Impact of Mental Health on HIV-related Outcomes in a South African Township

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Abstract

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HIV is a leading cause of death in sub-Saharan Africa, and South Africa has the largest number of HIV-infected people in the world. Mental illnesses have a high burden of disease worldwide, with HIV-infected individuals being more vulnerable to experiencing poor mental health. There is limited research exploring the potential effects of mental health on HIV-related outcomes in sub-Saharan Africa. Our objective was to better understand the impact of mental health on the course of HIV treatment and clinical outcomes. We conducted a prospective cohort study among 1,878 HIV-positive adults from the Umlazi township of KwaZulu-Natal, South Africa. We measured depression using the Patient Health Questionnaire (PHQ-9) and anxiety using the Generalized Anxiety Disorder (GAD-7) scale, both of which have been validated in sub-Saharan Africa. We used univariate and multivariate models, adjusted for socio-demographic characteristics, to examine the effects of baseline depression and anxiety on several HIV-related outcomes. In adjusted models, HIV-infected adults with depression had a lower odds of initiating antiretroviral therapy within 90 days of testing positive (OR=0.72 p=0.03), and a slower ART initiation rate throughout the one-year study period (HR=0.84 p=0.01). However, among those who initiated ART, depression was associated with a lower likelihood of missing medication refills (OR=0.66, p=0.04) and missing clinic visits (OR=0.56, p<0.01). Anxiety had a similar effect, with individuals who

reported anxiety symptoms having a lower likelihood of missing clinic visits (OR=0.58, 95% CI=0.40-0.85, $p<0.01$). These results suggest that poor mental health is a significant barrier to initiating care. Once these individuals are engaged in treatment, other mechanisms such as receiving mental health treatment may improve ART adherence. Thus, not only is it important to provide mental health screenings alongside HIV testing, but also more intensive follow-up is required to ensure that these patients are initiating care. Further, integrated care models that offer mental health treatment alongside usual HIV care may improve ART adherence.

Introduction

The 90-90-90 goal is an objective set by the Joint United Nations Programme on HIV/AIDS (UNAIDS) that aims to have 90% of individuals aware of their HIV status, of which 90% initiate treatment, of which 90% should reach viral suppression by the year 2020.[1] Despite recommendations for universal anti-retroviral therapy, regardless of CD4 T-cell count, for HIV-infected people in low- and middle-income countries, many people in LMICs do not achieve viral suppression.[2] Additionally, the global burden of mental health issues has been increasing, with many countries around the world reporting mental disorders more commonly.[3] Given the higher risk of poor mental health among HIV-infected individuals, mental health issues may present barriers that would prevent many countries from achieving the 90-90-90 goal.

Persons living with HIV are more vulnerable to experiencing poor mental health, as compared to those without HIV. HIV-infected individuals have nearly double the risk of depression compared to HIV-uninfected adults.[4] Studies of HIV-infected individuals in sub-Saharan Africa have shown depression and anxiety to be associated with poor treatment-related outcomes such as declining adherence,[5,6] increases in viral load,[7,8] increased risk of suicide,[9] and increased mortality risk.[9] Furthermore, it is still rare for mental health care to be integrated into HIV treatment.[10]

South Africa has nearly seven million HIV-positive persons, accounting for approximately 19% of persons living with HIV globally,[11] and operates the largest antiretroviral treatment (ART) program in the world. However, further efforts still need to be made regarding the initiation of treatment—only 65% of those who knew their HIV status were on treatment and only 26% of HIV+ individuals have achieved viral suppression.[11] Many HIV-infected individuals are still affected by treatment-related issues, such as low retention in care and treatment

adherence.[12] There is limited research assessing the impact of mental health on HIV-related outcomes in low- and middle-income countries, particularly in South Africa. Exploring the relationship between mental health and HIV-care in South Africa may be beneficial in achieving the 90-90-90 goal. Thus, the purpose of this study was to better understand the role of mental health, specifically depression and anxiety, on the course of HIV treatment and clinical outcomes.

Methods

Site and Participants

We conducted a prospective cohort study consisting of HIV-positive adults recruited from the outpatient department of iThembalabantu Clinic in Umlazi Township, South Africa from September 12, 2013 to April 22, 2017. Eligible participants were those who were 18 years of age or older, English or Zulu speaking, HIV seropositive and not receiving ART, and willing and able to provide written informed consent to participate in the study. We excluded those who had confirmed pregnancy, had received anti-fungal therapy within 3 month, had experience with ART, or were unable or unwilling to give informed consent to participate in the study. Ethical approvals were obtained for conducting this study.

Data Collection

A combination of personal information, clinical data, and biological specimens were collected for this study. After research staff determined eligibility and obtained informed consent, participants were enrolled into the study. Basic demographic information and baseline

health-related information, including measurements for depression and anxiety, were collected before HIV testing, so as not to bias the respondent results from receiving HIV testing results.

HIV testing was conducted by the clinic staff following standard of care procedures. Participants who tested positive for HIV were seen by a research nurse, who obtained vital signs and collected biological specimens, which included samples of blood, urine, and sputum. After the research nurse visit, all participants then proceeded with routine medical care for HIV, which includes testing to monitor CD4 and initiation of ART according to South African guidelines.[13] Research staff monitored participants' course of treatment through medical records and conducted follow-up phone calls at 3, 6, and 12 months. Participants were followed for up to 12 months.

Measurement of Exposures: Depression and Anxiety

We assessed depression using the PHQ-9 questionnaire,[14] a 9-item questionnaire asking the participant about his or her depressive symptoms. This measure has been validated for use among populations in sub-Saharan Africa.[16,17] For each item, responses were scored on a 4-point Likert scale (0 for "Not at all" through 4 for "Nearly every day"), with a total range from 0 to 27. The PHQ-9 has standardized categories reflecting levels of symptom severity: none (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27).

We assessed anxiety using the GAD-7,[15] a 7-item questionnaire asking the participant about his or her anxiety symptoms. For each item, responses were scored on a 4-point Likert scale (0 for "Not at all" through 4 for "Nearly every day"), with a total range from 0 to 21. The GAD-7 also has standardized categories reflecting levels of symptom severity: none (0-4), mild

(5-9), moderate (10-14), and severe (15-21). This measure has been validated for use among populations in sub-Saharan Africa.[17]

For the analysis, we assessed depression and anxiety status as binary indicator variables. We used a cutoff of PHQ ≥ 10 to indicate depression and GAD ≥ 10 to indicate anxiety. These are recommended cutoff scores for assessing depression and anxiety in clinical settings, optimizing sensitivity and specificity. These cutoffs are commonly used for measuring mental health in sub-Saharan Africa.[18,19,20]

Outcome Definitions

We recorded the date of ART initiation, and defined linkage to care as initiation of ART within 90 days of the date of testing HIV-positive at the clinic. We defined retained in care as participants who had picked up their medications within the past two months at the 12-month follow-up visit. Research staff recorded whether a participant had missed refilling their ARV medications or missed any clinic visits at any point throughout the study period. We obtained data for follow-up CD4+ cell count and HIV viral load test results closest to the 12-month end of study exit visit. We accessed medical records from local hospitals, including the Prince Mshiyeni Memorial Hospital in Umlazi and the King Edward VIII Hospital at the University of KaZulu-Natal, to record hospitalization events or death. We also matched a participant's South African ID number with the South African death registry to assess mortality at study end.

Statistical Analyses

We used t-tests and chi-square tests to examine associations between cohort demographic characteristics and outcomes. The correlation between depression and anxiety was measured

using Pearson's correlation coefficient. Univariate regression models were used to examine associations between depression and anxiety with outcomes of interest. Cox proportional hazards models were used to analyze time-to-event outcomes (ART initiation, hospitalizations, and death); logistic models were used to analyze binary indicator outcomes (linkage to care, retention in care, missed refills, and missed visits); linear models were used to analyze continuous outcomes (CD4+ cell count and viral load). Cohort demographic characteristics that were significantly associated with depression and anxiety were included in the multivariate models. The analyses were conducted in R (version 3.4.3) through the RStudio interface (version 1.1.419).

Results

Cohort Characteristics

Of 6,749 participants who were enrolled, 1,989 were HIV-positive and also met the inclusion criteria. Among these, we excluded 39 participants did not have data collected for their 12-month follow up visit and 72 participants did not have complete PHQ and GAD entries. Therefore, we included 1,878 participants in this study (Table 1).

The average age of study participants was 33.1 years (SD=9.1). Among this cohort, 1,110 were female (59.1%), most were Zulu (93.1%), and 446 did not complete high school (23.7%). About half were employed (56.5%), and the majority earned less than 2,000 ZAR per month (80%). Not many participants were married (6.8%), and the majority had attended church (80.7%). About half had a normal BMI range (45.7%). The median CD4+ cell count at baseline was 313 cells/mm^3 (IQR=171-484 cells/mm^3). In this cohort, 592 (31.5%) had used alcohol, and 409 (21%) had smoked a cigarette within the past month. (Table 1).

Prevalence of Depression and Anxiety

The prevalence of depression (PHQ >=10) was 15.3% (N=287). The prevalence of anxiety (GAD-7 >=10) was 11.1% (N=210). In this cohort, depression and anxiety were found to be strongly correlated ($r=0.77$, $p < 0.01$), with 166 individuals (8.8%) having both depression and anxiety (Table 1).

On average, participants with depression and anxiety were older (35.2 years and 35.8 years, respectively) than participants without (32.8 years). It was also more common for individuals with depression or anxiety to have higher education and higher income. Approximately 43% and 42.6% of depressed and anxious individuals (respectively) held higher degrees, compared to 38% and 39.5% of individuals without depressive or anxious symptoms. There were also less participants with low income among depression (71.4% vs. 81.5%) and anxiety (68.8% vs.81.3%) groups. Cigarette smoking was only significantly associated with anxiety, with anxious individuals smoking more frequently than those without anxiety (29.2% vs. 20.9%). Clinical characteristics such as BMI and baseline CD4+ cell count also appeared to differ among depression and anxiety groups. There was a higher prevalence of underweight BMI in depressed (12.9%) and anxious (12.9%) individuals compared to those without depression (5.3%) or anxiety (5.6%). Depressed and anxious participants had a, respectively, 57 cells/mm^3 and 69.5 cells/mm^3 lower median CD4+ cell count than those without depression or anxiety.

Depression

In univariate analyses, depression was significantly associated with less likelihood to initiate ART, less likelihood of missing medication of missing medication refills and clinic visits, and lower CD4+ cell count at the end of the study period (Table 4). Depression was associated with a 28% lower odds of being linked to care (OR=0.72, p=0.03) after adjusting for age and sex. Additionally, individuals with depression had 21% lower rate of enrolling into ART within a year after testing positive for HIV (HR=0.79, p<0.01). On average, depressed individuals had a 43.87 lower CD4+ cell count than those without depression (p=0.01). Among those who did initiate ART, multivariate models adjusting for age and sex showed depression to be associated with a lower likelihood of missing refills (OR=0.66, p=0.04) and missing visits (OR=0.58, p<0.01). (Table 4).

Anxiety

Similar to depression, the average CD4+ cell count appeared to be lower among individuals with anxiety compared to those without anxiety (β=-56.86, p<0.01) after adjusting for age and sex. Anxiety did not have a significant association with linkage to care or ART initiation for up to one year, but it was associated with lower odds of missing visits in multivariate analysis (OR=0.58, p<0.01). Anxiety was not found to be significantly associated with other outcomes (Table 4).

Discussion

In this study of HIV-positive adults in the township of Umlazi, South Africa, baseline mental health status prior to HIV testing was found to be associated with several clinical HIV-related outcomes. Depressed individuals were slower to initiate ART and less likely to be linked to

care—defined as initiating ART within 3 months of HIV testing. However, among individuals who had initiated ART, those who reported depressive symptoms were less likely to miss a medication refill or a clinic visit compared to non-depressed individuals. A similar pattern was observed for anxiety, with individuals who reported anxiety symptoms also being less likely to miss a clinic visit once enrolled in treatment. Poor mental health appears to be an initial barrier for patients to engage in care. Although once linked to care, other factors such as receiving mental health treatment may improve ART adherence and lead to better HIV-related outcomes. Thus not only should mental health screening be offered alongside HIV testing, but intensive follow-up efforts need to made immediately after testing to ensure that these patients are engaging in care.

The effect of depression on ART initiation found in this study is consistent with recent studies examining the role of mental health in HIV-care seeking behavior. Findings from other research also show an association between depression and poor linkage to care,[21] as well as delayed initiation of care and treatment.[22] This may be expected, since depression is negatively correlated with patient activation,[23] suggesting that individuals who report depressive symptoms are less likely to actively take steps towards managing their own healthcare. Lower likelihood to initiating care can lead to poorer HIV-related outcomes, such as lower CD4+ cell count—something that was found in this study as well as in other research.[24] Because depression can be a barrier to being linked to care, increased efforts in offering mental health treatment could benefit other areas of HIV care and treatment.

Our findings also demonstrated that depression may be associated with a lower likelihood of missing refills and both depression and anxiety being associated with a lower likelihood of missing visits. Overall, research on mental health and ART adherence in sub-Saharan Africa

have linked depression with poor ART adherence.[25,26,27] However, one scenario in which depressed individuals might actually display higher adherence would be if they were to receive mental health treatment. A number of studies conducted in sub-Saharan Africa have shown that treating depression actually improves ART adherence[28,29,30,31] and clinic attendance.[28] While few patients in our cohort were receiving treatment for depression, this could have impacted engagement in HIV care through more frequent medication refills and clinic visits.

Another possible explanation is that the same personal or interpersonal resources that enables a person with HIV and depression to begin ART treatment may also function to encourage treatment adherence. Recognizing depression or anxiety in a patient could prompt healthcare providers to actively encourage patients to stay engaged in care.

This study had several strengths and limitations. Overall, we had a limited number of hospitalizations and deaths, so we were underpowered to detect significant differences in these outcomes. We also did not routinely collect data on mental health referrals and treatment, but this is known to be extremely low in our study population. Including measures such as these would help to further elucidate the relationships between mental health and HIV-related outcomes. A major strength of the study was measuring depression and anxiety before patients were tested for HIV, the potential bias of knowledge of a positive HIV diagnosis on mental health status was avoided. Additionally, the prospective cohort design enables us to establish the temporal sequence between patient mental health status and subsequent HIV-related outcomes. Finally, the rate of patient follow-up was quite high—only 2% of patients did not have a documented 12-month follow-up visit. Among variables that had missing responses, there were no detectable patterns of missingness associated with other variables or outcomes.

Our results suggest that encouragement and support are needed to promote ART initiation among HIV+ patients who present with mental health symptoms. Starting treatment early is crucial to the care and maintenance of HIV. Reducing delays in early linkage to care could be supported by encouraging same-day initiation of ART and increased follow-up efforts immediately after testing. Understanding the barriers that are keeping patients with depression and anxiety from initiating ART earlier, and further research could explore and identify these potential obstacles. Additionally, future studies that document mental health treatment, social support, and personal motivation will enable us to understand the mechanisms by which patients with depressive and anxious symptoms sustain their involvement in treatment once they have started ART.

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Appendix

Table 1. Cohort characteristics.

Characteristic	Baseline Total (N=1,878) N (%)
Age, mean (SD)	33.1 (9.1)
Sex (female)	
Female	1,110 (59.1)
Male	768 (40.9)
Education	
None (primary not completed)	446 (23.7)
Some high school (but not matric)	639 (34)
Higher degree (university)	793 (42.2)
Employed (>20 hours)	817 (43.5)
Income < 2,000 ZAR/mo	1,484 (80)
Marital status (married)	127 (6.8)
Church attendance (N=1,696)	1,369 (80.7)
Alcohol use within last 30 days	592 (31.6)
Cigarette smoking within last 30 days	409 (21.8)
BMI	
Underweight (<18.5)	121 (6.4)
Normal (18.5-24.9)	858 (45.7)
Overweight (25.0-29.9)	486 (25.9)
Obese (30+)	411 (21.9)
CD4+ cell count at baseline, median (IQR)	313 (171-484)
Depression	
Yes (PHQ=10-27)	287 (15.3)
No (PHQ=0-9)	1,591 (84.7)
Anxiety	
Yes (GAD=10-27)	210 (11.1)
No (GAD=0-9)	1,668 (88.8)
Both depression and anxiety	166 (8.8)

Table 2. Cohort characteristics across mental health status groups.

			Depression			Anxiety
Characteristic	**No (N=1,591)**	**Yes (N=287)**	***p***	**No (N=1,668)**	**Yes (N=210)**	***p***
Age, mean (SD)	32.8 (8.8)	35.2 (10.1)	<0.01	32.8 (8.9)	35.8 (10.3)	<0.01
Sex						
Female	940 (59.1)	170 (59.2)	0.96	988 (59.2)	122 (58.1)	0.80
Male	651 (40.9)	117 (40.8)		680 (40.8)	88 (41.9)	
Education						
None (primary not completed)	419 (26.3)	27 (9.4)	<0.01	428 (25.7)	18 (8.6)	<0.01
Some high school (but not matric)	488 (30.7)	151 (52.6)		530 (31.8)	109 (51.9)	
Higher degree (university)	684 (43.0)	109 (38)		710 (42.6)	83 (39.5)	
Employed	679 (42.7)	138 (48.1)		723 (43.3)	94 (44.8)	
Income <2,000 ZAR/mo	1,284 (81.5)	200 (71.4)	<0.01	1,343 (81.3)	141 (68.8)	<0.01
Marital status (married)	109 (6.9)	18 (6.3)	0.87	107 (6.4)	20 (9.5)	0.14
Church attendance (N=1,696)	1,398 (80.1)	1,667 (85.4)	0.09	1400 (80.8)	1,665 (80.3)	0.96
Alcohol use within last 30 days	498 (31.5)	94 (33.0)	0.64	524 (31.5)	68 (32.4)	0.78
Cigarette smoking within last 30 days	334 (21)	75 (26.3)	0.05	348 (20.9)	61 (29.2)	0.008
BMI						
Underweight (<18.5)	84 (5.3)	37 (12.9)	<0.01			<0.01
Normal (18.5-24.9)	729 (45.8)	129 (44.9)		754 (45.2)	104 (49.5)	
Overweight (25.0-29.9)	421 (26.5)	65 (22.6)		443 (26.6)	43 (20.5)	
Obese (30+)	356 (22.4)	55 (19.2)		376 (22.5)	35 (16.7)	
CD4+ cell count at baseline, median (IQR)	321 (163.5-478.5)	264 (124.3-404.8)	<0.01	320.5 (162.8-478.3)	251 (122-380)	<0.01

Table 3. Distribution of outcome characteristics across depression groups.

Characteristic	**Total**	**Depression**			**Anxiety**		
	(N=1,878)	**No (N=1,591)**	**Yes (N=287)**	***p***	**No (N=1,668)**	**Yes (N=210)**	***p***
Linkage to care (ART initiation within 3 months), (N=1,714)	1,277 (74.5)	1,094 (75.1)	183 (71.2)	<0.01	1,136 (74.7)	141 (73.1)	0.36
ART Initiation by 12 months (N=1,727)	1,408 (81.5)	1,197 (81.6)	211 (81.2)	<0.01	1,245 (81.2)	163 (84.0)	0.39
Missed refills (N=1,389)	283 (20.4)	253 (21.4)	30 (14.7)	<0.01	260 (21.1)	23 (14.6)	<0.01
Missed visits (N=1,698)	557 (32.8)	500 (34.6)	57 (22.5)		514 (30.8)	43 (20.5)	<0.01
Retention in care at 12 months (N=1,694)	1,067 (63.0)	910 (62.9)	157 (63.3)	0.96	952 (63.1)	115 (62.2)	0.86
CD4 (end), median (IQR)	345 (192-508)	349 (191.8-506.3)	327 (180-474)	<0.01	350 (191.3-508.8)	300.5 (167.4-433.6)	<0.01
Viral load[1] (end), mean (SD)	5.66 (2.12)	5.70 (2.17)	5.45 (1.84)	0.03	5.68 (2.15)	5.50 (1.86)	0.19
Hospitalized	45 (5.0)	38 (5.2)	7 (4.0)	0.66	39 (5.0)	6 (4.6)	0.99
Mortality	52 (2.8)	41 (2.6)	11 (3.8)	0.93	43 (2.6)	9 (4.3)	0.4

[1]Log-transformed viral load

Table 4. Associations between mental health status and categorical outcomes.

	Depression				Anxiety			
	Univariate		**Multivariate[1]**		**Univariate**		**Multivariate[1]**	
	OR	***p***	**OR**	***p***	**OR**	***p***	**OR**	***p***
Linkage to care	0.82 (0.61-1.1)	0.18	0.72 (0.53-0.98)	0.03	0.92 (0.65-1.29)	0.62	0.79 (0.56-1.12)	0.19
Missed refills	0.63 (0.42-0.96)	0.03	0.66 (0.43-0.99)	0.04	0.64 (0.4-1.02)	0.06	0.67 (0.42-1.08)	0.09
Missed visits	0.55 (0.4-0.75)	<0.01	0.58 (0.43-0.80)	<0.01	0.57 (0.4-0.81)	<0.01	0.61 (0.43-0.89)	<0.01
Retention in care	1.01 (0.77-1.34)	0.9102	0.97 (0.73-1.29)	0.84	0.96 (0.7-1.32)	0.80	0.91 (0.66-1.25)	0.55
	HR	***p***	**HR**	***p***	**HR**	***p***	**HR**	***p***
ART initiation	0.84 (0.72-0.97)	0.01	0.81 (0.70-0.95)	<0.01	0.93 (0.79-1.09)	0.36	0.91 (0.77-1.07)	0.24
Hospitalization	0.72 (0.3-1.7)	0.4481	0.66 (0.28-1.58)	0.35	1.0 (0.42-2.37)	0.99	0.94 (0.39-2.24)	0.88
Death	1.37 (0.68-2.75)	0.381	1.15 (0.87-0.57)	0.69	1.74 (0.84-3.6)	0.13	1.43 (0.69-3.00)	0.33
	β	***p***	**β**	***p***	**β**	***p***	**β**	***p***
CD4+ count	-52.16 (-87.18, -17.14)	<0.01	-43.87 (-78.73, -9.01)	0.01	-64.56 (-104.3, -24.8)	<0.01	-53.86 (-93.71, -14.00)	<0.01
Viral load[2]	-0.26 (-0.50, -0.02)	0.03	-0.23 (-0.47-0.01)	0.06	-0.18 (-0.45, 0.09)	0.18	0.14 (-0.42-0.13)	0.30

[1]Adjusted for age and sex.
[2]Log-transformed viral load.

Figure 1A. Distribution of PHQ-9 scores of study participants at baseline.

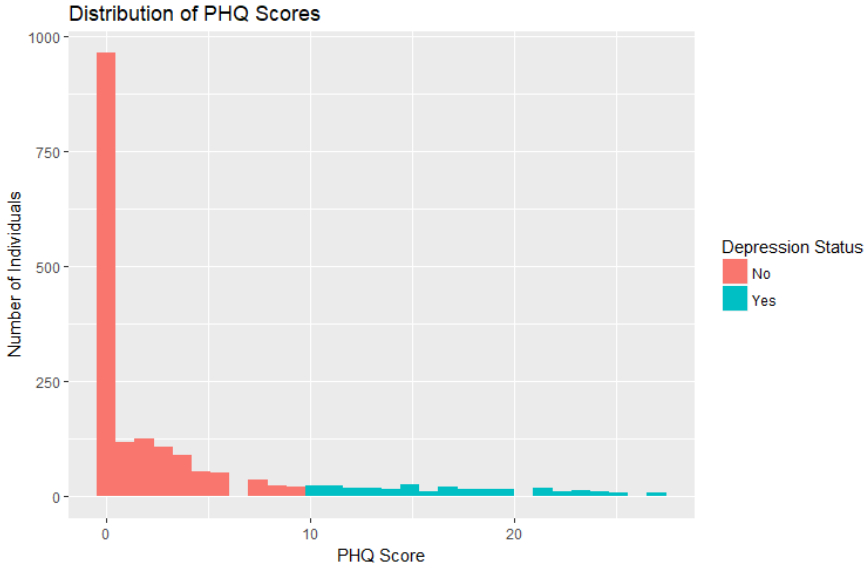

Figure 1B. Distribution of GAD-7 scores of study participants at baseline.

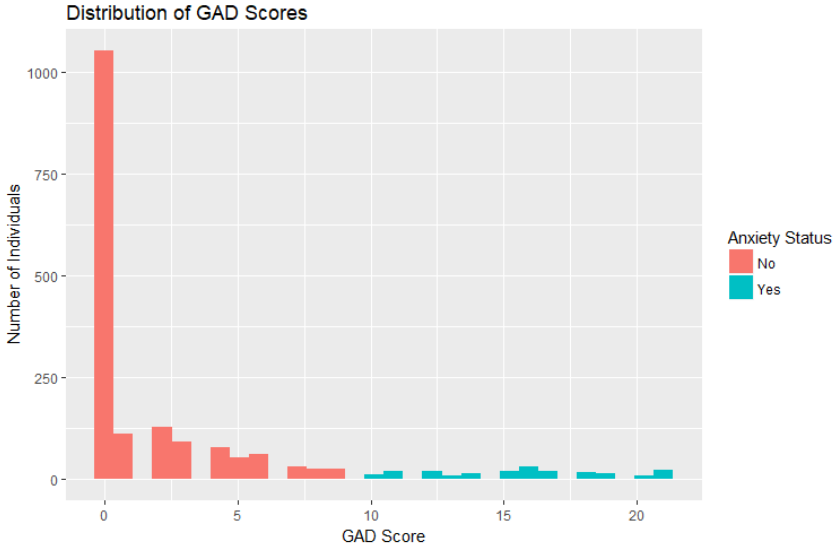

Figure 2A. ART initiation across depression status.

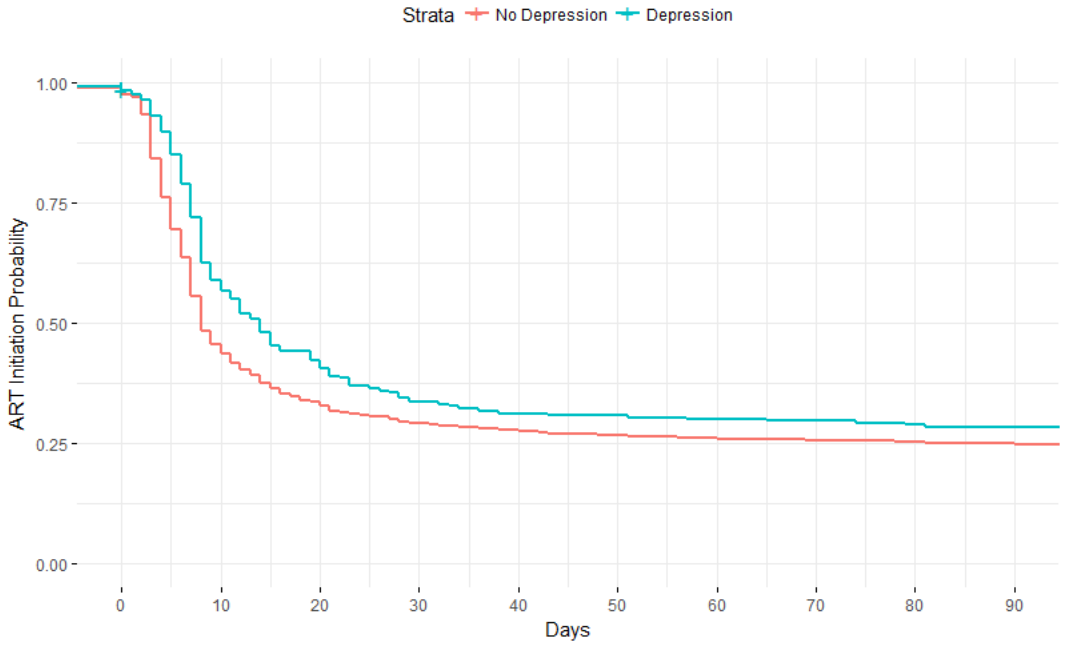

Figure 2B. ART initiation across anxiety status.