depression and increased disease progression and mortality. At the population level, HIV-infected people who are depressed are more likely to have a higher viral load and also to engage in risky behaviors, thus increasing the likelihood of transmitting HIV.

The association between depression and adherence has held true in sub-Saharan African settings as well, with a recent systematic review reporting that patients with

depression symptoms had a 55% lower likelihood of being adherent to ART compared to patients without depression.[1, 27, 49] Of note, only eleven studies examining the relationship between depression and adherence in all of sub-Saharan Africa were identified for inclusion in this systematic review, highlighting the critical need for further research in this high-burden setting.

For the reasons explained above, comorbid depression among HIV-infected people poses a significant threat to the success of population level HIV-related outcomes. Treatment of depression among HIV-infected people should be of high interest to policy makers, especially in South Africa, where the world's largest ART roll-out program is underway.

Depression may also influence engagement in HIV care

Recently, delayed engagement and poor retention in care have emerged as major operational challenges to HIV treatment programs.[19, 50-52] Like ART adherence, engagement in care among HIV-infected persons improves outcomes at the individual and population levels. Engagement in care is conceptualized as a continuum that includes timely linkage or access to clinical services after HIV diagnosis, immediate retention during the pre-ART stage if ineligible for ART, and long-term retention after ART initiation (Figure 2.1).[50, 52-54] Delayed linkage or poor retention in care is associated with subsequent ART non-adherence, incomplete viral suppression and poor survival among persons with HIV infection.[50, 55-58] At the population level, engagement in care decreases HIV transmission through behavioral risk reduction and viral load suppression.[56] Costly universal ART programs, motivated by the promising test-and-treat strategy for population-level HIV prevention, are being rolled-out in sub-Saharan Africa. The success of these

programs is contingent on adequate engagement in care among HIV-infected persons.[52, 59, 60]

In sub-Saharan Africa, many HIV-infected people know their status but do not remain engaged in care, especially prior to ART initiation.[60-63] Loss to care in the pre-ART time period following HIV diagnosis, but preceding treatment initiation, is poorly described in sub-Saharan African contexts.[51] Estimates of loss to care after HIV diagnosis among adults in sub-Saharan Africa range from 25% to 50% implying that up to half of all diagnosed HIV-infected persons in this setting do not access clinical services after HIV diagnosis.[61, 64-69] Patients who delay this initial step in the HIV engagement in care continuum often present for care with low CD4 counts, when ART is a much less effective intervention. In a recent study done at Witkoppen Health and Welfare Center (WHWC), where this dissertation research was conducted, it was found that pre-ART attrition was approximately 30% [69]. The reasons for this large attrition rate are not well understood but are likely to be influenced by mental health and related psychosocial factors that could be modifiable targets for intervention.

To our knowledge only one published study in the United States has explicitly addressed the relationship between mental health and engagement in care.[70] This prospective study was conducted among 180 patients diagnosed with HIV infection in the preceding 90 day period. Results suggested that depression among newly diagnosed HIV infected people might be associated with poor linkage to care. In sub-Saharan Africa only two studies have explored this relationship, albeit in differing study populations.[20, 71] One study conducted in Uganda among HIV-infected people with severe mental illness at ART initiation found that 65% (95%CI: 61-69%) of patients without mental illness had continuous

retention in care at 12 months after ART initiation compared to 47% (95% CI: 39-55%) among patients with mental illness.[71] In this study severe mental illness was defined as any clinically diagnosed organic brain syndrome, affective disorder or psychotic disorder. Another study conducted in Durban, South Africa found that depressive symptoms preceding HIV diagnosis were associated with decreased linkage to care.[20] The study in Durban was conducted particularly among patients presenting for HIV testing. One focus of this dissertation research was to examine the association between underlying depression and linkage to care among HIV-infected people seeking medical services at a primary healthcare clinic in Johannesburg, South Africa.

Depression often goes undetected and untreated in HIV-infected patients

Due to the high burden of mental illness among HIV-infected people, basic mental health services have been integrated into many HIV programs in wealthy countries. Both cognitive behavioral and pharmacological interventions are known to be effective depression therapies among HIV-infected people.[72] Despite this evidence and the availability of services, a large treatment gap remains in these high-income settings. [73, 74] In the United States it is estimated that only 45% of major depressive disorder (MDD) cases among HIV patients are ever clinically recognized.[74] Further, up to 82% of depressed HIV-infected patients do not receive any treatment for depression.

In sub-Saharan African, the situation is almost certain to be worse. In a South African household survey among over 4000 participants, less than 6% of patients with a diagnosed mental disorder had received mental health services in the preceding 12 months[16]. Even for the most severe mental illnesses such as schizophrenia and other psychotic disorders, the

treatment gap in sub-Saharan Africa can exceed 90%.[73] Estimates demonstrating the treatment gap among HIV-infected patients are not available for sub-Saharan African settings. Even at best, given the shortage of mental health resources and the lack of awareness regarding mental health, estimates of the depression treatment gap among HIV-infected would be more disappointing than the data presented above from the United States.

Depression screening among HIV-infected people

Treatment guidelines in the United States recommend routine systematic mental health screening in primary health care settings.[75, 76] Routine screening increases clinical recognition of depression and can also improve response to depression treatment, particularly in programs where case managers or mental health staff are available. In HIV-clinic settings in the United States depression screening has also been shown to be feasible and effective for identifying and improving depressive symptoms among patients accessing care. [77] Integration of front-line mental health screening into routine HIV care is recommended in settings where mental health resources are readily available and effective treatment and referral strategies are in place. Several brief, accurate tools that can be implemented by health care workers with a range of education and training levels have been validated for this purpose.[77-79]

In sub-Saharan Africa, due to the scarcity of skilled mental health care personnel in overburdened health care systems and a limited understanding of the relationship between mental health and HIV, psychiatric services for HIV patients remain rare. The use of rapid mental health screening tools in sub-Saharan Africa in HIV clinic settings has been suggested as one potential mode for integrating HIV and mental health services. [3, 17, 80, 81]

Depression screening that can be implemented by lay-workers to identify patients who might require further assessment in resource-scarce settings could indeed be a potentially valuable and cost-effective intervention that targets patients already engaged with the health care system. As most patients seek care for both HIV and mental health conditions in the general primary care sector in South Africa, outpatient primary healthcare clinics are an important place for deploying and evaluating such front-line depression screening interventions. [16] However, the availability of subsequent mental health treatment options and methods for prioritizing and referring patients after depression diagnosis in these settings is an important issue. In the United States, a systematic review of depression screening programs incorporated into primary care showed that programs without additional staff assistance such as that of a case manager or mental health specialist have shown little benefit and are unlikely to improve depression related outcomes. [82] This issue would be particularly important when implementing screening programs in sub-Saharan African contexts with limited mental health resources.

As cultural understandings of mental health constructs, literacy rates, language differences, and other culturally specific factors can greatly influence the accuracy of instruments, local validation of screening tools is critical. A lack of validated instruments has hindered the possibility of evaluating integration of mental health screening into HIV programs in sub-Saharan Africa.[8, 17] Importantly, this has also inhibited mental health research in sub-Saharan Africa as researchers are forced to use long diagnostic instruments that require specialized clinical training such as the Mini International Neuropsychiatric Interview. Such tools are not ideal for strained primary healthcare settings as they require substantial resources. Some researchers have chosen to use screening tools without

validation. This has likely lead to misclassification and possibly explains the wide variation in prevalence estimates of mental illness among HIV patients in sub-Saharan Africa. A handful of validation studies with at least 4 different depression screening tools (K-10, CES-D, PHQ-9, and SRQ-20) have been conducted in sub-Saharan African contexts. However, these studies have had varied results and have been done in widely differing study populations and settings, making them difficult to generalize.[3, 21, 81, 83-89] None of the existing studies have validated depression screening tools in primary care settings.

Understanding the relationship between depression and HIV in sub-Saharan Africa has important implications for the long-term success of HIV care and treatment programs.

As discussed above, failure to diagnose and treat depression among HIV-infected people comes at high individual and societal costs, and threatens the success of large-scale HIV programs. The ongoing expansion of routine HIV counseling and testing (HCT) services and universal antiretroviral treatment (ART) programs throughout sub-Saharan Africa potentially provide unique opportunities for the integration of longitudinal mental health services with HIV care and treatment programs.[3, 20] Such collaboration would allow for the early detection and treatment of depression and the identification of HIV-infected patients at risk for negative clinical outcomes. There is substantial evidence that cost-effective and feasible interventions are available to identify and treat mental illness- innovative systems for distribution of these interventions in resource-scarce settings are urgently needed.

Summary and Rationale

Depression is highly prevalent among HIV-infected people in sub-Saharan Africa, yet most depression in sub-Saharan Africa likely goes undetected and untreated. Despite substantial evidence that depression decreases ART adherence, there is a poor understanding of how comorbid depression influences other health-care utilization behaviors among HIV-infected people. In particular very little work has focused on the relationship between depression and engagement in HIV care. In the context of the rapid scale-up of large HCT and ART programs in South Africa, a better understanding of depression among HIV-infected patients is important.

This dissertation attempts to address these knowledge gaps by conducting two related studies at a high HIV-burden primary care clinic in Johannesburg, South Africa. We first conducted a diagnostic validation study of a brief, pragmatic depression screening tool implemented by lay health among patients undergoing routine, opt-out HCT. Second, among patients who tested positive for HIV we examined the association between depression immediately prior to HIV diagnosis and engagement in HIV care (both linkage to care and ART initiation).

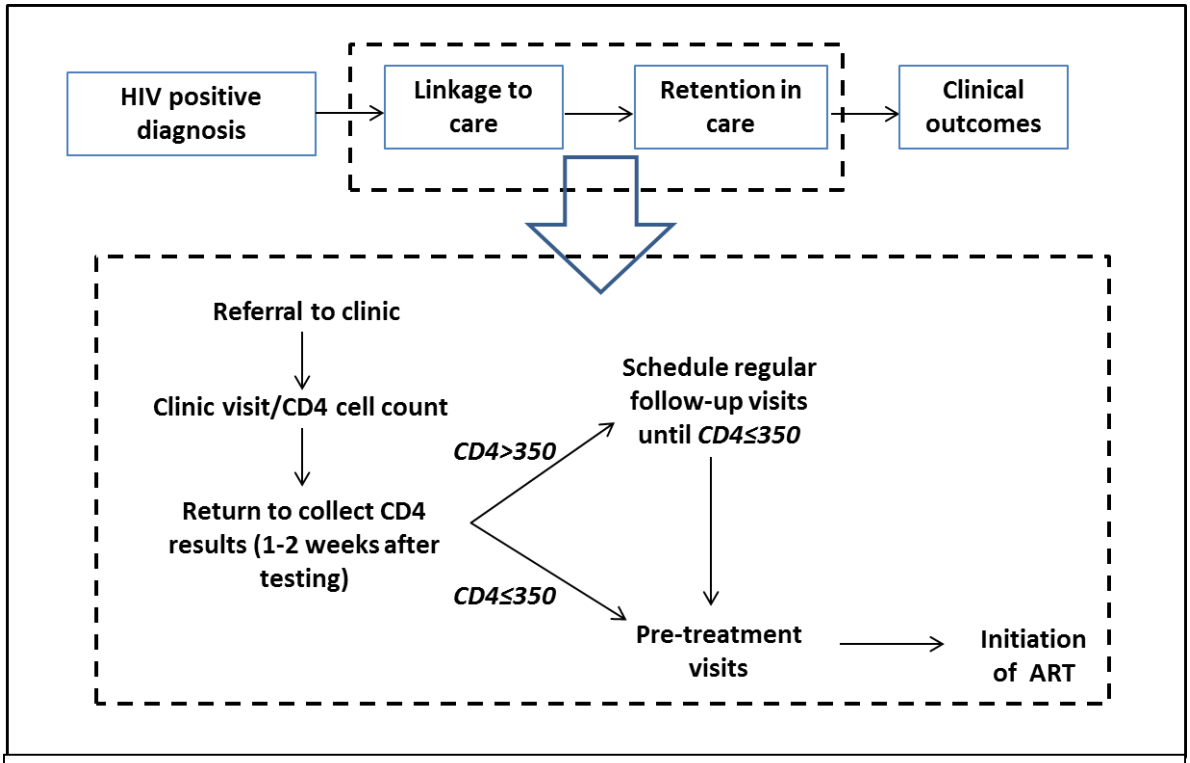


Figure 2.1 The engagement in HIV care continuum in South Africa. Loss to care can occur at any point along the continuum.

CHAPTER III: RESEARCH DESIGN AND METHODS

Study Design Overview

From September 2012 through April 2013 we invited 1944 randomly selected adult patients presenting for medical care at an urban primary healthcare clinic in Johannesburg, South Africa to participate in this study (Figure 3.1). Patients were recruited while waiting to undergo routine HIV counseling and testing (HCT). Of these 1944 patients, 9.3% (n=181) were ineligible and 4.1% (n=80) refused to participate. We enrolled a total of 1683 patients for participation in this study. Patients were screened for depression by lay interviewers prior to HCT. To validate the PHQ-9 depression screening tool, a subset of approximately 400 patients were asked to participate in a second blinded diagnostic interview using the Mini International Neuropsychiatric Interview (MINI), a diagnostic instrument which has been used as a reference-standard in South Africa (aim 1). [3]

Of 397 patients found to be HIV-infected, nearly 60 were excluded due to prior knowledge of HIV status. Among the remaining 340 HIV-infected we determined the association between underlying depressive symptoms and linkage to HIV care within 3 months of HIV diagnosis (aim 2). Among the patients who linked to HIV care we determined the association between underlying depressive symptoms and initiation of ART within 3 months of linkage to care.

The Institutional Review Board at the University of North Caroline (UNC) at Chapel Hill and the Human Research Ethics Committee at the University of Witwatersrand approved this study.

Study Setting

Witkoppen Health and Welfare Center (WHWC) is a high-volume primary health care clinic in northern Johannesburg that provides services predominantly to persons living in densely populated, resource-scarce areas comprised of formal and informal settlements. Approximately half of the population seeking care at Witkoppen is comprised of immigrant populations, typically from neighboring Zimbabwe, who are often highly mobile. Comprehensive, integrated medical and social services are provided at WHWC, including HIV/AIDS care, antenatal care, family planning services, child and adult mental health services, dental care, and social welfare services. WHWC receives both public and private funding, and is administered by a non-governmental organization.

On average, 8,500 patients are seen at WHWC each month, of whom approximately 40% are HIV-positive. During the study period about 200 people were newly diagnosed with HIV at WHWC each month and about 130 people started antiretroviral treatment (ART) each month.

Study Population

At WHWC, every clinic client with an unknown HIV status or with an HIV test with negative result more than three months old routinely undergoes opt-out universal HCT. Patients who test positive for HIV by two rapid dried blood spot tests have blood drawn for

CD4 count testing on the same day. Patients are also registered in TherapyEdge (TE), the electronic health record system for HIV-infected patients. Blood is then sent to an off-site laboratory for CD4 testing and patients are asked to return to WHWC within 1-2 weeks for HIV staging. In this study, returning to WHWC to obtain CD4 test results was considered the first step in linking to HIV care.

When patients return to WHWC for their CD4 test results, patients eligible for ART undergo a clinical examination and attend the first of at least two adherence counseling sessions. These ART-eligible patients are then asked to return within a month for further adherence counseling and ART initiation. Patients with very low CD4 counts are sometimes fast-tracked so that ART initiation can occur almost immediately. Patients who are not yet eligible for ART when they obtain their CD4 result also undergo a clinical examination but are scheduled to return to WHWC in six months.

Regardless of ART eligibility, patients who do not return for any scheduled HIV visit at WHWC are automatically flagged in TE and called by WHWC staff. Patients not reached by multiple phone attempts are referred for community tracing by local non-governmental organization tracing teams. The timing of phone or community tracing of patients varies, with patients who have defaulted treatment receiving highest priority, followed by ART-eligible patients, and then pre-ART patients.

The overall study population for this work included nearly 1700 adults at WHWC of unknown HIV status who were sent to undergo HCT upon registration at WHWC. All participants were recruited for this study *prior* to HCT.

Aim 1: Validation of PHQ-9

The study population for aim 1 was comprised of 397 participants who were randomly selected from of the 1681 patients screened for depression. All enrolled participants (regardless of HIV status) were eligible for inclusion in aim 1 with the exception of the five patients who were found to be acutely suicidal during depression screening.

Aim 2: Depression and engagement in care

The study population for aim 2 included all patients who tested positive for HIV. Patients who reported prior knowledge of their positive HIV status were excluded from the sample.

Eligibility Criteria

Inclusion criteria

- Adult (over age 18) patient at WHWC
- Unknown HIV status (aim 2 only)

Exclusion criteria

- Unable to provide informed consent
- Pregnant by self-report
- Known psychiatric diagnosis

- Any reason that staff felt might jeopardize the well-being of the participant or staff
- Patients found to be acutely suicidal

Recruitment

Participants were chosen randomly from the cohort of people who were sent for HCT each morning – choosing 1 person from every 4, for example. Up to 25 people were randomly selected to participate in the study each day. Patients were invited to complete informed consent and complete the interviewer-administered study questionnaire before proceeding with HCT.

Informed Consent

The interviewer explained the proposed research study and criteria for participation to each patient who was invited to participate in the study. During the informed consent process, study staff described the procedures to be followed, the risks and benefits of participation, the duration of participation, and the steps taken to protect participant's confidentiality. Participants provided their signature on the consent form. Participants who could not write were asked to make a mark of their choice on the signature line. Signed copies of the consent form were given to the participants.

Data Collection

Depression Screening Questionnaire

PHQ-9: Participants were screened for depression by using the 9-item Patient Health Questionnaire (PHQ-9, Appendix A). The PHQ-9 asks specifically about the previous

2 weeks and determines the presence and frequency of the 9 core depressive symptoms identified in the DSM-IV. This tool has been widely used in Western settings and has also been used in several studies in sub-Saharan Africa.[84, 86, 89, 90] Scores on the PHQ-9 can range from 0-27, with a score of 10 or higher often used to indicate the presence of a depressive disorder. This instrument is easy for non-clinicians to implement and takes less than 5 minutes to complete. Although the PHQ-9 was developed as a self-administered tool, similar performance has been reported when these instruments are interviewer-administered.[91] Due to the low level of literacy in the study population the screening tool was interviewer-administered for this study.

Covariates: In addition to the PHQ-9 the screening questionnaire also included a brief anxiety screening tool (data presented in Appendix C), questions about alcohol use and substance abuse, perceived general health status, and prior knowledge of HIV. Questions regarding prior knowledge of HIV were added to the questionnaire in November 2013, 2 months after the start of data collection.

Sociodemographic and clinical covariates For both research aims, we obtained data on patient's sociodemographic characteristics, including age, gender, employment status. This information was obtained by medical record review for patients who were HIV-negative. For HIV-positive patients, this information was obtained from TherapyEdge, the electronic health record database for HIV-infected patients at WHWC. In addition, clinical

information such as CD4 count, ART prescription, and clinical diagnoses were also obtained from TherapyEdge.

Aim 1 Assessments

MINI: Of the participants enrolled in the study, 25% were randomly selected (n=397) to complete a second, blinded, diagnostic interview comprising the depression and anxiety modules of the MINI. The MINI is a short, structured interview that is designed to detect psychiatric disorders.[92] It takes approximately 15-20 minutes to complete. It has been used as the reference-standard in other studies in South Africa as it was used here.[3, 5] The MINI modules we used included the sections for major depressive disorder, anxiety disorders (generalized anxiety disorder, panic disorder, social anxiety disorder, and post-traumatic stress disorder), suicidality, and bipolar disorder, so that we could distinguish between a depressive episode that is part of bipolar disorder versus major depressive disorder. This comprised modules A-H and module N of version 6 of the MINI.

The MINI interview took place immediately following the depression screening interview, and prior to HCT. Interviewers conducting the second interview were not aware of the results from the screening interview. The MINI was administered in the same language used for the first interview. Along with myself, two practitioners at WHWC- a trauma counselor and a trained counseling psychologist- administered the MINI. All interviewers administering the MINI participated in a training session via Skype with Department of Psychiatry personnel from UNC Chapel Hill. On a bi-weekly basis, MINI diagnoses were discussed and resolved with the psychologist.

Aim 2 Assessments

Engagement in HIV care: The primary outcome for aim 2 was linkage to care among HIV-infected patients. Linkage to care was defined as returning to WHWC to collect CD4 count results within a 3 month time period after HIV diagnosis. The secondary outcome for aim 2 was initiation of ART within 3 months among HIV-infected patients who linked to care. Information on whether a patient returned to collect CD4 count results or initiated ART was obtained up to 6 months after enrollment in the study. Patients who did not collect CD4 counts within 6 months of HIV diagnosis were considered lost to care. We obtained this data from TherapyEdge, the electronic clinical database kept at WHWC.

Language of Interviews

Most patients at WHWC have at least basic English speaking capabilities, but the majority are not fluent in English. Because patients were asked questions about complex mental health issues, questions were asked in a language in which the patient was comfortable. The predominant languages in the area are Isizulu, Ndebele (Zimbabwean), Isixhosa, Sesotho, Setswana, and Sepedi (Northern Sotho).

The screening questionnaire was translated from English into Isizulu (closely related to Isixhosa and Ndebele) and Sesotho (closely related to Setswana and Sepedi). Study interviewers were able to communicate using both questionnaires and English, which allowed us to interview the majority of patients at WHWC. Patients who spoke other languages such as Xitsonga, Xivenda, Shona, and Chichewa, and who were not comfortable in English were not interviewed.

None of the three MINI interviewers was able to speak the South African languages that were used for the screening interviews. Therefore, the MINI was translated into Isizulu and Sesotho and an interpreter was used so that the MINI was always administered in the same language that was used for the screening interviews.

Referral Procedures

Study staff members referred patients according to the procedures below. In addition, patients who appeared to be in significant psychological distress or who reported traumatic events such as rape or violence during the course of the screening interview were offered a referral to the clinic psychologist.

Suicidality

Question 9 on the PHQ-9 asks the patient: "During the past two weeks how often have you had thoughts that you would be better off dead or of hurting yourself in some way?"

Answer options include: not at all, several days, more than half the days, and nearly every day. Any patient who answers positively (any option except "not at all") is asked a series of 5 questions to assess suicide risk (Appendix B).

Patients experiencing suicidal ideation were referred using the following rules:

a) Patients experiencing passive suicidal ideation according to the suicide risk assessment were allowed to continue with the screening interview. At the end of the interview they were offered a referral to see a psychologist.

b) Patients experiencing moderate or high suicidal ideation as defined by the suicide risk assessment also completed the screening interview. However, these patients were escorted to a psychologist or clinician after the screening interview to undergo clinical assessment prior to HCT. The clinician made a recommendation as to whether the patient was stable enough to undergo HCT.

c) Patients experiencing acute suicidal ideation (these patients stated that they may hurt themselves in the near future) were immediately escorted to a psychologist or clinician. The screening interview was not resumed and these patients were excluded from the study.

PHQ-9 Scores

Patients who scored in the severe range for depression (≥20 on the PHQ-9) were offered an immediate referral to see the clinic psychologist.[93] These cut-offs were previously determined in Western study settings but were used here to identify patients very likely to need further evaluation.

Data Management and Analysis

Data management: Study data was entered by either the principal investigator or study staff into a password protected online Research Electronic Data Capture (REDCap) database hosted at the University of North Carolina, Chapel Hill. All responses from the study questionnaire including the PHQ-9 and questions addressing substance abuse and prior knowledge of HIV status were entered into the database. Additionally, demographic data for patients who were not infected with HIV were extracted from medical records on to a standardized paper form prior to entry in the REDCap database. Weekly quality control was

conducted and inconsistent data was resolved through review of medical records and consultation with the monitoring and evaluation team at WHWC.

All clinical and demographic data for HIV-infected patients were electronically obtained from the TherapyEdge clinical database for HIV-infected patients.

Data Analysis

Aim 1: For this aim sociodemographic characteristics of all patients included in the validation subset were described. Additionally alcohol use and perceived health status were reported. Among the randomly selected sample on whom the MINI was performed, test characteristics, including sensitivity and specificity, of the PHQ-9 were calculated.

A severity score of 10 or higher for the PHQ-9 is typically considered to be indicative of possible depression and was considered a positive screen in these analyses.[84, 94] Additional cut-off scores of 8 and 12 were also considered. The PHQ-9 asks about symptoms in the last 2 weeks so we specifically compared screening diagnoses to current diagnoses on the MINI, which also asks about the last 2 weeks.

Sensitivity, specificity, and categorical likelihood ratios were calculated and we used ROC curve analyses to examine the overall performance of the screening instrument. Exact confidence intervals were calculated for sensitivity and specificity. Confidence intervals for likelihood ratios and ROC curves were calculated using standard methods. Post-test probabilities (analogous to predictive values for a dichotomous test) were calculated for the observed prevalence of depression in the study population as well as a range of prevalence values using the categorical likelihood ratios.

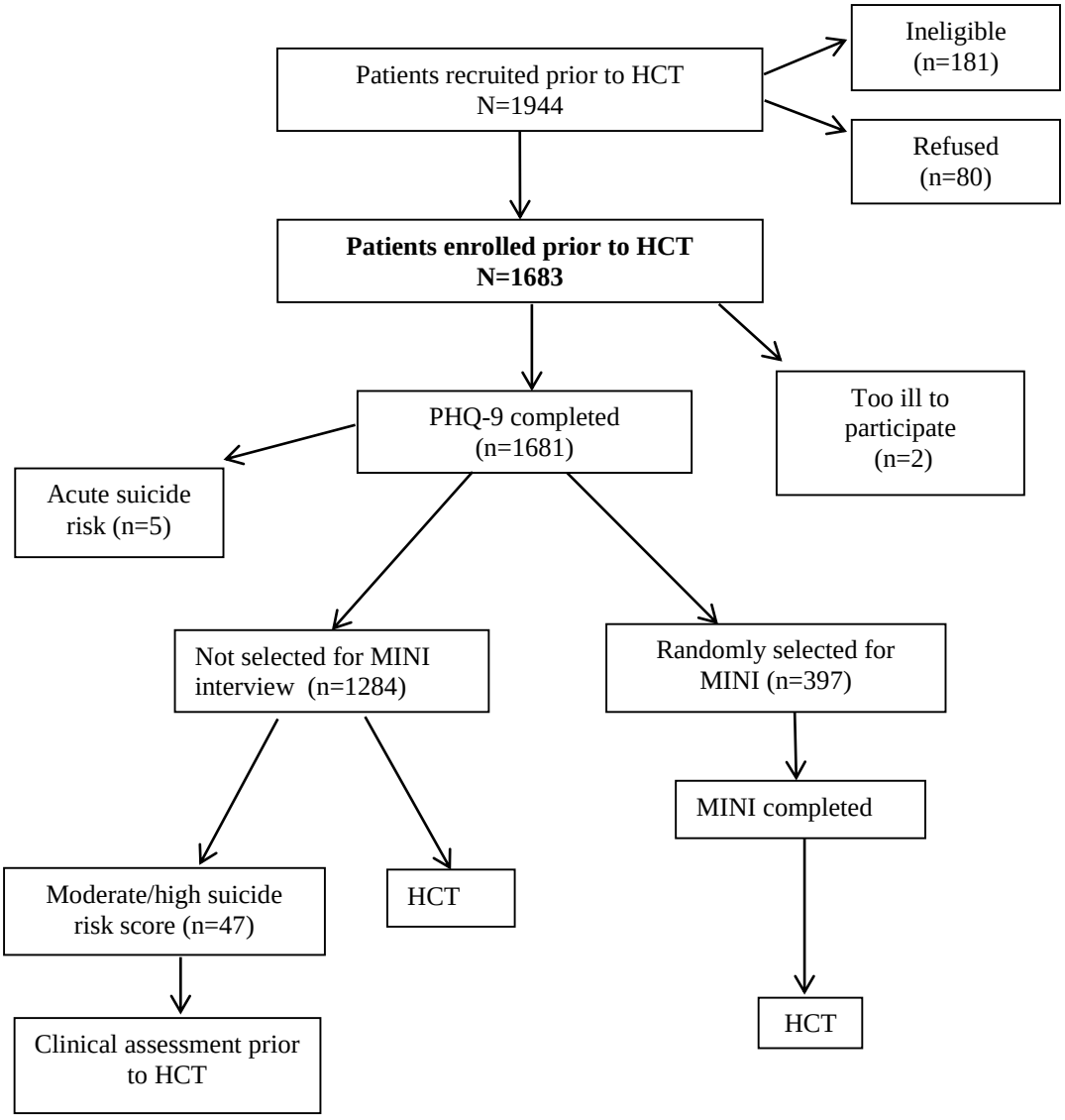
Sensitivity analyses were conducted to assess the possible bias in PHQ-9 test performance produced by misclassification of a current major depressive episode by the MINI. Varying combinations of sensitivity and specificity of the MINI reference standard were considered. In conditional independence scenarios, which did not assume any relationship between a patient's score on the PHQ-9 and their score on the MINI, MINI sensitivity was varied from 0.75 to 1.00 and specificity from 0.97 to 1.00. In conditional dependence scenarios, it was theorized that patients who underreported depressive symptoms on the PHQ-9 might also underreport on the MINI. For the conditional dependence assessments, a range of reduced sensitivities of the MINI was considered for the population who screened negative on the PHQ-9.

Aim 2: The primary outcome for this aim was linkage to care, defined as returning to WHWC for CD4 staging within 3 months of the diagnosis visit. A secondary outcome among those who were eligible for ART (CD4 < 350) was initiation of ART within 3 months of the staging visit. The main factor of interest in these analyses was probable major depression, defined as a PHQ-9 score of 10 or higher. Additional variables included in multivariable analyses include age, gender, employment status, country of birth, alcohol use, perceived health status, and baseline CD4 count. Age was categorized and modeled using indicator variables, with the youngest age group (<30 years) as the referent.

We conducted preliminary analyses to assess the distribution of variables and any impact of missing data or extreme values. Baseline patient characteristics were summarized using frequencies and proportions for categorical variables and medians and interquartile ranges (IQR) for continuous variables. Poisson regression with a robust variance estimator

was used to estimate risk ratios (RRs), adjusted risk ratios (aRRs), and 95% confidence intervals (CIs). For the linkage to care outcome we assessed for but found no evidence of interaction between CD4 count and depression, and perceived health status and depression. Stata version 13 (StataCorp, College Station, TX, USA) was used for all analyses.

Figure 3.1. Study design flowchart describing recruitment, enrollment, depression screening, and selection for MINI



CHAPTER IV: VALIDITY OF THE PATIENT HEALTH QUESTIONNAIRE-9 TO SCREEN FOR DEPRESSION IN A HIGH-HIV BURDEN PRIMARY HEALTHCARE CLINIC IN JOHANNESBURG, SOUTH AFRICA

Introduction

Mental illness imposes an immense global disease burden, particularly in low and middle-income countries where access to mental health services is lacking [95, 96]. Major depressive disorder (MDD) is the second leading contributor to years lived with disability (YLD) globally, and ranks within the top four causes of YLDs in all regions worldwide [97]. In sub-Saharan Africa more than two-thirds of patients with severe mental illness are unable to access mental health care and this number rises to approximately 80% for patients with moderate or mild mental illness [98]. To address these challenges, the integration of mental health screening approaches in primary care has been suggested as a mode for increasing access to care in low and middle-income settings [99, 100].

The implementation of routine mental health screening in sub-Saharan African primary health care (PHC) settings requires validated rapid screening instruments that can be easily administered by lay healthcare workers in busy clinics [17, 96]. A limited number of validation studies of depression screening tools have been conducted against diagnostic reference standards in such settings, but these studies, done in varying study populations and contexts, have had inconsistent results [3, 21, 81, 83-89, 101]. The populations included in these studies, such as university students, household survey participants, or HIV-infected patients, are not easily generalizable to a PHC setting. To our knowledge, brief depression screening tools have not been validated for a general PHC context in sub-Saharan Africa.

Depression is a common and debilitating comorbidity of HIV in sub-Saharan Africa. The reported prevalence of depression in HIV-infected African adults in ranges from 8-60%, several times greater than prevalence estimates in the general population [3, 5, 7, 20, 23, 26-30]. The relationship between MDD and HIV is complex, as depression can be a risk factor for HIV acquisition as well as a consequence of HIV infection [8, 102]. However, MDD has long been recognized as a predictor of negative clinical outcomes among people with HIV [8, 22, 103, 104]. Persons with depression initiate anti-retroviral treatment (ART) at lower CD4 counts than people without mental illness, and depressed patients are much less likely to adhere to ART than patients who are not depressed [9, 24, 27, 47].

Routine depression screening is recommended for HIV infected patients in high-resource settings and can be an effective way to identify patients at risk for negative outcomes [77, 78, 82]. Depressed HIV-infected patients who receive treatment for mental health illness have improved ART adherence and increased quality of life [105, 106]. As interventions to increase access to early ART are scaled up throughout sub-Saharan Africa and universal HIV counseling and testing (HCT) becomes the norm, integration of mental health services and HIV programs could be an important component of ensuring optimal care and treatment utilization for these two highly comorbid conditions [107]. Routine mental health screening in PHC settings, where most HIV-infected patients are diagnosed and seek regular care, might be a valuable approach to identify both HIV-infected and HIV-uninfected patients who require further mental health assessment.

Here, we have conducted a validation study of an interviewer-administered brief screening tool for depression, in a high HIV burden, low literacy PHC population in Johannesburg, South Africa. We sought to validate the PHQ-9 as a depression screening tool

compared to the internationally validated Mini International Neuropsychiatric Interview (MINI) among patients undergoing routine HCT in a primary care setting. We also sought to provide additional evidence of the utility of the PHQ-9 among HIV-infected people in sub-Saharan Africa.

Methods

Ethical Approvals

The Institutional Review Board at the University of North Carolina (No. 12-1730) and the Human Research Ethics Committee at the University of Witwatersrand (No. M120725) approved this study.

Study Setting and Population

Witkoppen Health and Welfare Center (WHWC) is a high-volume primary health care clinic in northern Johannesburg, South Africa that provides comprehensive services predominantly to persons living in densely populated peri-urban formal and informal settlements. At WHWC, every clinic client with an unknown HIV status or with a negative HIV test more than three months old routinely undergoes opt-out HCT.

The study population comprised a randomly selected subset of patients who were undergoing routine HCT at WHWC between September 2012 and April 2013. Participants were eligible for enrollment if they presented at WHWC for any reason, were at least 18 years old, not pregnant by self-report, could communicate in one of 5 common languages used by interviewers (English, isiZulu, isiXhosa, seSotho, seTswana), and were able to

provide informed consent. Persons found to be experiencing acute suicidal ideation during the PHQ-9 were excluded and referred for immediate assistance.

Measures

PHQ-9

The PHQ-9 is a 9-item depression screening tool that determines the presence and frequency of the 9 core depressive symptoms identified in the DSM-IV over the previous 2 weeks. This tool has been widely utilized in Western settings and more recently in sub-Saharan Africa [84, 86, 89, 101]. Scores range from 0-27, with a score of 10 or higher typically used to indicate the presence of a depressive disorder that would benefit from treatment. While the PHQ-9 was developed to be self-administered, interviewer-administration has yielded similar results [91].

MINI

The MINI International Neuropsychiatric Interview (MINI) is a short, structured diagnostic interview for major psychiatric disorders. The MINI served as the reference standard in this study [92]. The MINI is a reliable and valid diagnostic tool that has been used successfully in South African populations [3, 5]. We used the MINI modules for major depressive disorder (MDD), anxiety disorders (generalized anxiety disorder, panic disorder, social anxiety disorder, post-traumatic stress disorder), suicidality, and bipolar disorder.

Study Procedures

Eligible patients were selected randomly for recruitment each day. Patients were recruited after clinic registration but prior to undergoing HCT. After providing informed consent, the patient completed the screening interview, including the PHQ-9, with a trained lay-interviewer. Questions about substance abuse and knowledge of HIV status (from prior testing experiences) were also included in the questionnaire. Socio-demographic information and clinical information was obtained from the patient's WHWC clinic file. Due to low literacy in the study population, the questionnaire was administered by the interviewer and responses were recorded on a paper form. The questionnaire was translated and conducted in 5 common languages (English, isiZulu, isiXhosa, seSotho, seTswana).

After the screening interview, participants immediately completed the MINI interview with a second study team member who was blinded to the results of the PHQ-9. The MINI interview was conducted by health care professionals trained in use of the instrument. The MINI was administered in the same language as the screening interview; an interpreter was used when needed. Translations of the MINI were completed in the same languages used for the screening tools and these standard translations were used when needed.

Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at the University of North Carolina, Chapel Hill [108].

Analyses

A positive screen for probable depression was defined as a score ≥10 on the PHQ-9 [84, 89, 101]. Test characteristics including sensitivity, specificity, and categorical likelihood

ratios for the PHQ-9 were calculated relative to a diagnosis of a current major depressive episode (MDE) on the MINI. A range of cut-off scores (8, 10, and 12) was considered for the PHQ-9. Categorical likelihood ratios were calculated for the standard scores of ≥5 (mild depression/anxiety), ≥ 10 (moderate depression/anxiety), ≥ 15 (moderately severe depression/severe anxiety), and ≥20 (severe depression). Post-test probabilities (analogous to positive predictive values for a dichotomous test) were calculated for a range of prevalence values of depression using categorical likelihood ratios. Receiver operating characteristic (ROC) plots were graphed and the area under the curve (AUC) is reported. Sensitivity analysis was conducted to assess the possible bias in PHQ-9 test performance produced by misclassification of MDE by the MINI. Varying combinations of sensitivity and specificity of the MINI reference standard were considered and conditional independence and dependence scenarios were assessed.

Results

Between September 2012 and April 2013, 397 persons provided informed consent to participate in this study. Participants had a median age of 35 years (IQR: 28- 46 years) and most were female (60%). About half of the participants were from South Africa (48%) and more than a third were from Zimbabwe (37%). Nearly 60% were employed and 30% reported drinking alcohol (Table 4.1). Of the 397 participants, 257 (64.7%) tested negative for HIV on the enrollment date or within the previous 2 weeks and 113 (28.5%) tested positive at enrollment or were not tested because they told the HIV counselor that they knew their positive status and were enrolled in HIV care at another clinic (n=9). About two-thirds of patients (65%) rated their general health status as good, very good, or excellent, while the

remainder reported poor or fair health. Patients with probable depression (PHQ9≥10) had similar demographic characteristics compared to patients without probable depression (PHQ9<10), except that patients with probable depression reported poor or fair health more often (p<0.0001) and were more likely to be HIV-infected (p<0.0001). According to the PHQ-9, 44% of the participants reported no depression (PHQ9= 0-4), 32% reported mild depression (PHQ9=5-9), 18% reported moderate depression (PHQ9=10-14), 5% reported moderately severe depression (PHQ9=15-19), and 1% reported very severe depression (PHQ9≥20).

PHQ-9

Of the 397 persons completing the MINI, 47 (11.8%) met the diagnostic criteria for a current MDE on the MINI. Of the 47 patients, 19 (40.4%) were experiencing a comorbid anxiety disorder and 3 (0.76%) met criteria for bipolar spectrum disorder. The most common comorbid anxiety disorders were generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD). Compared to the MINI, the PHQ-9 performed modestly in this population. Of the 47 persons meeting criteria for MDE, 37 had a positive PHQ-9 depression screen with the standard cut-off score of 10 or higher, yielding a sensitivity of 78.7% (95% CI: 64.3-89.3) (Table 4.2). Of the 350 participants who did not meet criteria for current major depression on the MINI, 292 had a negative depression screen on the PHQ-9, corresponding to a specificity of 83.4% (95% CI: 79.1-87.2). An alternate PHQ-9 cut-off score of 8 in the overall sample yielded a higher sensitivity of 87.2% (95% CI: 74.3-95.2) and a lower specificity of 73.4% (95% CI: 68.5-78.0). A higher alternate cut-off score of 12 yielded a

lower sensitivity of 55.3% (95% CI: 40.1-69.8) and a higher specificity of 89.1% (95% CI: 85.4-92.2).

In ROC analysis, the PHQ-9 had an area under the curve (AUC) of 0.88 (95% CI: 0.83-0.92), indicating moderately high accuracy (Figure 1). Likelihood ratios for the commonly used PHQ-9 categories representing mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27) depression were 0.09, 0.50, 3.89, 6.77, and 22.3 respectively (Table 4.3). Post-test probabilities for these categories were calculated for a range of pre-test probability (prevalence) values (Figure 2). At the 11.8% prevalence of MDE seen in the study population (indicated by vertical line, Figure 2), the post-test probability of depression for a PHQ-9 score between 10-14 is 34.2%, for a score between 15-20 it is 47.5%, and for a score higher than 20 it is 75%.

Among HIV-positive participants, 15.0% (n=17) met the criteria for MDE compared to 8.9% of the HIV-negative participants. The PHQ-9 performed similarly in the HIV-positive and HIV-negative populations (Table 4.2). Among the 113 HIV-infected patients, the PHQ-9 yielded a slightly higher sensitivity and a lower specificity compared to the HIV-negative population, although these estimates are imprecise as there were only 17 cases of MDE in the HIV-infected group.

The performance of the PHQ-9 did not differ according to the language in which the interview was conducted. Additionally, sensitivity analyses showed that misclassification of true MDE by the MINI was not likely to have produced substantial bias. All scenarios where conditional independence was considered (MINI sensitivity was varied from 0.75 to 1.00 and specificity from 0.97 to 1.00) suggested that the true values of sensitivity and specificity of the PHQ-9 were underestimated by the observed estimates. Corrected estimates for

sensitivity of the PHQ-9 ranged from 0.84 to 0.99 and corrected estimates for specificity of the PHQ-9 ranged from 0.84 to 0.86. Conditional dependence may have occurred if patients underreporting depressive symptoms on the PHQ-9 were also more likely to underreport on the MINI. However, reducing the sensitivity of the MINI for patients screening negative on the PHQ-9 only slightly changed the observed results. Given our observed data, a MINI specificity of anything less than 1 would suggest that the reported sensitivity of the PHQ-9 is an underestimate of the true sensitivity. Our data were inconsistent with a MINI specificity less than 0.97 because of the low number of MDE cases among patients screening negative on the PHQ-9.

Discussion

In this high HIV burden PHC population in Johannesburg, South Africa, the PHQ-9 showed high accuracy in correctly classifying cases of current MDE (AUC 0.88) relative to the reference standard MINI. At the standard cut-off score of 10, the PHQ-9 had moderately high sensitivity and specificity in the study population. The performance of the PHQ-9 was similar to that from a range of other settings outside of sub-Saharan Africa [109, 110]. Compared to other studies within sub-Saharan Africa , the PHQ-9 performed slightly worse than it did among university students in Nigeria [89] or HIV-infected persons in Uganda [101], but it performed significantly better in this study than it did among HIV-infected patients in Cameroon [84]. To our knowledge, ours is the only diagnostic validation study of the PHQ-9 conducted among a general PHC population in sub-Saharan Africa, and it underscores both the importance of a primary care setting in this region as an access point for identifying depression and as well an accurate tool to do so.

We found an 11.8% prevalence of MINI-defined current MDE in the overall study sample. This estimate is much higher than the prevalence estimate of MDE in a nationally representative household survey which found that 4.9% of South Africans had suffered from MDE in the previous 12 months, as measured by the World Health Organization's (WHO) Composite International Diagnostic Interview (CIDI) [26]. We would expect our estimate to be higher than the prevalence from a household survey as our sample includes chronically ill and disenfranchised patients who are more likely to experience mental illness. Other estimates of depression from sub-Saharan Africa are either derived from screening instruments or focused particularly among HIV-infected patients. Among the HIV-infected subset of this population, depression prevalence was 15%, comparable to other prevalence estimates of MDD among HIV-infected African persons in studies using diagnostic tools (range ~3-35%) [3, 29, 87-89, 101]. The high prevalence of comorbid anxiety disorders, particularly GAD and PTSD, among depressed patients in this population reiterates the need to assess patients presenting with depressive symptoms for comorbid psychiatric diagnoses, which can lead to increased psychiatric severity and treatment resistance [111, 112].

When evaluating the clinical utility of the PHQ-9 for depression screening and choosing an ideal cut-off score for this setting, we considered the prevalence of depression in the population, the benefits and harms of screening, and the resources available for screening and follow-up. In our study context, a busy PHC clinic in a resource-scarce setting with one part-time mental health professional, patients screened by lay-workers using the PHQ-9 would then be evaluated by a PHC clinician who could confirm that a clinical depression exists and decide whether to begin treatment in the PHC setting or refer to a mental health professional. In this scenario, the categorical likelihood ratios, which capture the magnitude

of depression, are particularly useful in prioritizing patients compared to the standard dichotomous cut-off score alone. The standard score of 10 groups together all patients with a score of 10 or higher- so those who have a score of 11 (moderate depression) and those who have a score of 20 (severe depression) are considered the same, discarding valuable information about the degree of illness. In contrast, the categorical likelihood ratios allow the clinician to prioritize patients based on the magnitude of the depression score and the post-test probability of disease for a particular value of the PHQ-9. By multiplying the categorical likelihood ratio for a particular score by the pre-test odds of disease, a post-test odds can be calculated and easily converted to a post-test probability [113]. A patient with a PHQ-9 score of 11 at WHWC has a post-test probability of approximately 34% of being depressed as compared to a post-test probability of approximately 75% for a patient with a PHQ-9 score of 20. Using the categorical likelihood ratios would allow these two patients with different likelihoods of depression to be prioritized accordingly for the limited mental health resources available at WHWC. The categorical likelihood ratios also allow decision-makers to adjust the pre-test probability value for different groups of patients by taking into account factors such as medical history (e.g. HIV infection status) or laboratory data, rather than only the overall prevalence of depression in the general clinic population. In this more sophisticated approach, one standard cut-off score is not applicable to all patients in a clinic, but rather the cut-off score differs depending on a number of important variables specific to each patient.

In choosing an ideal cut-off score for the PHQ-9, we also considered the relative cost of a false negative versus a false positive result. In our study setting, where many patients were coping with chronic diseases such as HIV, it might be reasonable to consider a false

negative, or missing a true case of depression, to be worse than a false positive. Patients with chronic conditions and comorbid depression are at risk for a multitude of negative outcomes including poor adherence to treatment and increased morbidity and mortality [114]. Therefore, identifying the maximum number of true depression cases might be considered a priority, especially among HIV infected patients in whom treatment initiation and adherence is a significant concern. This approach would come at the expense of a higher number of false positive screens, creating a higher burden on the clinic to spend time and resources evaluating patients who are not true depression cases. These choices are ultimately dependent on the setting in which the tool is applied and the resources available for follow-up.

The strengths and limitations of this study should be considered. The cultural construct of depression or anxiety in our study setting is likely to be very different from the Western settings in which the PHQ-9 was first developed. The version of the PHQ-9 used in this study was the same as that used in Cameroon among HIV-infected patients, which had been adapted slightly through focus group feedback in Cameroon [84]. While we were able to translate the PHQ-9 into local languages, we were unable to conduct additional focus groups or qualitative interviews in our study setting that would have allowed us to further adapt the PHQ-9 for culturally- relevant use in this context and ensure that the tool was well understood by the study population. Although our results did not differ according to the language in which the PHQ-9 was administered, such qualitative research might have increased the diagnostic properties of the PHQ-9 in our study. We would encourage other researchers to conduct preliminary qualitative work when adapting and optimizing screening tools for use outside of the context in which the tool was originally developed and validated.

While the MINI was used as the reference standard in our study, it is imperfect, especially in light of the cultural considerations discussed above. However, the MINI has been validated against other diagnostic interviews, including the CIDI and the Structured Clinical Interview for DSM Disorders (SCID) and has itself been used as a reference standard for the validation of many other psychiatric scales [92]. Misclassification or reference-test bias with use of the MINI is likely to occur to some degree, and will depend partly on the experience level of the interviewer. Given the rigorous DSM-IV criteria utilized in the MINI, we believe that false positives will be rare, although false negatives or missing cases of true MDE is possible. This would have biased our measured estimates of PHQ-9 sensitivity and specificity downwards. Our sensitivity analyses were consistent with observed estimates of sensitivity and specificity of the PHQ-9 being underestimated. An additional source of bias could have arisen through interviewer-administration of the PHQ-9 as participants may be less likely to report mental health symptoms to an interviewer due to fear of stigmatization. This could lead to conditional dependence through lower sensitivity of the MINI among patients who screen negative on the PHQ-9, but sensitivity analysis showed that this would only slightly affect our observed estimates of PHQ-9 performance.

Mental health screening in this study was conducted among patients prior to undergoing HCT. The advantage to this approach is that it allowed us to evaluate the performance of screening instruments among patients who were HIV-negative as well as the 28.5% of the study population who tested HIV positive after their participation in this study. Because patients received their HIV test results after depression screening, new knowledge of an HIV diagnosis would not have influenced HIV infected patients to screen positive for depression due to an acute adjustment disorder with a depression reaction. We recognize that

the HIV-infected patients in this population are different from those engaging in ongoing HIV care who have been coping with long-term knowledge of HIV status, and that the prevalence of mental illness may differ at various time points in HIV care. Other research on depression and HIV in sub-Saharan Africa has focused mostly on patients who are aware of their HIV status rather than those who are testing for HIV. Our results contribute important information to the field as the mental health of HIV-infected patients prior to HCT has not been evaluated. Identifying patients with underlying depression as early as HCT could help identify patients at risk of defaulting treatment or care early on. Ideally, we would screen patients for mental health illness at several time points in HIV care, if resources for follow-up exist.

The PHQ-9 performed reasonably well as a screening tool in this high HIV-burden South African clinic population and was easily implemented by lay health workers. Our results provide insight on how we can screen for and prioritize often overlooked and highly prevalent depressive symptoms in low-resource PHC settings in sub-Saharan Africa. Such an intervention might be especially useful for monitoring high-risk subsets of the population such as HIV-infected people at risk for defaulting treatment, although further research will be required to determine how screening for depression can contribute to improved clinical outcomes. This study provides a framework for implementing depression screening programs in resource-scarce sub-Saharan African contexts and establishes the PHQ-9 as a useful screening instrument in these settings.

Table 4.1.

Characteristics of the Validation Study Population by Depression (N=397)

Characteristic	**Total study population***	**Depressive symptoms** n (%) or median (IQR)	
	(n=397)	PHQ-9<10 (n=302)	PHQ-9≥10 (n=95)
Age (years)			
<=25	59 (14.9)	49 (16.2)	10 (10.5)
26-35	147 (37.0)	113 (37.4)	34 (35.8)
36-45	87 (21.9)	62 (20.5)	25 (26.3)
46-55	71 (17.9)	51 (16.9)	20 (21.1)
>55	33 (8.3)	27 (8.9)	6 (6.3)
Gender			
Male	159 (40.1)	125 (41.7)	34 (35.8)
Female	236 (59.5)	175 (58.3)	61 (64.2)
Employment status			
Employed	230 (63.7)	179 (65.8)	51 (57.3)
Unemployed	131 (36.3)	93 (34.2)	38 (42.7)
Country of birth			
South Africa	190 (49.9)	141 (49.1)	49 (52.1)
Other country	191 (50.1)	146 (50.9)	45 (47.9)
Alcohol use			
Any	118 (30.0)	95 (31.5)	23 (25.0)
None	276 (70.1)	207 (68.5)	69 (75.0)
Perceived health status			
Excellent	60 (15.2)	51 (16.9)	9 (9.8)
Very good	57 (14.5)	48 (15.9)	9 (9.8)
Good	139 (35.3)	112 (37.1)	27 (29.4)
Fair	79 (20.1)	58 (19.2)	21 (22.8)
Poor	59 (15.0)	33 (10.9)	26 (28.3)
HIV status			
Positive	113 (28.5)	71 (23.5)	42 (44.2)
Negative	257 (64.7)	212 (70.2)	45 (47.4)
Unknown†	27 (6.8)	19 (6.3)	8 (8.4)

*Categories may not sum to the total because of missing data

† Twenty seven participants are of unknown HIV status because they were either: 1) found to be either suicidal or mentally distressed during this study so HCT was deferred (n=5, 1.3%); 2) they refused to test for HIV after undergoing pre-test counseling (n=6, 1.5%); or 3) the patient skipped HCT (n=16, 4%).

Table 4.2.

PHQ-9 Test Characteristics at Various Cut-Off Scores among Whole Study Population (n=397)

Table 4.2. PHQ-9 Test Characteristics at Various Cut-Off Scores among Whole Study Population (n=397)						
Cut-off	TP*	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)
≥ 8	41	93	257	6	87.2 (74.3-95.2)	73.4 (68.5-78.0)
≥ 10	37	58	292	10	78.7 (64.3-89.3)	83.4 (79.1-87.2)
≥ 12	26	38	312	21	55.3 (40.1-69.8)	89.1 (85.4-92.2)
PHQ-9 test characteristics at various cut-off scores among HIV-positive patients only (n=113)						
Cut-off	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)
≥ 8	15	39	57	2	88.2 (63.6-98.5)	59.4 (48.9-69.3)
≥ 10	14	28	68	3	82.4 (56.6-96.2)	70.8 (60.7-79.7)
≥ 12	11	15	81	6	64.7 (38.3-85.8)	84.4 (75.5-91.0)
PHQ-9 test characteristics at various cut-off scores among HIV-negative patients only (n=257)						
Cut-off	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)
≥ 8	20	48	186	3	87.0 (66.4-97.2)	79.5 (73.7-84.5)
≥ 10	17	28	206	6	73.9 (51.6-89.8)	88.0 (83.2-91.9)
≥ 12	12	22	212	11	52.2 (30.6-73.2)	90.6 (86.1-94.0)

*TP= True positive, FP= False positive, TN= True negative, FN= False negative

Table 4.3.

Likelihood Ratios for Commonly Used PHQ-9 Decision Thresholds

Symptom severity	**PHQ-9 category**	**Likelihood ratio**
No depression	<5	0.09
Mild depression	5-9	0.50
Moderate depression	10-14	3.89
Moderately severe depression	15-19	6.77
Severe depression	20-27	22.3

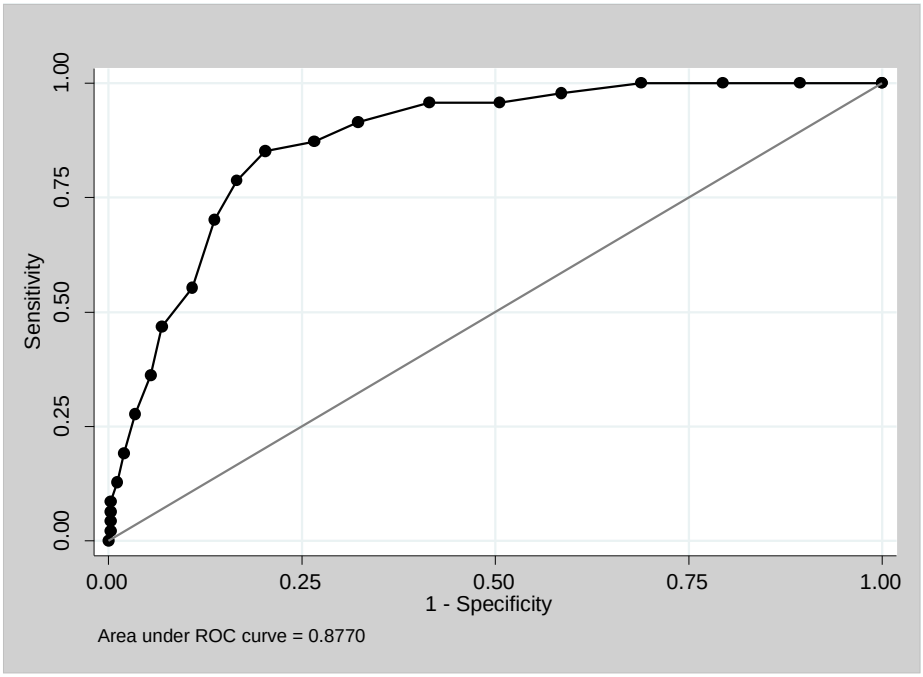


Figure 4.1. Receiver operating characteristic (ROC) curve for PHQ-9

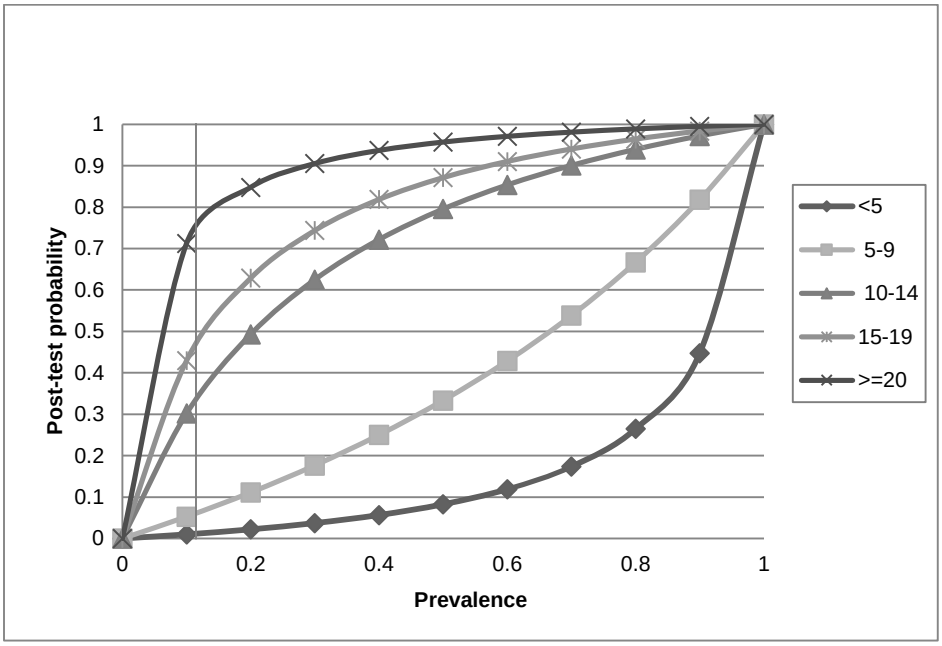


Figure 4.2. Post-test probability for varying PHQ-9 categories, based on categorical likelihood ratios.

CHAPTER V: UNDERLYING DEPRESSION DOES NOT INFLUENCE LINKAGE TO CARE OR ART INITIATION AMONG NEWLY DIAGNOSED HIV-INFECTED ADULTS IN JOHANNESBURG, SOUTH AFRICA

Introduction

In sub-Saharan Africa, the prevalence of depression among HIV-infected people is reported to be 30-60%, several times greater than prevalence in the general population. [1-9] The relationship between depression and HIV infection is complex, as depression can be a risk factor for HIV acquisition as well as a consequence of HIV infection. [10, 11] Depression also has been recognized as a predictor of poor outcomes among people with HIV infection, including faster disease progression and a greater risk of HIV-associated morbidity and mortality. [12-14]

Delayed linkage or poor retention in HIV care has emerged as a major operational challenge to HIV treatment programs and may be impacted by poor mental health.[15-19] Among people enrolled in HIV care, depression appears to negatively affect health care utilization behaviors, leading to delayed initiation of antiretroviral treatment (ART), missed clinic visits, and reduced adherence to ART.[11, 12, 20-24] Although the effect of depression on ART adherence is well-documented, the impact of depression on linkage to care has been less clearly delineated. [25-27]

We conducted an observational study to examine the relationship between underlying depression immediately prior to HIV diagnosis and engagement in care among a cohort of 340 persons presenting for primary care who were tested for HIV and received a new diagnosis of HIV infection during their visit at an urban clinic in Johannesburg, South Africa.

We hypothesized that HIV-infected patients with depressive symptoms preceding diagnosis would be less likely to engage in care compared to their counterparts without depression. Among those who did link to care, we hypothesized that depressed patients who were eligible for ART would be less likely to initiate ART than those who were not depressed.

Methods

Study Setting and Population

Witkoppen Health and Welfare Center (WHWC) is a high-volume primary health care clinic in northern Johannesburg, South Africa that provides comprehensive services predominantly to persons living in densely populated peri-urban formal and informal settlements. At WHWC, every clinic client with an unknown HIV status or with a negative HIV test more than three months old routinely undergoes opt-out HIV counseling and testing (HCT).

The study population comprised a randomly selected subset of patients who were undergoing routine HCT at WHWC between September 2012 and April 2013. Participants were eligible for enrollment if they presented at WHWC for any reason, had unknown HIV status, tested positive for HIV at the study visit, were at least 18 years old, not pregnant by self-report, could communicate in one of 5 common languages used by interviewers (English, isiZulu, isiXhosa, seSotho, seTswana), and were able to provide informed consent. Persons found to be experiencing acute suicidal ideation were excluded and referred for immediate assistance. The Institutional Review Board at the University of North Carolina and the Human Research Ethics Committee at the University of Witwatersrand approved this study.

Study Procedures

Eligible patients were selected randomly for recruitment each day, prior to undergoing HCT. After providing informed consent, the patient was interviewed by a trained lay-interviewer. Due to low literacy in the study population, an interviewer-administered study questionnaire was used and responses were recorded on a paper form.

Depression was measured using the Patient Health Questionnaire-9 (PHQ-9), a 9-item depression screening tool that determines the presence and frequency of the 9 core depressive symptoms identified in the DSM-IV over the previous 2 weeks.[28] This tool has been widely utilized in Western settings and in sub-Saharan Africa.[29-32] Additionally, the PHQ-9 was recently validated among patients at WHWC.[33] The PHQ-9 was administered prior to HIV testing to avoid any potential impact of the HIV test result on the PHQ-9 answers. The study questionnaire included questions about substance abuse and knowledge of HIV status from prior testing experiences. Questions regarding knowledge of HIV status were added to the study questionnaire after two months of data collection, so a small number of participants did not answer these questions; absence of this information should be unrelated to other variables, in particular to depression status and linkage to care. Based on the proportion of the population reporting prior knowledge of HIV infection, we estimate that an additional 6 or 7 persons may have known their positive HIV status.

After completing the questionnaire, patients were tested for HIV with rapid HIV tests. Patients who tested positive by two rapid dried blood spot tests were registered at the HIV clinic and blood was drawn for CD4 testing that day. HIV infected patients were counseled regarding their results and given an appointment to return for collection of CD4 results and HIV staging, typically within 2 weeks, but up to 4 weeks from the diagnosis date.

Socio-demographic information and clinical information from the date of HIV testing was obtained from TherapyEdge, the HIV electronic clinic record database. Electronic clinic records were reviewed at least 6 months after study enrollment to assess clinic visits and ART status. Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at the University of North Carolina, Chapel Hill.[34]

Statistical Analysis

The primary outcome was linkage to care, defined as returning to WHWC for CD4 staging within 3 months of the diagnosis visit. A secondary outcome among those who were eligible for ART (CD4 < 350) was initiation of ART within 3 months of the staging visit. The main factor of interest in these analyses was probable major depression, defined as a PHQ-9 score of 10 or higher. Analyses were also conducted using a higher cut-off score of 15 for the PHQ-9 but no difference was found compared to results with the standard cut-off score; these data are not reported further. Additional variables included in multivariable analyses include age, gender, employment status, country of birth, alcohol use, perceived health status, and baseline CD4 count. Age was categorized and modeled using indicator variables, with the youngest age group (<30 years) as the referent.

Baseline patient characteristics were summarized using frequencies and proportions for categorical variables and medians and interquartile ranges (IQR) for continuous variables. Poisson regression with a robust variance estimator was used to estimate risk ratios (RRs), adjusted risk ratios (aRRs), and 95% confidence intervals (CIs). For the linkage to care outcome we assessed for but found no evidence of interaction between CD4 count and

depression, and perceived health status and depression; these results are not reported further. Stata version 13 (StataCorp, College Station, TX, USA) was used for all analyses.

Results

Between September 2012 and April 2013, 1683 people provided informed consent to participate in this study. Nearly all (n=1681) completed depression screening and 82% (n=1386) subsequently tested for HIV. Those who were not tested either refused HIV testing, were still in the window period from an HIV test less than three months old, revealed that they knew their positive status during pre-test counseling, left the clinic prior to testing, were referred for urgent mental health care due to their responses on the depression screen, or were missing for unknown reasons. Patients who did not test for HIV were excluded from this analysis. Of the 1384 who did test for HIV, 60 were subsequently excluded because they knew they were HIV positive according to their responses to our study questionnaire. Of the remaining 1324, 26% (n=340) were found to be HIV-infected. Nearly a quarter of the 1324 patients (22%) were depressed. Depression was much more common among patients who subsequently tested positive for HIV compared to those who tested negative for HIV (30.3% versus 19.7%, $p<0.0001$). All 340 patients with newly diagnosed HIV infection were included and constitute the study population for the remaining analyses.

Participants with newly diagnosed HIV infection had a median age of 35 years (IQR: 30- 40 years) and just over half were female (54%). About half of the participants were from South Africa (46%) while most others were from Zimbabwe (42%). About a third reported drinking any alcohol (32%) and 59% were employed. Nearly half of the participants self-reported only fair or poor health status. The median baseline CD4 count at HIV diagnosis

was 188 cells/mm3 (IQR: 86-345 cells/mm3); three-quarters of the patients who had a reported CD4 count were eligible for ART at the time of diagnosis.

Among the 340 participants, 30% were considered depressed based on PHQ-9 criteria. Depressed patients were slightly older (37 years vs 35 years, p=0.019). Those who were depressed were also more likely to self-report fair or poor health rather than excellent, very good, or good health (p=0.002). Depressed patients with newly diagnosed HIV infection had a lower median CD4 count on the date of HIV diagnosis compared to patients who were not depressed (159 vs 209, p=0.018) (Table 5.1).

Most (75%) participants linked to care to obtain a CD4 count within 3 months of diagnosis. About 60% of the patients under age 30 linked to care, compared to 78% of those age 30-39, 89% of those age 40-49, and 68% of those who were 50 or older. Those who linked to care were also more likely to report fair or poor health status (p=0.026) and have lower mean CD4 counts (232 vs 295, p=0.042) compared to patients who did not link to care.

The proportion of patients who linked to care within 3 months was 80% in the depressed group and 73% in the group that was not depressed (unadjusted RR=1.08, 95% CI:0.96, 1.23). In a multivariable model adjusting for potential confounding variables, depression was not associated with linkage to care (adjusted RR=1.05, 95% CI:0.93, 1.1).

Among the 185 patients who did link to care, 8 reported transferring care to another clinic and 1 passed away within the 3 months after HIV diagnoses. Of the remaining 176, 81% (n=143) initiated ART within 3 months of obtaining a CD4 count. The percentage of depressed and not depressed patients who initiated ART within 3 months was 81% in both groups (unadjusted RR=0.99, 95% CI: 0.86, 1.15). In a multivariable model adjusted for all

potential confounders, we found no association between depression and ART initiation (RR= 1.01, 95% CI: 0.87, 1.17).

Discussion

In this population of HIV-infected people at a primary care clinic in Johannesburg, South Africa, the prevalence of depressive symptoms at the time of HIV testing was high, with 30% of patients experiencing probable depression. We found that underlying depression did not influence subsequent linkage to HIV care or initiation of ART. To our knowledge, this is only the second study in the literature that has assessed depression before HIV testing results were known.

Depression is both a cause and an effect of HIV infection. Consequently, depression, pre- or post-HIV diagnosis, might influence engagement in HIV care. The relationship between HIV diagnosis, depression status, and depression screening is complex, necessitating clear delineation of distinct study populations that should be considered separately. To address this issue and put the current study into context, we have formulated a framework to describe these populations relative to the HIV engagement in care continuum (Figure 5.1)[63, 74].

The first population (Population 0) includes all depressed HIV-infected patients in a community, prior to HIV diagnosis. A proportion of Population 0 seeks medical care, yielding the next group (Population 1). Population 1 comprises patients presenting for care, who are not yet diagnosed with HIV. This population includes two sub-groups who have differing motivations for seeking health care- a) patients presenting for primary care who undergo routine HIV testing, and b) patients who are either self-referred or provider-referred,

and present specifically for HIV testing. In Population 1, we can study the effect of being depressed immediately prior to HIV diagnosis on engagement in HIV care. This population was assessed in the current study. Population 2 includes patients who have already received an HIV diagnosis. Subgroups in this population vary with the timing of depression screening: a) immediately after diagnosis (subgroup a), b) during the pre-ART period, c) at ART initiation, or d) after a patient is maintained in continuous HIV care. People can also move into and out of the depressed group over time, necessitating regular depression screening to accurately represent the prevalence of depression. Some people might move from Population 1 into Population 2 as they move through the continuum, but others may remain in only one group. Both Populations 1 and 2 are typically clinic-based research populations.

Following Population 0 longitudinally through engagement in the HIV care continuum would give an estimate of the full effect of depression on engagement in HIV care, including people who are missed in the clinic-based populations. However, addressing the full impact of depression on HIV infection in Population 0 would require a challenging population-based approach in which people unaware of their HIV status are screened for depression in the community, and HIV tests are collected and banked for future analysis. Conducting research among Population 0 is logistically and financially difficult, and importantly, populations 1 and 2 are more straightforward targets for potential interventions. In our current study, we focused on Population 1a- patients who undergo routine HIV testing while seeking primary care.

Given that depression is associated with ART non-adherence, we hypothesized that depressed patients would be less likely to engage in HIV care after diagnosis compared to their counterparts without depression. However, the evidence that depressed patients are less

likely to adhere to ART or to display other decreased healthcare utilization behaviors has been collected almost exclusively in Population 2c, i.e. at ART initiation.[9] These patients could be experiencing depression as a result of the emotional stress related to coping with their HIV status, or as a sequelae of the virus itself. Additionally, depression may not affect linkage to care in the same way as ART adherence, because adherence to daily ARVs requires a different skill set than clinic visit adherence. ART adherence requires daily vigilance and independent motivation, whereas obtaining a CD4 count is a discrete event, and one that can easily be rescheduled if needed. Perceived stigma and social support in the home may also play more significant roles in daily ART adherence than linkage to care.

Our study adds to a limited knowledge base relating mental illness and engagement in care among HIV-infected people. In Uganda, severe mental illness was associated with worse retention in care among patients initiating ART (population 2c).[71] In Durban, South Africa, depression was very common (prevalence = 55%) among patients presenting for HIV testing who were also screened for depression (population 1b).[20] In this population, patients with depressive symptoms were less likely than those without depressive symptoms to link to HIV care, as we had hypothesized in the current study. The relationship between depression and linkage to HIV care differed according to referral method. Depressed patients referred for HIV testing by a provider showed decreased linkage to care compared to provider-referred patients who were not depressed. Interestingly, depressed patients who self-referred for HIV testing showed increased linkage to care compared to self-referred patients who were not depressed.

Similar to the study in Durban, we screened for depression prior to the time of HIV diagnosis. However, we targeted patients undergoing routine HIV testing during the course

of a primary care visit. Although underlying depressive symptoms were more common in people who tested positive for HIV compared to those who tested negative (30% versus 20%), we did not find a difference in returning to the clinic to obtain a CD4 count or initiating ART. In primary care settings, patients who are high utilizers of medical care commonly have a higher prevalence of depression, and seek care for minor illnesses at a greater rate than patients without mental illness. [115, 116] Because our study population comprised patients who presented to a primary care facility, we may have selected for high utilizers who are less likely to be at high risk for loss to HIV care. Our clinic-based study would not capture depressed HIV-infected people who are particularly unmotivated to seek care ("low-utilizers"), reflected in Population 0. Furthermore, when depression arises after HIV diagnosis (Population 2), some patients may transition into the low-utilizer group, accounting for the decreased health seeking behavior that we see among patients who are depressed post-HIV diagnosis.

Depressed patients in our cohort may have been more similar to the self-referred population in the Durban study who linked to care more effectively than patients without depressive symptoms. Our primary care population may have included some patients who self-referred for HIV testing or were referred for testing by a different care provider. We are not able to distinguish these groups as they are mixed in with the majority of our population who presented for a primary care visit and underwent routine HIV testing. Additionally, while the Durban study was not able to use a validated depression screening tool, we used a tool that has been validated in various sub-Saharan African settings, including a recent diagnostic validation study that we conducted at the same clinic in which this study was

conducted.[117] The differing measurement tools may have accounted for the substantial discrepancy in depression prevalence between our study and the Durban study.

To our knowledge, ours is the first study to examine underlying depression in patients undergoing routine HIV testing at a primary care clinic in sub-Saharan Africa. This context is particularly important as a large proportion of HIV testing and treatment in sub-Saharan Africa takes place in primary care settings. Our results suggest that depressed patients who actively seek out health care may not be at high risk for initial loss to follow-up. While these patients might initially link to HIV care effectively, further work will be required to explore ART adherence, retention in care, and durability of depression among these patients. Our results can only be generalized to patients presenting for medical care in a primary care clinic and should be confirmed in other similar settings.

This study emphasizes the complexity of studying the bidirectional relationship between depression and engagement in HIV care. The complexities of this relationship necessitate careful consideration of the differences in population, clinic setting, and context to ensure appropriate interpretation and generalization of results. The impact of depression prior to HIV diagnosis such as measured in our cohort may be substantially different than the impact of depression after HIV diagnosis. We recommend that these two populations be clearly delineated and explored longitudinally along the engagement in HIV care continuum. To facilitate this work, we have provided a population framework that can guide future research designed to address this important association. Further study of the impact of depression on HIV outcomes is paramount: a third of our HIV-infected population presented with underlying depressive symptoms, a quarter of the population did not link to care, and of

those who did link to care, 20% did not initiate ART. The HIV-care outcomes of this substantial population will only be improved with carefully designed interventions.

Table 5.1.

Characteristics of the Study Population for Aim 2, Stratified by Depression

Characteristic	**Total study population***	**Depressive symptoms n (%)**	
	(n=340)	PHQ-9<10 (n=237)	PHQ-9≥10 (n=103)
Age*			
<30	85 (25.0)	61 (25.7)	24 (23.3)
30-39	163 (47.9)	123 (51.9)	40 (38.8)
40-49	64 (18.8)	38 (16.03)	26 (25.2)
≥50	28 (8.2)	15 (6.33)	13 (12.6)
Gender			
Male	155 (45.6)	110 (46.4)	58 (56.3)
Female	185 (54.4)	127 (53.6)	45 (43.7)
Employment status, n(%)			
Employed	201 (62.6)	145 (64.4)	56 (58.3)
Unemployed	120 (37.4)	80 (35.6)	40 (41.7)
Country of birth, n(%)			
South Africa	156 (45.9)	107 (45.2)	49 (47.6)
Other country	184 (54.1)	130 (54.9)	54 (52.4)
Alcohol use, n(%)			
Any	109 (32.3)	76 (32.1)	33 (32.7)
None	229 (67.7)	161 (67.9)	68 (67.3)
Perceived health status, n(%)*			
Excellent	29 (8.6)	26 (11.0)	3 (3.0)
Very good	36 (10.7)	28 (11.8)	8 (7.9)
Good	115 (34.0)	85 (35.9)	30 (29.7)
Fair	66 (19.5)	50 (21.1)	16 (15.8)
Poor	92 (27.2)	48 (20.3)	44 (43.6)
CD4 count, n(%)			
<100	86 (28.6)	56 (27.3)	30 (31.3)
100-199	73 (24.3)	42 (20.5)	31 (32.3)
200-349	67 (22.3)	51 (24.9)	16 (16.7)
≥350	75 (24.9)	56 (27.3)	19 (19.8)

Table 5.2.

Population Characteristics According to Linkage to Care or ART Initiation

	Linkage to care (N=340)				**ART initiation (N=176)**		
Characteristic	**n**	**% Linked to care**	**p value***		**n**	**% Initiating ART**	**p value***
Age in years							
<30	85	62			29	83	
30-39	163	78	0.001		93	81	0.960
40-49	64	89			41	83	
≥50	28	68			13	77	
Gender							
Male	155	75	0.941		87	77	0.154
Female	185	75			89	85	
Employment status							
Employed	201	77	0.409		107	81	0.966
Unemployed	120	73			58	81	
Country of birth							
South Africa	156	75	0.908		76	82	0.922
Other country	184	76			100	81	
Alcohol use							
None	229	76	0.546		119	83	0.312
Any	109	73			56	77	
Perceived health status	180	71	0.026		79	85	0.261
Excellent/Very Good/Good	158	81			96	78	
Fair or Poor							
CD4 count							
<100	86	85			68	78	
100-199	73	78	0.396		55	85	0.569
200-349	67	82			53	81	
≥350	75	75			---	---	
Probable depression							
Depressed (PHQ≥10)	103	80	0.224		63	81	0.940
Not depressed (PHQ<10)	237	73			113	81	

*Tests based on Pearson's Chi-square for categorical variables

Table 5.3.

Risk Ratios for Linkage to Care or ART initiation for Patients with Depressive Symptoms Compared to Patients Without Depressive Symptoms

Linkage to care			
Model	**n**	**Risk Ratio**	**95% CI**
Unadjusted: Depressed (PHQ≥10) vs Not Depressed (PHQ<10)	340	1.08	(0.96, 1.23)
Adjusted*: Depressed (PHQ≥10) vs Not Depressed (PHQ<10)	280	1.05	(0.93, 1.18)
ART initiation			
Model	**n**	**Risk Ratio**	**95% CI**
Unadjusted: Depressed (PHQ≥10) vs Not Depressed (PHQ<10)	176	0.99	(0.86, 1.15)
Adjusted*: Depressed (PHQ≥10) vs Not Depressed (PHQ<10)	164	1.01	(0.87, 1.17)

*Adjusted for age, gender, employment, country of birth, alcohol, perceived health, CD4

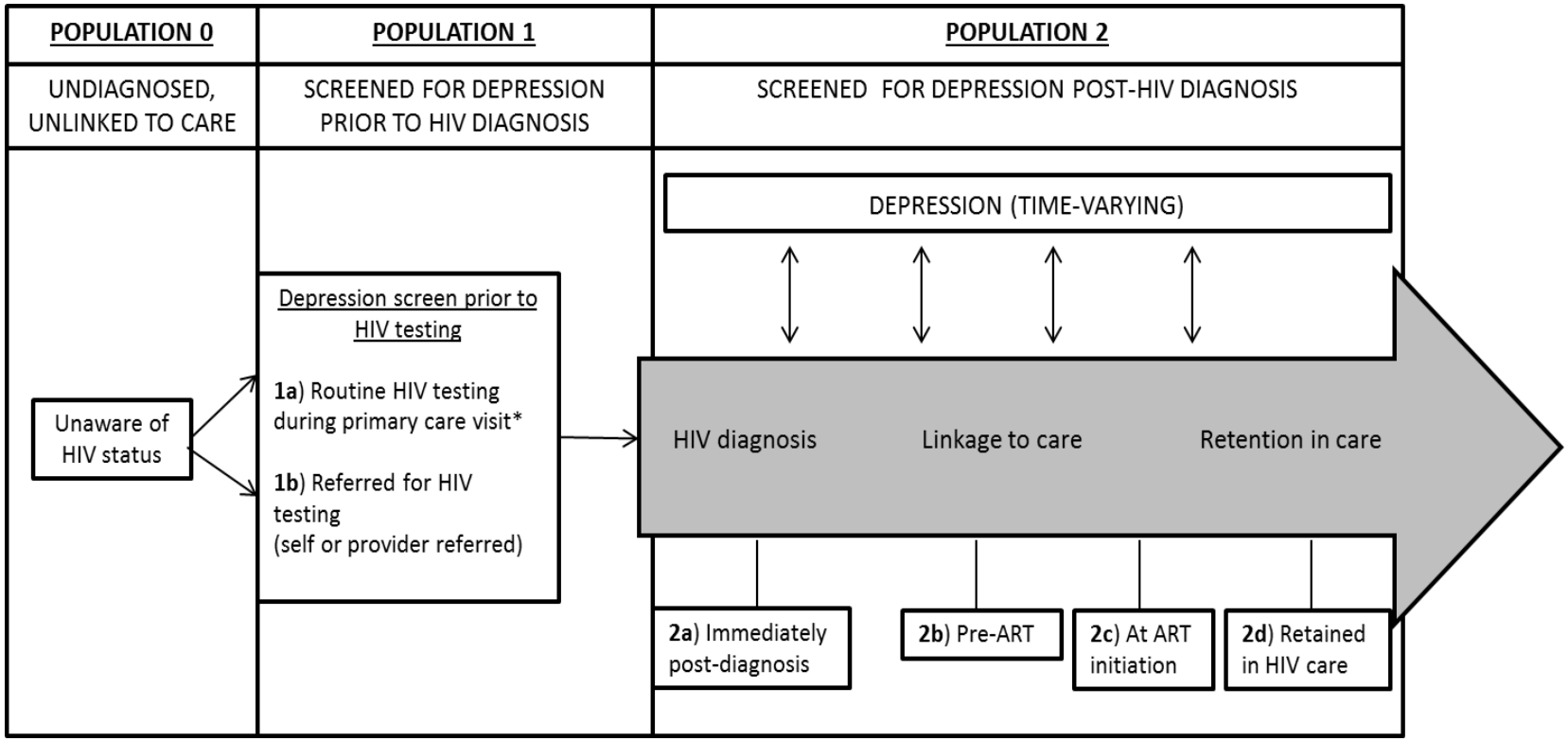


Figure 5.1. A population framework to conceptualize the relationship between timing of HIV diagnosis, depression status, and depression screening. *Population included in this study.

CHAPTER VI: DISCUSSION AND CONCLUSION

Depression is highly prevalent among HIV-infected people and is associated with a range of negative HIV-related consequences including increased morbidity and mortality.[1] For these reasons depression screening has been integrated into routine HIV care in many high-resource settings. In sub-Saharan Africa however, mental health resources remain scarce and all but the most severe mental illness typically remains undetected.

Over the past decade policy-makers have advocated for a shift to routine, provider-initiated opt-out HCT in sub-Saharan Africa.[118] As a result of this approach, much of the HCT in sub-Saharan Africa takes place during the course of universal opt-out HIV testing in primary care settings. This successful strategy has led to greatly increased uptake of HCT and unprecedented numbers of people becoming aware of their HIV status. This combined with the promising test-and-treat strategy for HIV infection has motivated policies to ensure earlier universal access to ART. However, several operational challenges exist in implementation of these policies, particularly related to linking patients to HIV care and retaining them in care throughout the course of their lives.

Given that depression is associated with negative health-care utilization behaviors, primarily non-adherence to ART, it may be that depression also impacts engagement in HIV care. Strategies to integrate depression screening and HIV services in primary care settings are important for identification of patients who might be at risk for poor HIV outcomes. This dissertation research was designed to address questions that might contribute to the

understanding of depression and HIV infection in sub-Saharan Africa, particularly in primary care settings.

Summary of Findings

This work was conducted in a population of nearly 1700 adults of unknown HIV status undergoing routine HIV testing at Witkoppen Health and Welfare Center (WHWC), a high HIV-burden primary care clinic in Johannesburg, South Africa. Patients were screened for underlying depression immediately prior to HIV testing. Two specific aims were addressed.

In the first aim, we sought to validate a brief depression screening tool for use in our study context and integrate its use into a routine opt-out HIV testing program. We conducted a diagnostic validation study among a subset of 400 participants to assess the performance of the Patient Health Quesitonnaire-9 (PHQ-9). The interviewer-administered PHQ-9, with a sensitivity of 78.7% (95% CI: 64.3-89.3) and specificity of 83.4% (95% CI: 79.1-87.2), demonstrated moderate discriminating abilities for the diagnosis of a current major depressive episode relative to the MINI, our diagnostic reference standard. The PHQ-9 performed similarly among both HIV-infected and uninfected patients. Additionally, the PHQ-9 was easily implemented by lay health workers in a busy primary care clinic, demonstrating its potential utility as a screening tool in similar settings.

In the second aim, we examined the effect of underlying depression on engagement in HIV care. Among the 1700 enrolled participants, nearly a third of the study population was diagnosed with HIV after depression screening. Additionally,30% of the HIV infected participants were depressed according to the standard PHQ-9 cut-off score. Three-quarters of

the HIV-infected population linked to HIV care, defined as returning to the clinic within 3 months to obtain a CD4 test results. Of those who linked, 80% initiated ART. We found no difference in linkage to HIV care or initiation of ART among HIV-infected patients who were depressed compared to those who were not depressed.

By using a clinic-based study sample we may have selected for patients who were high-utilizers of medical care and unlikely to be lost to care. To guide future work we developed a conceptual framework to outline the complex relationship between the population under study, the HIV engagement in care continuum, and the timing of depression screening.

Implications of Findings

This dissertation research contributes to the limited body of research on depression and HIV in sub-Saharan Africa. In particular, our work provides guidance for implementation of depression screening programs in the context of high HIV burden primary care settings, and provides a framework for studying depression and engagement in HIV care.

Given the high prevalence of depression among HIV-infected people and the negative outcomes associated with depression and HIV comorbidity, regular screening of HIV-infected people for depression is paramount. Depression screening has been incorporated into primary care settings and HIV programs in the United States for many years. However, most sub-Saharan African settings have not yet followed suit due to competing priorities for limited resources and few mental health personnel. As evidence accumulates showing that the burden of depression is high among HIV-infected patients in sub-Sahara Africa,

motivation to integrate mental health interventions and HIV care services in these resource-scarce contexts is increasing.

Our findings from Aim 1 suggest that depression screening can be feasibly conducted by lay health workers with populations undergoing HIV testing in busy resource-scarce primary care clinic settings. The PHQ-9 is a depression screening tool with reasonable test characteristics which could be used to quickly identify and prioritize patients who might require further evaluation. The tool is brief, taking only a few minutes to complete, and can be either self-administered or interviewer-administered for low-literacy settings. Although we screened patients for underlying depression prior to HCT, the PHQ-9 could be implemented at any stage of the engagement in HIV care continuum. The performance of the PHQ-9 in our study setting was moderate; test characteristics could potentially be improved through careful qualitative work to adapt the PHQ-9 to more accurately reflect culturally relevant constructs of mental health.

Our results from this aim also provide guidance for prioritization of patients after undergoing depression screening in contexts where there are limited mental health personnel. In a setting such as WHWC, where there is only one part-time mental health professional, prioritizing patients during the screening process is critical. The categorical likelihood ratios calculated in Aim 1 are important in this regard, as they capture the prevalence of depression in the population. Using these likelihood ratios with the pre-test probability of depression, which can account for factors such as a patient's medical history, allows the clinician or mental health professional to decide how to treat a patient based on the patient's post-PHQ probability of depression for a particular value of the continuous PHQ-9 score. Ideally the PHQ-9 would be used longitudinally to screen patients as they progress through the

engagement in HIV care continuum, and the pre-test probability of depression would change depending on the patient's CD4 count, their ART initiation status, or other aspects of HIV-related disease such as dementia. In these scenarios, the post-test probability of depression could be adjusted accordingly, allowing for a sophisticated, targeted approach that allows clinicians to allocate resources in order of where they are most needed. In settings where mental health resources are limited, categorical likelihood ratios are far more useful than a dichotomous cut-off score.

Our results from Aim 2 demonstrated a very high prevalence (30%) of underlying depression among HIV-infected patients presenting for HIV testing. Depression prevalence was much higher among HIV-infected patients than uninfected patients (30.3% versus 19.7%). Additionally, HIV-infected patients who were depressed were sicker at HIV diagnosis than HIV-infected patients who were not depressed. Depressed patients had a lower median CD4 count and worse self-reported health status at HIV diagnosis. These findings are consistent with literature suggesting that depression might be related to poor physical health function among HIV-infected people [119]. One interpretation of our results is that patients who delay linkage to HIV care become depressed as their physical health deteriorates. This research aim would have benefitted from use of a more detailed measure of physical health to further assess the association between depression and physical health function.

Similar to other studies in this context, a quarter of the population did not obtain a CD4 count and thus failed to complete the first step in engaging in HIV care within 3 months of HIV diagnosis.[69] Of the patients who did obtain a CD4 count and were eligible for ART, 20% did not initiate ART within 3 months. These results, while they are the norm for

the region, reemphasize the pressing need for interventions to address depression and engagement in care among HIV-infected people.

We found no difference in linkage to care or ART initiation according to depression status in this population. While this was unexpected, these results prompted us to consider how selection of particular study populations and the timing of depression screening and HCT might influence the generalizability and interpretation of studies examining the relationship between depression and engagement in HIV care. For example, in primary care settings like WHWC, patients who are high utilizers of medical care commonly have a higher prevalence of depression, and seek care for minor illnesses at a greater rate than patients without mental illness. Because our study population comprised depressed patients who presented to a primary care facility, we may have partially selected for these high utilizers who are less likely to be at high risk for loss to HIV care. This population of patients with underlying depressive symptoms may turn out to be a different group of people than those who become depressed after HIV diagnosis and have subsequent difficulty adhering to ART. We developed a conceptual framework to delineate these populations and we encourage researchers to consider these issues as they design studies focused on depression and engagement in HIV care.

Future Research Directions

First, our results demonstrated that a high proportion (22%) of patients presenting for primary healthcare services exhibited depressive symptoms. Although the prevalence of depression was higher in the HIV-infected group, a full 20% of patients in the uninfected group were depressed. This result highlights the importance of evaluating mental health

interventions that address the high burden of mental illness in the general primary care population in sub-Saharan Africa. Mental health treatment for this population may help to prevent the factors that increase transmission of HIV among depressed people. Although this dissertation is focused primarily on depression among people already infected with HIV, patients should ideally be treated for mental illness without regard to their HIV status. Interventions that harness the structure of primary care clinics to provide mental health services to both HIV-infected and uninfected patients, for example in the context of routine HCT, should be promoted.

We recommend that researchers use the conceptual model presented in aim 2 of this dissertation when considering the relationship between depression and HIV in future research studies. We suggest several potential research directions in the context of this conceptual model.

Routine Depression Screening in HIV Care

In aim 1 of this dissertation we suggest that routine depression screening integrated into existing HIV programs might be a feasible and cost-effective method for identifying patients who may be at risk for negative outcomes, and prioritizing them for further clinical evaluation.

Future research should evaluate such depression screening interventions in the context of resource-limited HCT programs in sub-Saharan Africa. In such settings, where there are few mental health personnel, screening would have to be accompanied by the use of careful referral methods to ensure that limited mental health resources are ethically prioritized where they are most needed. Researchers should aim to test novel management

and referral methods to facilitate the implementation of routine depression screening as well as subsequent depression treatment. This might include the use of trained depression case managers who are overseen by a mental health specialist, as implemented in other ongoing research in high-income settings. [120] We suggest that programs design and evaluate standardized systems that utilize categorical likelihood ratios as described in this dissertation. Use of these ratios would allow resources to be targeted in a setting-specific manner and may be an important tool for guiding clinical decisions. Lastly, further prospective research will be required to examine how depression screening programs in these settings influence HIV outcomes.

Depression and Engagement in HIV Care

As this dissertation research focused only on underlying depression prior to HCT, our results are not generalizable to several other important populations, including patients already aware of their HIV status. Regular, longitudinal depression assessment as HIV-infected patients progress along the HIV engagement in care continuum would allow for further elucidation of the complex relationship between population of study, the timing of depression screening, and the stage of engagement in HIV care. Such prospective depression evaluation among HIV-infected patients who are already engaged in care should aim to further clarify the populations presented in our conceptual framework. Particularly, researchers could examine: a) how depression status (depressed, not depressed, remitted, relapsed) changes over time relative to engagement in the HIV care continuum, b) factors that might predict depression status changes at each stage, c) the relationship between depression status and loss to care in each stage of the continuum, and d) whether there might be critical points for

behavioral or pharmacological mental health intervention during this process for populations at risk for loss to care.

Additionally, clarification of populations that may be high utilizers versus low utilizers of health care services is also important. Our results suggest that patients with underlying depression who present for primary care may not be at risk for immediate loss to HIV care. However, it remains to be seen whether this relationship holds true as these patients progress through the HIV care continuum.

Research to date on depression and engagement in HIV care has primarily focused on patients already engaged with the health care system. The burden of comorbid depression and HIV among people unaware of their HIV status and unlinked to medical care (Population 0 from our framework) is unknown. Designing an intervention to address depression and HIV in population 0 would require a creative, potentially costly, community-based approach. However, development of such an intervention might allow for earlier detection of both depression and HIV in a population prone to low-utilization of health services.

Physical Health and the Relationship between Depression and Linkage to Care

As discussed earlier, depressed patients in our population presented for care with lower CD4 counts and decreased self-reported health status compared to patients who were not depressed. These results suggest that depressed patients in this population may have delayed their initial care seeking visit compared to patients who were not depressed. Depressed patients may subsequently have increased motivation or support to utilize care because they are sicker than HIV-infected patients who are not depressed, suggesting that poor physical health might mediate the relationship between depression and linkage to care.

Reconciling this hypothesis into our existing conceptual framework will require further research.

Mental Health Comorbidities and the Relationship between Depression and Engagement in HIV Care

While this dissertation has focused entirely on depression and HIV, other mood and anxiety disorders such as generalized anxiety disorder and post-traumatic stress disorder can lead to increased psychiatric severity and may also influence HIV-related outcomes.[112] In this research we found that 11% of the validation study sample in aim 1 was experiencing a MINI-diagnosed anxiety disorder (Appendix C), and nearly half of the patients diagnosed with a current major depressive episode were also experiencing a comorbid anxiety disorder. How comorbid anxiety disorders might influence engagement in HIV care or adherence to ART among depressed patients merits further exploration. In the context of our conceptual model, patients who are depressed and also experiencing a comorbid anxiety disorder may be especially likely to be high-utilizers of primary care as compared to patients without a comorbid anxiety disorder.

Conclusions

Depression imposes an immense burden among HIV-infected people in sub-Saharan Africa. Early detection and treatment of depression in HIV patients is critical for optimizing the success of ART programs, especially in South Africa which houses the world's largest ART program. As HCT and ART uptake in primary care settings continues to increase, these settings may be an important place for integration of routine depression screening

interventions into HIV care. This dissertation research emphasizes the importance of depression and HIV comorbidity in sub-Saharan Africa, and highlights the urgent need for design of interventions to address this condition.

APPENDIX A: PHQ-9 Depression Screening Tool

I'm going to start by asking some questions about how you've been feeling lately. During the past two weeks, how often have you been bothered by each of the following symptoms? ***[Prompt each question as needed with "During the past two weeks, how often have you been bothered by…"]***				
	Not at all	**Several days**	**More than half the days**	**Nearly every day**
1. Feeling down, depressed, or hopeless (*closed spirits*)?	**0**	**1**	**2**	**3**
2. Little interest or pleasure in doing things; (*not having courage or anxiety; spirits are low*)?	**0**	**1**	**2**	**3**
3. Trouble falling or staying asleep (*insomnia, sleeplessness*), or sleeping too much?	**0**	**1**	**2**	**3**
4. Feeling tired, fatigued or having little energy?	**0**	**1**	**2**	**3**
5. Poor appetite or overeating?	**0**	**1**	**2**	**3**
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down (*feeling ashamed or disgraced*)?	**0**	**1**	**2**	**3**

7. Trouble concentrating on things, such as: ***[if male]* reading the newspaper or watching television?** ***[*if female] participating in meetings or watching television?**	**0**	**1**	**2**	**3**
8. Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual (*being a disturbance or not at peace*)?	**0**	**1**	**2**	**3**
9. Thoughts that you would be better off dead or of hurting yourself in some way? (*feelings of suicide or lost hope*)→ *If patient answers 1-3, skip immediately to Suicide Risk Assessment*	**0**	**1**	**2**	**3**
Interviewer: Do these calculations AFTER you are done with the participant. Skip to question 10.	**0**	**× 1 =**	**× 2 =**	**× 3 =**
***Grand total (add totals of columns)*→ If score ≥ 20, refer patient for psychological care at end of interview.**				**=**

[Interviewer: Skip questions 10 and 11 if all responses to questions 1-9 are "0"]

10. How difficult have these problems made it for you to do your work, take care of things at home or get along with other people?

[0] Not difficult at all [1] Somewhat difficult [2] Very difficult [3] Extremely difficult

[Interviewer: Skip question 11 if answer to question 10 is "Not difficult at all"]

11. Have they caused you difficulty for two years or more?

[0] Yes [1] No

APPENDIX B. Suicide Risk Assessment Form

Complete this form with all patients who reveal suicidal thinking during their participation in the study.

Date (DD/MMM/YYYY) ____ / ____ / _____ Patient Study ID _____

II. Differentiation of passive from active suicidal thoughts

"In the last two weeks, have you had any thoughts of hurting yourself in some way?"

1 – not at all 2 - several days 3 - more than half the days 4 - nearly every day

If "NOT AT ALL": Very low risk (passive suicidal thoughts only). Skip to Section IV.

OTHERWISE: Active suicidal thoughts. Continue with Section III.

III. Assessment of patients who demonstrate some evidence of *active* suicidal thinking.

1. *"In the past month, have you made any plans or considered a method that you might use to harm yourself"* (circle one)

YES NO

(If yes, ask, "*Please be specific about these plans or methods you have considered."*)

_____

_____

_____

2. *"Have you ever attempted to harm yourself?"* (circle one)

YES NO

(If yes, ask, "*When was this? What happened*?")

_____

_____

_____

3. "*There's a big difference between having a thought and acting on a thought. Do you think you might actually make an attempt to hurt yourself in the near future?"* (circle one)

YES NO

(If yes, ask, "*Can you be specific about how you might do this*?")

_____

_____

_____

4. *"In the past month have you told anyone that you were going to commit suicide, or threatened that you might do it?"* (circle one)

YES NO

(If yes, ask, "*Who have you told and what have you said to them?*")

_____

_____

_____

5. *"Do you think there is any risk that you might hurt yourself before you see your doctor the next time?*

YES NO

(If yes, ask, "*What do you think you might do?"*)

_____

_____

_____

If "YES" to Question 5: Acute (High) Suicide Risk.

Otherwise, if "YES" to any of Questions 1-4: Moderate to High Suicide Risk

If "NO" to ALL of Questions 1-5: Low Suicide Risk

IV. Summary of risk assessment. Check one.

__ Passive (very low) __ Low __ Moderate to high __ Acute

If Moderate/High or Acute Risk→ Escort patient to clinician immediately.

If Passive or Low→ Continue with questionnaire. Include referral letter in chart and send patient to schedule psychologist appointment after finishing interview.

Form completed by:

_____

Name Signature

APPENDIX C. Supplemental Results: GAD-7 (Anxiety) Screening

In addition to validation of the PHQ-9, we also attempted to validate the 7-item Generalized Anxiety Disorder Assessment (GAD-7) in aim 1. This tool was initially developed to diagnose generalized anxiety disorder, but has since been shown to have good sensitivity and specificity as a screening tool for other types of anxiety such as PTSD and panic disorder.[94] It has been used and validated widely worldwide but never in sub-Saharan Africa. It takes approximately 2-3 minutes to complete and is easy for non-clinicians to implement, similar to the PHQ-9. To our knowledge, very little work has been done to study anxiety in sub-Saharan Africa and validation studies have only been completed with the Kessler Psychological Scale (K-10).[21, 121] These studies show moderate to poor performance and the most recent of this work showed that the scale was especially unreliable among black South Africans.

Here we present preliminary results from our validation analyses of the GAD-7. Of the 394 patients who completed the anxiety screen and MINI, 43 (10.9%) met the diagnostic criteria for any current anxiety disorder on the MINI (Table C.1). The GAD-7 performed poorly in the study population. Fourteen of the MINI anxiety cases had a positive GAD-7 anxiety screen using a cut-off score of 10 or higher. Of the 354 persons who did not meet criteria for any anxiety disorder, 332 had a negative anxiety screen on the GAD-7. This corresponds to a sensitivity of 34.1% (95% CI: 20.1-50.6) and a specificity of 94.1% (95% CI: 91.0-96.3) for the GAD-7 at the standard cut-off score of 10. A lower cut-off score of 8 yielded a higher sensitivity of 53.7 (95% CI: 37.4-69.3) and a lower specificity of 87.5 (95% CI: 83.6-90.8), whereas a higher alternate cut-off score of 12 yielded a lower sensitivity of 24.4 (95% CI: 12.4-40.3) and a higher specificity of 95.5 (95% CI: 92.7-97.4).

In ROC analysis, the GAD-7 had an area under the curve (AUC) of 0.81 (95% CI: 0.74-0.88), indicating moderate accuracy (Figure C.1). Likelihood ratios for the commonly used GAD-7 cut-off scores representing mild (≥5), moderate (≥10), and severe (≥15) anxiety were 0.29, 1.53, 5.49, and 5.49 respectively (Table C.2). Post-test probabilities for these categories were calculated for a range of pre-test probability (prevalence) values (Figure C.2). At the anxiety disorder prevalence of 10.9% seen in this population, (indicated by vertical line, Figure C.2), the post-test probability of an anxiety disorder for a GAD-7 score between 10-14 is 37.4%, and for a score higher than 15 it is also 37.4%.

Table C.1.

GAD-7 Test Characteristics at Various Cut-Off Scores among Whole Study Population (n=394)

Cut-off	TP*	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)
≥ 8	22	44	309	19	53.7 (37.4-69.3)	87.5 (83.6-90.8)
≥ 10	14	21	332	27	34.1 (20.1-50.6)	94.1 (91.0-96.3)
≥ 12	10	16	337	31	24.4 (12.4-40.3)	95.5 (92.7-97.4)

*TP= True positive, FP= False positive, TN= True negative, FN= False negative

Table C.2.

Likelihood Ratios for Commonly Used GAD-7 Decision Thresholds

Symptom severity	GAD-7 cut-off	Likelihood ratio
No anxiety	<5	0.29
Mild anxiety	5-9	1.53
Moderate anxiety	10-14	5.49
Severe anxiety	15-21	5.49

Figure C.1 ROC curve for GAD-7

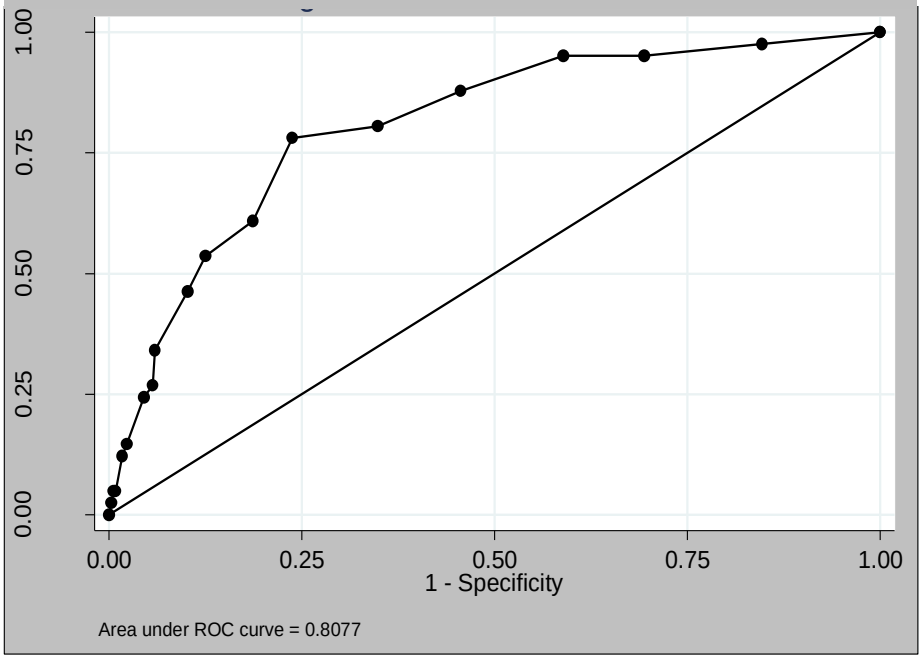
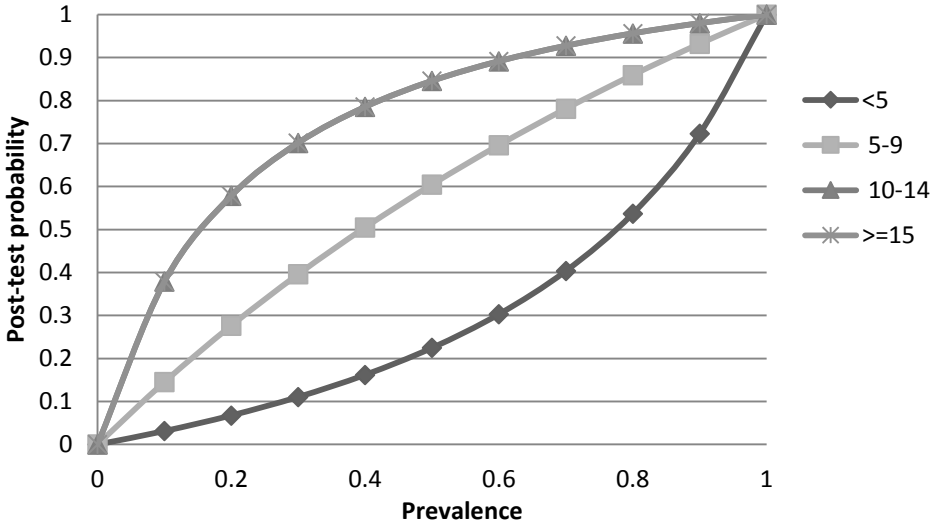


Figure C.2. Post-test probability for varying GAD-7 cut-off scores, based on categorical likelihood ratios



REFERENCES

1. Collins, P.Y., et al., *What is the relevance of mental health to HIV/AIDS care and treatment programs in developing countries? A systematic review.* AIDS, 2006. **20**(12): p. 1571-82.

2. Williams, D.R., et al., *Twelve-month mental disorders in South Africa: prevalence, service use and demographic correlates in the population-based South African Stress and Health Study.* Psychol Med, 2008. **38**(2): p. 211-20.

3. Myer, L., et al., *Common mental disorders among HIV-infected individuals in South Africa: prevalence, predictors, and validation of brief psychiatric rating scales.* AIDS Patient Care STDS, 2008. **22**(2): p. 147-58.

4. Myer, L., et al., *DSM-IV-defined common mental disorders: association with HIV testing, HIV-related fears, perceived risk and preventive behaviours among South African adults.* S Afr Med J, 2009. **99**(5 Pt 2): p. 396-402.

5. Olley, B.O., et al., *Predictors of major depression in recently diagnosed patients with HIV/AIDS in South Africa.* AIDS Patient Care STDS, 2004. **18**(8): p. 481-7.

6. Gaynes, B.N., et al., *Prevalence and Predictors of Major Depression in HIV-Infected Patients on Antiretroviral Therapy in Bamenda, a Semi-Urban Center in Cameroon.* PLoS One, 2012. **7**(7): p. e41699.

7. Nakimuli-Mpungu, E., et al., *Prevalence and factors associated with depressive disorders in an HIV+ rural patient population in southern Uganda.* J Affect Disord, 2011. **135**(1-3): p. 160-7.

8. Simoni, J.M., et al., *Challenges in addressing depression in HIV research: assessment, cultural context, and methods.* AIDS Behav, 2011. **15**(2): p. 376-88.

9. Gonzalez, J.S., et al., *Depression and HIV/AIDS treatment nonadherence: a review and meta-analysis.* J Acquir Immune Defic Syndr, 2011. **58**(2): p. 181-7.

10. Ironson, G., et al., *Psychosocial factors predict CD4 and viral load change in men and women with human immunodeficiency virus in the era of highly active antiretroviral treatment.* Psychosom Med, 2005. **67**(6): p. 1013-21.

11. Scott-Sheldon, L.A., et al., *Stress management interventions for HIV+ adults: a meta-analysis of randomized controlled trials, 1989 to 2006.* Health Psychol, 2008. **27**(2): p. 129-39.

12. Sikkema, K.J., et al., *Mental health treatment to reduce HIV transmission risk behavior: a positive prevention model.* AIDS Behav, 2010. **14**(2): p. 252-62.

13. Petersen, I., A. Bhana, and K. Baillie, *The feasibility of adapted group-based interpersonal therapy (IPT) for the treatment of depression by community health workers within the context of task shifting in South Africa.* Community Ment Health J, 2012. **48**(3): p. 336-41.

14. Petersen, I., et al., *A group-based counselling intervention for depression comorbid with HIV/AIDS using a task shifting approach in South Africa: a randomized controlled pilot study.* J Affect Disord, 2014. **158**: p. 78-84.

15. Sherr, L., et al., *HIV and depression--a systematic review of interventions.* Psychol Health Med, 2011. **16**(5): p. 493-527.

16. Seedat, S., et al., *Mental health service use among South Africans for mood, anxiety and substance use disorders.* S Afr Med J, 2009. **99**(5 Pt 2): p. 346-52.

17. Freeman, M., et al., *Integrating mental health in global initiatives for HIV/AIDS.* Br J Psychiatry, 2005. **187**: p. 1-3.

18. Larson, B.A., et al., *Early loss to follow up after enrolment in pre-ART care at a large public clinic in Johannesburg, South Africa.* Trop Med Int Health, 2010. **15 Suppl 1**: p. 43-7.

19. Rosen, S., M.P. Fox, and C.J. Gill, *Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review.* PLoS Med, 2007. **4**(10): p. e298.

20. Ramirez-Avila, L., et al., *Depressive Symptoms and Their Impact on Health-seeking Behaviors in Newly-diagnosed HIV-infected Patients in Durban, South Africa.* AIDS Behav, 2012.

21. Andersen, L.S., et al., *The psychometric properties of the K10 and K6 scales in screening for mood and anxiety disorders in the South African Stress and Health study.* Int J Methods Psychiatr Res, 2011. **20**(4): p. 215-23.

22. Bing, E.G., et al., *Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States.* Arch Gen Psychiatry, 2001. **58**(8): p. 721-8.

23. Kagee, A. and L. Martin, *Symptoms of depression and anxiety among a sample of South African patients living with HIV.* AIDS Care, 2010. **22**(2): p. 159-65.

24. Kaharuza, F.M., et al., *Depression and CD4 cell count among persons with HIV infection in Uganda.* AIDS Behav, 2006. **10**(4 Suppl): p. S105-11.

25. Pappin, M., E. Wouters, and F.L. Booysen, *Anxiety and depression amongst patients enrolled in a public sector antiretroviral treatment programme in South Africa: a cross-sectional study.* BMC Public Health, 2012. **12**: p. 244.

26. Tomlinson, M., et al., *The epidemiology of major depression in South Africa: results from the South African stress and health study.* S Afr Med J, 2009. **99**(5 Pt 2): p. 367-73.

27. Nakimuli-Mpungu, E., et al., *Depression, Alcohol Use and Adherence to Antiretroviral Therapy in Sub-Saharan Africa: A Systematic Review.* AIDS and Behavior, 2012. **16**(8): p. 2101-2118.

28. Hughes, J., et al., *The health-related quality of life of people living with HIV/AIDS.* Disabil Rehabil, 2004. **26**(6): p. 371-6.

29. Lawler, K., et al., *Depression among HIV-positive individuals in Botswana: a behavioral surveillance.* AIDS Behav, 2011. **15**(1): p. 204-8.

30. Kinyanda, E., et al., *Prevalence and risk factors of major depressive disorder in HIV/AIDS as seen in semi-urban Entebbe district, Uganda.* BMC Psychiatry, 2011. **11**: p. 205.

31. Senn, T.E., M.P. Carey, and P.A. Vanable, *Childhood and adolescent sexual abuse and subsequent sexual risk behavior: evidence from controlled studies, methodological critique, and suggestions for research.* Clin Psychol Rev, 2008. **28**(5): p. 711-35.

32. Parillo, K.M., et al., *Association between early sexual abuse and adult HIV-risky sexual behaviors among community-recruited women.* Child Abuse Negl, 2001. **25**(3): p. 335-46.

33. Meade, C.S., et al., *Long-term correlates of childhood abuse among adults with severe mental illness: adult victimization, substance abuse, and HIV sexual risk behavior.* AIDS Behav, 2009. **13**(2): p. 207-16.

34. Gonzalez, J.S., et al., *Latinos and HIV/AIDS: examining factors related to disparity and identifying opportunities for psychosocial intervention research.* AIDS Behav, 2009. **13**(3): p. 582-602.

35. Pence, B.W., et al., *Childhood trauma and health outcomes in HIV-infected patients: an exploration of causal pathways.* J Acquir Immune Defic Syndr, 2012. **59**(4): p. 409-16.

36. Lundberg, P., et al., *Poor mental health and sexual risk behaviours in Uganda: a cross-sectional population-based study.* BMC Public Health, 2011. **11**: p. 125.

37. Sikkema, K.J., et al., *Effects of a coping intervention on transmission risk behavior among people living with HIV/AIDS and a history of childhood sexual abuse.* J Acquir Immune Defic Syndr, 2008. **47**(4): p. 506-13.

38. Okeke, E.N. and G.J. Wagner, *AIDS treatment and mental health: Evidence from Uganda.* Soc Sci Med, 2013. **92**: p. 27-34.

39. Treisman, G. and A. Angelino, *Interrelation between psychiatric disorders and the prevention and treatment of HIV infection.* Clin Infect Dis, 2007. **45 Suppl 4**: p. S313-7.

40. Joska, J.A., et al., *Clinical correlates of HIV-associated neurocognitive disorders in South Africa.* AIDS Behav, 2010. **14**(2): p. 371-8.

41. Wagner, G.J., et al., *A closer look at depression and its relationship to HIV antiretroviral adherence.* Ann Behav Med, 2011. **42**(3): p. 352-60.

42. Himelhoch, S., et al., *Does the presence of a current psychiatric disorder in AIDS patients affect the initiation of antiretroviral treatment and duration of therapy?* J Acquir Immune Defic Syndr, 2004. **37**(4): p. 1457-63.

43. O'Cleirigh, C., et al., *Functional impairment and health care utilization among HIV-infected men who have sex with men: the relationship with depression and post-traumatic stress.* J Behav Med, 2009. **32**(5): p. 466-77.

44. Leserman, J., *Role of depression, stress, and trauma in HIV disease progression.* Psychosom Med, 2008. **70**(5): p. 539-45.

45. Carrico, A.W., et al., *Psychiatric risk factors for HIV disease progression: the role of inconsistent patterns of antiretroviral therapy utilization.* J Acquir Immune Defic Syndr, 2011. **56**(2): p. 146-50.

46. Cook, J.A., et al., *Depressive symptoms and AIDS-related mortality among a multisite cohort of HIV-positive women.* Am J Public Health, 2004. **94**(7): p. 1133-40.

47. Tegger, M.K., et al., *The effect of mental illness, substance use, and treatment for depression on the initiation of highly active antiretroviral therapy among HIV-infected individuals.* AIDS Patient Care STDS, 2008. **22**(3): p. 233-43.

48. Springer, S.A., A. Dushaj, and M.M. Azar, *The impact of DSM-IV mental disorders on adherence to combination antiretroviral therapy among adult persons living with HIV/AIDS: a systematic review.* AIDS Behav, 2012. **16**(8): p. 2119-43.

49. Mayston, R., et al., *Mental disorder and the outcome of HIV/AIDS in low-income and middle-income countries: a systematic review.* AIDS, 2012. **26 Suppl 2**: p. S117-35.

50. Ulett, K.B., et al., *The therapeutic implications of timely linkage and early retention in HIV care.* AIDS Patient Care STDS, 2009. **23**(1): p. 41-9.

51. Losina, E., et al., *The "ART" of linkage: pre-treatment loss to care after HIV diagnosis at two PEPFAR sites in Durban, South Africa.* PLoS One, 2010. **5**(3): p. e9538.

52. Mugavero, M.J., et al., *From access to engagement: measuring retention in outpatient HIV clinical care.* AIDS Patient Care STDS, 2010. **24**(10): p. 607-13.

53. Mugavero, M.J., W.E. Norton, and M.S. Saag, *Health care system and policy factors influencing engagement in HIV medical care: piecing together the fragments of a fractured health care delivery system.* Clin Infect Dis, 2011. **52 Suppl 2**: p. S238-46.

54. Mugavero, M.J., *Improving engagement in HIV care: what can we do?* Top HIV Med, 2008. **16**(5): p. 156-61.

55. Berg, M.B., et al., *Nonadherence to medical appointments is associated with increased plasma HIV RNA and decreased CD4 cell counts in a community-based HIV primary care clinic.* AIDS Care, 2005. **17**(7): p. 902-7.

56. Giordano, T.P., et al., *Retention in care: a challenge to survival with HIV infection.* Clin Infect Dis, 2007. **44**(11): p. 1493-9.

57. Park, W.B., et al., *One-year adherence to clinic visits after highly active antiretroviral therapy: a predictor of clinical progress in HIV patients.* J Intern Med, 2007. **261**(3): p. 268-75.

58. Feldacker, C., et al., *Who Starts? Factors Associated with Starting Antiretroviral Therapy among Eligible Patients in Two, Public HIV Clinics in Lilongwe, Malawi.* PLoS One, 2012. **7**(11): p. e50871.

59. Granich, R.M., et al., *Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model.* Lancet, 2009. **373**(9657): p. 48-57.

60. Jarvis, J.N., et al., *Testing but not treating: missed opportunities and lost lives in the South African antiretroviral therapy programme.* AIDS, 2010. **24**(8): p. 1233-5.

61. Kranzer, K., et al., *Quantifying and addressing losses along the continuum of care for people living with HIV infection in sub-Saharan Africa: a systematic review.* J Int AIDS Soc, 2012. **15**(2): p. 17383.

62. Lessells, R.J., et al., *Retention in HIV care for individuals not yet eligible for antiretroviral therapy: rural KwaZulu-Natal, South Africa.* J Acquir Immune Defic Syndr, 2011. **56**(3): p. e79-86.

63. Rosen, S. and M.P. Fox, *Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review.* PLoS Med, 2011. **8**(7): p. e1001056.

64. Lawn, S.D., et al., *Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa.* AIDS, 2008. **22**(15): p. 1897-908.

65. Fairall, L.R., et al., *Effectiveness of antiretroviral treatment in a South African program: a cohort study.* Arch Intern Med, 2008. **168**(1): p. 86-93.

66. Bassett, I.V., et al., *Who starts antiretroviral therapy in Durban, South Africa?... not everyone who should.* AIDS, 2010. **24 Suppl 1**: p. S37-44.

67. Mulissa, Z., D. Jerene, and B. Lindtjorn, *Patients present earlier and survival has improved, but pre-ART attrition is high in a six-year HIV cohort data from Ethiopia.* PLoS One, 2010. **5**(10): p. e13268.

68. Amuron, B., et al., *Mortality and loss-to-follow-up during the pre-treatment period in an antiretroviral therapy programme under normal health service conditions in Uganda.* BMC Public Health, 2009. **9**: p. 290.

69. Clouse, K., et al., *Patient retention from HIV diagnosis through one year on antiretroviral therapy at a primary healthcare clinic in Johannesburg, South Africa.* J Acquir Immune Defic Syndr, 2012.

70. Bhatia, R., et al., *Persons newly diagnosed with HIV infection are at high risk for depression and poor linkage to care: results from the Steps Study.* AIDS Behav, 2011. **15**(6): p. 1161-70.

71. Nachega, J.B., et al., *Severe mental illness at ART initiation is associated with worse retention in care among HIV-infected Ugandan adults.* Trop Med Int Health, 2013. **18**(1): p. 53-7.

72. Himelhoch, S. and D.R. Medoff, *Efficacy of antidepressant medication among HIV-positive individuals with depression: a systematic review and meta-analysis.* AIDS Patient Care STDS, 2005. **19**(12): p. 813-22.

73. Patel, V., *Global mental health: from science to action.* Harv Rev Psychiatry, 2012. **20**(1): p. 6-12.

74. Pence, B.W., J.K. O'Donnell, and B.N. Gaynes, *Falling through the cracks: the gaps between depression prevalence, diagnosis, treatment, and response in HIV care.* AIDS, 2012. **26**(5): p. 656-8.

75. Pignone, M.P., et al., *Screening for depression in adults: a summary of the evidence for the U.S. Preventive Services Task Force.* Ann Intern Med, 2002. **136**(10): p. 765-76.

76. MacMillan, H.L., et al., *Screening for depression in primary care: recommendation statement from the Canadian Task Force on Preventive Health Care.* CMAJ, 2005. **172**(1): p. 33-5.

77. Schumacher, J.E., et al., *Routine Depression Screening in an HIV Clinic Cohort Identifies Patients with Complex Psychiatric Co-morbidities Who Show Significant Response to Treatment.* AIDS Behav, 2012.

78. Shacham, E., et al., *Routine screening for depression: identifying a challenge for successful HIV care.* AIDS Patient Care STDS, 2009. **23**(11): p. 949-55.

79. *Incorporating HIV prevention into the medical care of persons living with HIV. Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.* MMWR Recomm Rep, 2003. **52**(RR-12): p. 1-24.

80. Akena, D., D.J. Stein, and J. Joska, *Does Screening HIV-Positive Individuals in Uganda for Major Depressive Disorder Improve Case Detection Rates and Antidepressant Prescription?* AIDS Behav, 2012.

81. Akena, D., et al., *Comparing the accuracy of brief versus long depression screening instruments which have been validated in low and middle income countries: a systematic review.* BMC Psychiatry, 2012. **12**: p. 187.

82. O'Connor, E.A., et al., *Screening for depression in adult patients in primary care settings: a systematic evidence review.* Ann Intern Med, 2009. **151**(11): p. 793-803.

83. Akena, D., et al., *Sensitivity and specificity of a visual depression screening instrument among HIV-positive individuals in Uganda, an area with low literacy.* AIDS Behav, 2012. **16**(8): p. 2399-406.

84. Pence, B.W., et al., *Validity of an interviewer-administered patient health questionnaire-9 to screen for depression in HIV-infected patients in Cameroon.* J Affect Disord, 2012.

85. Chishinga, N., et al., *Validation of brief screening tools for depressive and alcohol use disorders among TB and HIV patients in primary care in Zambia.* BMC Psychiatry, 2011. **11**: p. 75.

86. Monahan, P.O., et al., *Validity/reliability of PHQ-9 and PHQ-2 depression scales among adults living with HIV/AIDS in western Kenya.* J Gen Intern Med, 2009. **24**(2): p. 189-97.

87. Nakimuli-Mpungu, E., et al., *Cross-cultural adaptation and validation of the self-reporting questionnaire among HIV+ individuals in a rural ART program in southern Uganda.* HIV AIDS (Auckl), 2012. **4**: p. 51-60.

88. Spies, G., et al., *Validity of the K-10 in detecting DSM-IV-defined depression and anxiety disorders among HIV-infected individuals.* AIDS Care, 2009. **21**(9): p. 1163-8.

89. Adewuya, A.O., B.A. Ola, and O.O. Afolabi, *Validity of the patient health questionnaire (PHQ-9) as a screening tool for depression amongst Nigerian university students.* J Affect Disord, 2006. **96**(1-2): p. 89-93.

90. Pence, B.W., et al., *Prevalence of psychological trauma and association with current health and functioning in a sample of HIV-infected and HIV-uninfected Tanzanian adults.* PLoS One, 2012. **7**(5): p. e36304.

91. Pinto-Meza, A., et al., *Assessing depression in primary care with the PHQ-9: can it be carried out over the telephone?* J Gen Intern Med, 2005. **20**(8): p. 738-42.

92. Sheehan, D.V., et al., *The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10.* J Clin Psychiatry, 1998. **59 Suppl 20**: p. 22-33;quiz 34-57.

93. Kroenke, K., et al., *The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review.* Gen Hosp Psychiatry, 2010. **32**(4): p. 345-59.

94. Kroenke, K., et al., *Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection.* Ann Intern Med, 2007. **146**(5): p. 317-25.

95. Kessler, R.C., et al., *The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys.* Epidemiol Psichiatr Soc, 2009. **18**(1): p. 23-33.

96. Becker, A.E. and A. Kleinman, *Mental health and the global agenda.* N Engl J Med, 2013. **369**(1): p. 66-73.

97. Vos, T., et al., *Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010.* Lancet, 2012. **380**(9859): p. 2163-96.

98. Wang, P.S., et al., *Use of mental health services for anxiety, mood, and substance disorders in 17 countries in the WHO world mental health surveys.* Lancet, 2007. **370**(9590): p. 841-50.

99. Collins, P.Y., et al., *Grand challenges in global mental health: integration in research, policy, and practice.* PLoS Med, 2013. **10**(4): p. e1001434.

100. Tomlinson, M., et al., *Setting priorities for global mental health research.* Bull World Health Organ, 2009. **87**(6): p. 438-46.

101. Akena, D., et al., *Sensitivity and specificity of clinician administered screening instruments in detecting depression among HIV-positive individuals in Uganda.* AIDS Care, 2013.

102. Smit, J., et al., *Mental health and sexual risk behaviours in a South African township: a community-based cross-sectional study.* Public Health, 2006. **120**(6): p. 534-42.

103. Owe-Larsson, B., et al., *HIV infection and psychiatric illness.* Afr J Psychiatry (Johannesbg), 2009. **12**(2): p. 115-28.

104. Lopes, M., et al., *Gender, HIV status, and psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions.* J Clin Psychiatry, 2012. **73**(3): p. 384-91.

105. Yun, L.W., et al., *Antidepressant treatment improves adherence to antiretroviral therapy among depressed HIV-infected patients.* J Acquir Immune Defic Syndr, 2005. **38**(4): p. 432-8.

106. Elliott, A.J., J. Russo, and P.P. Roy-Byrne, *The effect of changes in depression on health related quality of life (HRQoL) in HIV infection.* Gen Hosp Psychiatry, 2002. **24**(1): p. 43-7.

107. Stein, D.J., et al., *HIV/AIDS in Africa--a role for the mental health practitioner?* S Afr Med J, 2005. **95**(3): p. 167-8.

108. Harris, P.A., et al., *Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support.* J Biomed Inform, 2009. **42**(2): p. 377-81.

109. Gilbody, S., et al., *Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis.* J Gen Intern Med, 2007. **22**(11): p. 1596-602.

110. Manea, L., S. Gilbody, and D. McMillan, *Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis.* CMAJ, 2012. **184**(3): p. E191-6.

111. Kessler, R.C., et al., *Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication.* Arch Gen Psychiatry, 2005. **62**(6): p. 617-27.

112. Gaynes, B.N., et al., *Does a coexisting anxiety disorder predict persistence of depressive illness in primary care patients with major depression?* Gen Hosp Psychiatry, 1999. **21**(3): p. 158-67.

113. Sonis, J., *How to use and interpret interval likelihood ratios.* Fam Med, 1999. **31**(6): p. 432-7.

114. Katon, W.J., *Epidemiology and treatment of depression in patients with chronic medical illness.* Dialogues Clin Neurosci, 2011. **13**(1): p. 7-23.

115. Olde Hartman, T., et al., *Mental health problems and the presentation of minor illnesses: data from a 30-year follow-up in general practice.* Eur J Gen Pract, 2008. **14 Suppl 1**: p. 38-43.

116. Berghofer, A., et al., *Screening for Depression and High Utilization of Health Care Resources Among Patients in Primary Care.* Community Ment Health J, 2014.

117. Cholera R., G.B.N., Pence B.W., Bassett J., Qangule N., Macphail C., Bernhardt S., Pettifor A., and Miller W.C., *Validity of the patient health questionnaire-9 to screen for depression in a high-HIV burden primary healthcare clinic in Johannesburg, South Africa.* Manuscript submitted for publication., 2014.

118. Roura, M., et al., *Provider-initiated testing and counselling programmes in sub-Saharan Africa: a systematic review of their operational implementation.* AIDS, 2013. **27**(4): p. 617-26.

119. Wagner, G.J., et al., *Impact of HIV antiretroviral therapy on depression and mental health among clients with HIV in Uganda.* Psychosom Med, 2012. **74**(9): p. 883-90.

120. Pence, B.W., et al., *Assessing the effect of Measurement-Based Care depression treatment on HIV medication adherence and health outcomes: rationale and design of the SLAM DUNC Study.* Contemp Clin Trials, 2012. **33**(4): p. 828-38.

121. Kessler, R.C., et al., *Screening for serious mental illness in the general population with the K6 screening scale: results from the WHO World Mental Health (WMH) survey initiative.* Int J Methods Psychiatr Res, 2010. **19 Suppl 1**: p. 4-22.