Depression and Engagement in Care Among Newly Diagnosed HIV-Infected Adults in Johannesburg, South Africa

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Abstract Delayed engagement in HIV care threatens the success of HIV treatment programs in sub-Saharan Africa and may be influenced by depression. We examined the relationship between depression prior to HIV diagnosis and engagement in HIV care at a primary care clinic in Johannesburg, South Africa. We screened 1683 patients for depression prior to HIV testing using the Patient Health Questionnaire-9. Among patients who tested positive for HIV we assessed linkage to HIV care, defined as obtaining a CD4 count within 3 months. Among those who linked to care and were eligible for ART, we assessed ART initiation within 3 months. Multivariable Poisson regression with a robust variance estimator was used to assess the association between depression and linkage to care or ART initiation. The prevalence of HIV was 26 % (n = 340). Among HIV-infected participants, the prevalence of depression was 30 %. The proportion of linkage 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). Depression was not associated with engagement in HIV care in this South African primary care setting. Our unexpected findings suggest that some depressed HIV-infected patients might be more likely to engage in care than their counterparts without depression, and highlight the complex relationship between depression and HIV infection. These findings have led us to propose a new framework relating HIV infection, depression, and the population under study.

Keywords Depression · HIV · Engagement in care · Africa

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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 affected 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 detected immediately prior to HIV diagnosis and engagement in HIV care among a cohort of 340 persons presenting for primary care an urban clinic in Johannesburg, South Africa. We hypothesized that HIV-infected patients with depressive symptoms preceding HIV 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. Finally, we designed a conceptual framework to contextualize the complex association between depression and engagement in care among HIV-infected people—this framework is presented in the discussion section of this manuscript.

Methods

Study Setting and Population

Witkoppen Health and Welfare Centre (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 3 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 (12-1730) and the Human Research Ethics Committee at the University of Witwatersrand (M120725) 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]. A 4-point Likert scale is used to rate the severity of each item by asking respondents how often they have experienced the symptom over the past 2 weeks (0 = not at all, 1 = several days, 2 = more than half the days, 3 = nearly every day). The total PHQ-9 score is determined by summing the scores for each item. 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. This tool has been widely utilized in Western settings and in sub-Saharan Africa [29–33]. Additionally, the PHQ-9 was recently validated against the Mini Neuropsychiatric Interview among patients in our study population, and found to have a sensitivity of 78.7 % (95 % CI 64.3–89.3) and specificity of 83.4 % (95 % CI 79.1–87.2) when using the standard cutoff score of $\geq$10 [34]. 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 2 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.

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 [35].

Sample Size

The sample size we aimed to enroll for this study was at least 300 HIV-infected patients in order to have 80 % power to detect a 15 % difference in linkage to care between patients who were depressed versus those who were not depressed. Based on previous estimates in the region we assumed: (1) a 35 % prevalence of depression among HIV-infected individuals, and (2) that 75 % of the population of HIV-infected patients would link to care [19]. We hypothesized that 60 % or less of those patients who were depressed would link to care.

Statistical Analysis

The primary outcome was linkage to care, defined as returning to WHWC for CD4 staging within 3 months of the diagnosis visit [19]. 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. Higher PHQ-9 cutoff scores of 12 and 15 were also considered, with no change in results. 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 3 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 already knew they were HIV positive according to their responses to our study questionnaire. Participants enrolled during the first 2 months of the study were not asked about knowledge of their HIV status. 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.

Of the final 1324 participants, 26 % (n = 340) were HIV-infected. Nearly a quarter of the 1324 participants (22 %) were depressed. Depression was much more common among patients who subsequently tested HIV positive compared to those who tested HIV negative (30.3 vs 19.7 %, $X^2 = 16.6$, $p < 0.0001$). 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 women (54 %). About half of the participants were from South Africa (46 %) while most others were from Zimbabwe (42 %). A third reported drinking any alcohol (32 %) and 59 % were employed. Nearly half (47 %) of the participants self-reported only fair or poor health status. The median baseline CD4 count at HIV diagnosis was 188 cells/mm^3 (IQR 86–345 cells/mm^3); 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 vs 35 years, t-statistic = −2.4, $p = 0.019$). Those who were depressed were also more likely to self-report fair or poor health rather than excellent, very good, or good health ($X^2 = 9.3$, $p = 0.002$). Depressed patients with newly diagnosed HIV infection had a lower mean CD4 count on the date of HIV diagnosis compared to patients who were not depressed (201 vs 264, t-statistic = 2.4, $p = 0.018$) (Table 1).

Overall, three-quarters (75 %) of 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 more likely to report fair or poor health status ($X^2 = 5.0$, $p = 0.026$) and have lower mean CD4 counts (232 vs 295, t-statistic = 2.0, $p = 0.042$) compared to patients who did not link to care (Table 2).

Table 1 Characteristics of the study population by depression

Characteristic	Total study population (n = 340)	Depressive symptoms n (%)	
		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)
# of clinic visits in first 3 months			
HIV diagnosis visit	83 (24.4)	62 (26.2)	21 (20.4)
1	53 (15.6)	38 (16.0)	15 (14.6)
≥2	204 (60.0)	137 (57.8)	67 (65.0)

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) (Table 3).

Among the 185 patients who linked 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. This corresponds to about two-thirds (63 %) of the study population eligible to initiate ART at the time of enrollment initiating treatment within the 6 months after HIV diagnosis. The percentage of depressed and not depressed patients who linked to care and 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.

Table 2 Population characteristics according to linkage to care or ART initiation

Characteristic	Linkage to care (N = 340)			ART initiation (N = 176)		
	n	% Linked to care	*p* value[a]	n	% Initiating ART	*p* value[a]
Age in years						
<30	85	62	0.001	29	83	0.960
30–39	163	78		93	81	
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						
Excellent/very good/good	180	71	0.026	79	85	0.261
Fair or poor	158	81		96	78	
CD4 count						
<100	86	85	0.396	68	78	0.569
100–199	73	78		55	85	
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	

[a] Tests based on Pearson's Chi-square for categorical variables

Table 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[a]			
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[a]			
Depressed (PHQ ≥ 10) vs not depressed (PHQ < 10)	164	1.01	(0.87, 1.17)

[a] Adjusted for age, gender, employment, country of birth, alcohol, perceived health, CD4

We found that underlying depression did not influence subsequent linkage to HIV care or initiation of ART. To our knowledge, this study is the first to assess depression in a primary care population undergoing HIV testing, and is only the second to assess depression before HIV testing results were known.

The primary care context is particularly important for optimizing engagement in HIV care as a large proportion of HIV testing and treatment in sub-Saharan Africa takes place in these settings. Overall we found significant rates of loss to care after HIV testing and CD4 count testing among both depressed and not depressed patients. We observed that depressed patients who actively seek out health care may link to HIV care and initiate ART at rates higher than or comparable to people without depression, although this study did not have enough power to find a statistically significant difference between the two groups. While this population might initially link to HIV care and initiate ART effectively, further work will be required to explore ART adherence, retention in care, and durability of depression among these patients.

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 [26]. In Durban, South Africa, depressive symptoms were very common (prevalence = 55 %) among patients presenting for HIV testing who were also screened for depression [27]. In the Durban 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. However, 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. In contrast, 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 vs 20 %), we did not find a difference in returning to the clinic to obtain a CD4 count or initiating ART. As this study was powered to detect a larger difference in linkage to care than was seen, the null effect may in part be due to limited sample size. However, though are results are not statistically significant they suggest that depressed patients with HIV may link to care at higher or at least similar rates compared to patients who are not depressed, contrary to our original hypothesis. 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 [36, 37]. Because our study population comprised patients who presented to a primary care facility, one explanation for our unexpected findings is that we may have selected for high utilizers who have high rates of depression but are less likely to be lost to HIV care. Our clinic-based study would not capture depressed HIV-infected people who are particularly unmotivated to seek care ("low-utilizers"). These interpretations must be taken in light of our sample size limitations discussed above, and future studies will need to be carefully designed to test the new hypotheses suggested by this work.

The variation in results between our study and the Durban study highlights the complexities inherent in studying depression and engagement in HIV care. Depression is both a cause and an effect of HIV infection, and consequently, depression either 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 (Fig. 1) [38, 39].

The first population (Population 0) in this framework 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 people with HIV infection after 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 in 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.

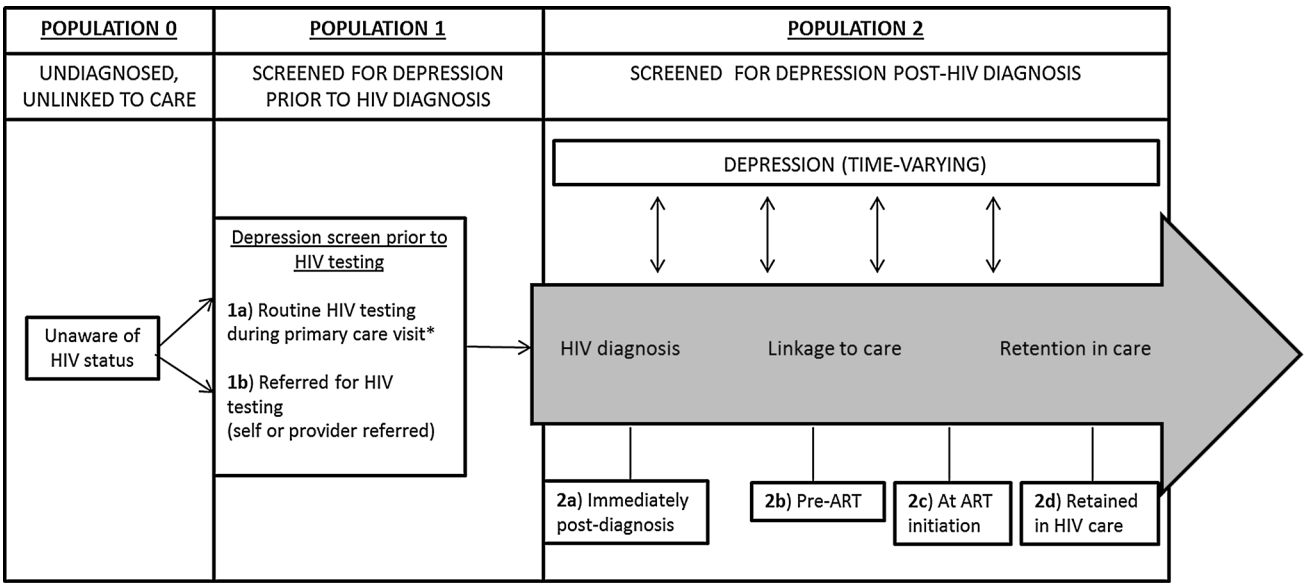

Fig. 1 A population framework to conceptualize the relationship between timing of HIV diagnosis, depression status, and depression screening. *Asterisk* Population included in this study

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 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 [22]. These patients could be experiencing depression as a result of the emotional stress related to coping with their HIV status, or as a sequela 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.

This study emphasizes the difficulty 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 were eligible for ART, a third did not initiate treatment. The HIV-care outcomes of this substantial population will only be improved with carefully designed interventions.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board at the University of North Carolina and the Human Research Ethics Committee at the University of Witwatersrand and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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