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ORIGINAL PAPER

Psychiatric Comorbidity of Unipolar Mood, Anxiety, and Trauma Disorders Prior to HIV Testing and the Effect on Linkage to Care Among HIV-Infected Adults in South Africa

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Abstract
Psychiatric comorbidity, the presence of two or more psychiatric disorders, leads to worse HIV outcomes in the United States; this relationship has not been studied in sub-Saharan Africa. We conducted a preliminary study to describe the prevalence of psychiatric comorbidity (unipolar mood, anxiety, and trauma disorders) among 363 adults *prior* to HIV testing at Witkoppen Health and Welfare Centre, a primary care clinic in Johannesburg, South Africa. We also examined whether psychiatric comorbidity predicted subsequent linkage to HIV care 3 months later. Prevalence of psychiatric comorbidity prior to HIV testing was approximately 5.5%. In the final HIV-positive subsample ($n=76$), psychiatric comorbidity of unipolar mood, anxiety, and trauma disorders did not predict linkage to care [adjusted relative risk = 1.01 (0.59, 1.71)] or number of follow-up appointments (adjusted relative risk = 0.86 (0.40, 1.82)]. A similar psychiatric profile emerged for HIV-positive and HIV-negative individuals before becoming aware of their HIV status. The psychiatric burden typically seen in HIV-positive individuals may manifest over time.

Keywords Psychiatric comorbidity · Psychiatric disorders · HIV · Linkage to care · South Africa

Introduction

Up to one-third of HIV-infected people in sub-Saharan Africa meet criteria for clinical levels of depression, the most common psychiatric disorder [1]. Depression is associated with a number of negative outcomes along the HIV care continuum, including an increased likelihood of non-adherence to antiretroviral therapy (ART) [1] and faster HIV disease progression [2]. Psychiatric comorbidity, the co-occurrence of psychiatric disorders, is common in HIV-infected populations in the United States [3–8] and is associated with more HIV symptoms [3], prolonged time to ART initiation [9], and poorer ART adherence [7], compared to patients with just one psychiatric disorder. HIV-infected people with psychiatric comorbidity may require more complex management strategies. But psychiatric comorbidity has typically been assessed years after HIV diagnosis, making it difficult to tease apart the independent effect of psychiatric morbidity on HIV outcomes from the known negative effects of HIV status on psychiatric well-being, through factors such as stigma and discrimination [10].

The current study had two related goals. The first goal was to describe the prevalence of psychiatric disorders (unipolar mood, anxiety, and trauma) and psychiatric comorbidity in adults undergoing HIV testing in a South African primary care setting, immediately *prior* to being tested for HIV. We hypothesized that rates of psychiatric comorbidity in the HIV-infected group would be significantly higher than in the HIV-uninfected group, given that some lifestyle factors such as alcohol use [11, 12] or relationship violence [13, 14] have an association with acquiring HIV and meeting

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criteria for various psychiatric disorders. Our second goal was to examine how psychiatric comorbidity prior to HIV testing affects HIV outcomes, specifically, linkage to care. Previous work with a similar sample examined the role of depression prior to HIV diagnosis in predicting linkage to care [15]. We wanted to extend this work by understanding how psychiatric comorbidity prior to HIV diagnosis would impact linkage to care, given the high levels of psychiatric comorbidity observed in HIV-positive samples in the United States. We hypothesized that greater psychiatric comorbidity would result in reduced likelihood of linkage to care, given previous research demonstrating a link between psychiatric comorbidity and worse HIV-related outcomes.

Methods

Participants

The study sample comprised a randomly selected subset of 397 patients who were participating in a larger study on depression screening in a primary care setting and completed a diagnostic interview for psychiatric diagnoses [16]. Patients selected for the larger study were recruited between September 2012 and April 2013 and were undergoing routine HIV Counseling and Testing (HCT) at Witkoppen Health and Welfare Centre, a high-volume primary care clinic in Johannesburg, South Africa. The clinic provides comprehensive services predominantly to persons living in densely-populated peri-urban formal and informal settlements. Patients who present to Witkoppen are provided with opt-out provider-initiated HCT if they have an unknown HIV status or tested HIV negative more than 3 months previously.

Participants were eligible for the current study if they were at least 18 years old, presented to the clinic for any reason, had an unknown HIV status at the time of testing (i.e., were tested as HIV-negative more than 3 months prior or were unaware of their status), 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. People who endorsed acute suicidal ideation during study enrolment were excluded and referred for immediate assistance ($n=5$). People with previously known HIV status or receiving care elsewhere ($n=22$) or indeterminate status ($n=27$) after HCT were excluded from the analysis.

Procedure

Eligible patients attending the primary care clinic were randomly selected each day and invited to participate in the study prior to undergoing HCT. A total of 1681 participants completed a questionnaire on depressive symptoms, of which 397 individuals were randomly selected to participate in diagnostic interviews. The diagnostic interviews were completed in the participants' language of choice and were conducted by health care professionals who were trained in the use of the Mini International Neuropsychiatric Interview (MINI). After completing the interviews, participants underwent HIV testing using rapid HIV tests. Individuals who tested positive for HIV using two rapid dry blood spots had blood drawn for CD4 testing that day and were also registered at the HIV clinic. These patients received counseling regarding their results and were 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 the clinic's electronic record database. The study was granted ethics approval at the University of North Carolina in the United States and University of Witwatersrand in South Africa. Informed consent was obtained for all individual participants included in the study.

Measures

Psychiatric Comorbidity

The MINI [17] was used to identify the presence of psychiatric diagnoses at enrollment. The MINI is a brief structured diagnostic interview and has been successfully used with South African populations [18–20]. We assessed the following diagnoses: major depressive disorder (MDD), posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), social anxiety disorder, and panic disorder.[1] Clinicians who administered the MINI underwent a 90-minute training via Skype with both a research psychiatrist and a depression care manager, who as a team have had experience in training multiple researchers in use of the MINI. Clinicians then practiced using the diagnostic modules in role-play scenarios in a 2-hour training session, after which questions were discussed with the trainers in follow-up sessions. The study PI reviewed MINIs weekly for quality control. Participants who met criteria for two or more psychiatric diagnoses were considered to have psychiatric comorbidity.

Linkage to Care

Because all participants who were HIV-infected were newly diagnosed as part of the study, we were able to examine whether participants returned to the clinic for subsequent

[1] Bipolar disorder was also assessed, but only two participants met diagnostic criteria (out of $N=348$) so it was not included as a diagnostic category in the analysis.

Table 1 Sample demographic information by HIV status

Variable	*N*		HIV− (*N* = 256) *n* (%)	HIV+ (*N* = 92) *n* (%)	*p* value
	HIV−	HIV+			
Age *M* (SD)	256	92	37.81 (12.61)	34.97 (8.10)	0.04
Female	256	92	103 (40.2)	41 (44.6)	0.47
Employed	228	89	152 (66.7)	54 (60.7)	0.32
SA country of origin	245	92	127 (51.8)	39 (42.4)	0.12
Language	249	92			0.006
English			96 (38.6)	27 (29.4)	
Xhosa or Zulu			92 (37.0)	52 (56.5)	
Sotho, Tswana, Sepedi			59 (23.7)	12 (13.0)	
Other			2 (0.80)	1 (1.1)	
Health status	255	90			0.04
Excellent			45 (17.7)	12 (13.3)	
Very good			44 (17.3)	8 (8.9)	
Good			92 (36.1)	32 (35.6)	
Fair			49 (19.2)	20 (22.2)	
Poor			25 (9.8)	18 (20.0)	
Hazardous/harmful alcohol use (AUDIT-C)	255	90	57 (22.4)	24 (26.7)	0.41
At least weekly use of other substances	255	90	19 (7.5)	4 (4.4)	0.33
CD4 count *M* (SD)	–	81	–	224.90 (202.82)	

medical appointments related to their HIV care. Linkage to care was defined as an individual returning to the clinic for CD4 staging within 3 months of the initial diagnosis visit, consistent with previous studies [15, 21]. A secondary measure of linkage to care was assessing the number of times each person visited the clinic in the 3 months following his or her diagnostic HIV test. The total number of visits included their initial diagnostic test visit.

Health Status

During their initial clinic visit (study baseline), participants self-reported their overall health status, which was scored on a 5-point Likert scale ranging from 0 *(Excellent)* to 5 *(Poor).* For the purposes of the analyses, participants with either *excellent*, *very good,* or *good* health were combined and those reporting their health to be either *fair* or *poor* were also combined.

Statistical Analysis

The primary outcome of interest was linkage to care at 3-month follow-up (measured dichotomously and as a count variable with the number of appointments attended) and the main explanatory variable of interest was psychiatric comorbidity, assessed immediately prior to HIV testing. Covariates of interest included in the multivariate analyses were age, gender, employment status, perceived health status, and baseline CD4 count. Age and CD4 count were continuous, whereas all other variables were treated as categorical. A Poisson regression with robust error variance and no offset was used to estimate relative risk ratios (RRs), adjusted risk ratios (aRRs), and 95% confidence intervals (CIs) for the model predicting dichotomous linkage to care. The model predicting number of follow-up appointments was assessed using a zero-truncated negative binomial regression model with no offset, which is appropriate for data where the outcome excludes zeros. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

Of the 348 patients with psychiatric diagnostic data and who met eligibility criteria, 92 (26.4%) were HIV-positive and 256 (73.6%) were HIV-negative after completing routine HCT at the clinic. People with HIV were younger, spoke Xhosa or Zulu as their primary language, and their self-reported health status was poorer than HIV-negative persons (Table 1). Overall, 16.4% of the sample ($n = 57$) met diagnostic criteria for at least one psychiatric disorder (Table 2). Depression was most prevalent for both groups (15% for HIV-positive, 9% for HIV-negative). Social anxiety (4%) and PTSD (4%) were second and third most prevalent in the HIV-positive group while GAD (5%) and PTSD (5%) had the second and third highest prevalence in the HIV-negative group. There were no statistically significant differences between the HIV-positive and HIV-negative groups in the

Table 2 Prevalence of psychiatric disorders and psychiatric comorbidity in HIV–uninfected and HIV-infected Individuals

Disorder	HIV − ($N=256$) *n* (%)	HIV+ ($N=92$) *n* (%)	Prevalence ratio [95% CI]
None	216 (84)	75 (82)	
At least 1 disorder	40 (16)	17 (19)	1.18 [0.71, 1.98]
Major depressive disorder	22 (9)	14 (15)	1.77 [0.95, 3.31]
Posttraumatic stress disorder[a]	13 (5)	4 (4)	0.87 [0.23, 2.59]
Any anxiety disorder	22 (9)	5 (5)	0.63 [0.25, 1.62]
Generalized anxiety disorder[b]	12 (5)	1 (1)	0.24 [0.03, 1.81]
Social anxiety disorder	6 (2)	4 (4)	1.86 [0.54, 6.43]
Panic disorder	5 (2)	3 (3)	1.67 [0.41, 6.85]
Subsample with psychiatric disorders	$n=40$	$n=17$	
1 disorder only (any)	26 (65)	12 (71)	
2 + disorders (psychiatric comorbidity)	14 (35)	5 (29)	0.84 [0.36, 1.96]

Prevalence ratios compare HIV-positive group to HIV-negative group

[a]$N=91$ for HIV+ group

[b]$N=89$ for HIV+ group

$N=255$ for HIV− group

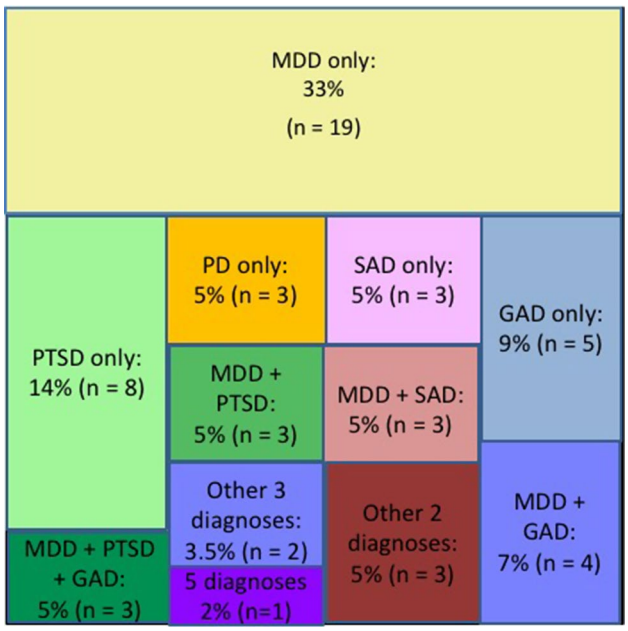

Fig. 1 Visual representation of psychiatric diagnoses and comorbidity in entire sample with at least one psychiatric disorder ($n=57$). *MDD* major depressive disorder, *PTSD* posttraumatic stress disorder, *PD* panic disorder, *SAD* social anxiety disorder. Other 2 diagnoses are: MDD + PD ($n=1$); PTSD + PD ($n=1$); PD + SAD ($n=1$). Other 3 diagnoses are: MDD + PTSD + SAD ($n=1$); MDD + PD + SAD ($n=1$)

prevalence of any given disorder. However, the prevalence ratio of depression in the HIV-positive group was 1.77 [95% CI (0.95, 3.31)] times larger than in the HIV-negative group. Similarly, the prevalence ratio of social anxiety in the HIV-positive group was 1.86 times larger [95% CI (0.54, 6.43)] than the analogous rates in the HIV-negative group.

Of those with a psychiatric disorder, 33.3% ($n=19$) had psychiatric comorbidity—that is, they met diagnostic criteria for two or more of the disorders assessed (Fig. 1). There was no difference in the prevalence of psychiatric comorbidity between the HIV-positive group and the HIV-negative group, with a prevalence ratio of 0.84 [95% CI (0.36, 1.96)].

Psychiatric comorbidity, with respect to unipolar mood, anxiety, and trauma disorders, was subsequently examined as a predictor of dichotomous linkage to care and number of follow-up clinic visits in the HIV-positive group. Results of these analyses are presented in Table 3. The proportion of patients who linked to care within 3 months was 80% for those with psychiatric comorbidity and 65% for those without any psychiatric disorder [unadjusted RR = 1.22, 95% CI (0.77, 1.96)]. In a multivariate model adjusted for potential confounders ($n=76$ in the final model due to some missing data), psychiatric comorbidity was not associated with linkage to care [adjusted RR = 1.01, 95% CI (0.59, 1.71)]. With regard to number of follow-up appointments attended, those with psychiatric comorbidity attended on average 3.20 ($SD=1.64$) and those without any psychiatric disorder attended on average 3.17 ($SD=2.19$) [unadjusted RR = 1.01, 95% CI (0.38, 2.72)]. In the multivariate model adjusted for potential confounders, psychiatric comorbidity was also not associated with number of follow-up appointments [adjusted RR = 0.86, 95% CI (0.40, 1.82)].[2]

[2] We also ran models for both outcomes using depressive symptoms as a predictor instead of psychiatric comorbidity and results were unchanged. Results of these analyses can be obtained from the first author.

Table 3 Predicting linkage to care from psychiatric comorbidity and other covariates in HIV-infected individuals

Characteristics	Returned to clinic for staging appointment (y/n)				Number of follow-up appointments			
	RR	95% CI	ARR	95% CI	RR e^b	95% CI	ARR e^b	95% CI
Psychiatric comorbidity								
1 diagnosis	0.76	[0.43, 1.37]	0.85	[0.49, 1.47]	1.00	[0.51, 1.94]	1.09	[0.61, 1.95]
2 + diagnoses	1.22	[0.77, 1.96]	1.01	[0.59, 1.71]	1.01	[0.38, 2.72]	0.86	[0.40, 1.82]
Age	1.00	[0.98, 1.02]	1.00	[0.98, 1.02]	1.00	[0.98, 1.03]	1.00	[0.98, 1.02]
Male	0.95	[0.70, 1.29]	1.13	[0.86, 1.48]	0.88	[0.56, 1.37]	1.11	[0.77, 1.61]
Employed[a]	0.90	[0.67, 1.22]	0.90	[0.69, 1.18]	1.01	[0.64, 1.60]	0.99	[0.68, 1.44]
Fair/poor health status[b]	1.37	[1.01, 1.85]	1.17	[0.88, 1.53]	1.53	[1.00, 2.33]	1.22	[0.85, 1.76]
CD4 (per 100)[c]	0.94	[0.86, 1.02]	0.95	[0.88, 1.03]	0.86	[0.78, .96]	0.88	[0.79, 0.98]

The sample size for the univariate models was 92 unless otherwise specified. The sample size was 76 for the multivariate models

RR risk ratio in univariate model, *ARR* adjusted risk ratio in multivariate model, *CI* confidence interval

[a] $N = 87$

[b] $N = 90$

[c] $N = 81$

Discussion

This study contributes to the limited evidence describing psychiatric comorbidity in people living with HIV in sub-Saharan Africa [22]. Prior studies have observed an increased psychiatric burden in HIV-infected people, compared to HIV-uninfected persons [23]. The rate of having at least one psychiatric disorder in the study's HIV-positive sample was 19%; about 5.5% of the entire HIV-positive group met criteria for psychiatric comorbidity (i.e., 2 or more disorders), with respect to unipolar mood, anxiety, and trauma disorders, which were assessed as part of the study. Previously documented rates of psychiatric comorbidity in sub-Saharan Africa range from 32 to 40% [19, 24], though these samples include studies that selected participants on the basis of having a particular psychiatric disorder (e.g., meeting criteria for PTSD), which likely results in higher rates of psychiatric comorbidity. In our sample, of the people who met criteria for a diagnosable disorder, 29% had psychiatric comorbidity.

With regard to the documented rates of individual psychiatric disorders for HIV-positive people in the literature, rates are generally high, ranging between 13–69% for depression [1, 25], 4–26% for PTSD [18, 19, 26–28], 1–3% for social anxiety disorder [26–28], and 0.5–7% for GAD [18, 26–29]. Although the prevalence of depression, social anxiety, and panic disorder trended higher in the HIV-positive subsample in this study, there was no statistically significant difference in the prevalence of any psychiatric disorders or the level of psychiatric comorbidity between the HIV-positive and HIV-negative groups. We assessed psychiatric disorders and comorbidity immediately *prior* to HIV testing, rather than at a time point after diagnosis as most other studies have done [4–8]. We hypothesized that HIV-infected persons would be more likely to have a psychiatric diagnosis due to overlapping risk factors for HIV and psychopathology. However, our findings, which should be viewed as preliminary, suggest that without awareness of one's HIV status, the level of observed psychiatric burden may be similar between HIV-infected and HIV-uninfected persons. It is important to note that South Africa has a generalized HIV epidemic, in contrast to countries like the United States or other high income Western countries where HIV transmission is concentrated in key populations [30]. Psychiatric disorders, alongside other syndemic factors, may play a larger role in increasing HIV risk behaviors in these key populations in non-generalized HIV epidemics [31]. Future studies examining psychiatric comorbidity prior to HIV diagnosis in non-generalized HIV epidemics may find a different pattern of results.

Our results, taken together with previous research demonstrating consistently more psychiatric disorders in HIV-infected adults measured after HIV diagnosis, suggest that the psychiatric burden experienced by this group may be primarily related to the knowledge of being HIV positive. It is possible that the presence of HIV makes an individual more biologically vulnerable to having a psychiatric disorder [32]. However, the psychosocial stressors that follow an HIV diagnosis, such as the process of disclosure and potential rejection from family, friends, and community members [33], experiences of discrimination and stigma [10, 34], and managing a chronic disease [35] make learning about an HIV diagnosis a time of high stress and low support; stress

and lack of social support are both known risk factors for psychopathology [36].

However, it should be noted that this study had a relatively small sample size of HIV-positive individuals, limiting the power to discern differences between the HIV-positive and HIV-negative groups. The HIV-positive group had prevalence ratios for psychiatric disorders that were 1.5–2 times larger than the HIV-negative group, suggesting that there may be increased psychiatric morbidity in this group but that this study was not adequately powered to detect. Future research should use larger samples of HIV-positive individuals to further evaluate this question.

In addition, we did not assess all common groups of psychiatric disorders, including substance use disorders, psychotic spectrum disorders, obsessive–compulsive disorders, or eating disorders, a limitation of the current study. We did, however, screen for substance use (although not a formal diagnostic assessment) and found that almost 27% of the HIV-positive sample had hazardous/harmful alcohol use and about 4.5% used other substances weekly, which may indicate the possibility of a diagnosable substance use disorder [37]. Thus, our rates of psychiatric comorbidity, which included an assessment of only five psychiatric disorders, are likely underestimated. Similarly, we excluded five participants with acute suicidal ideation who may have had greater psychiatric comorbidity. Future research should find ways to ethically include individuals with acute suicidal ideation in order to more accurately assess the full extent of psychiatric burden in this population.

These findings highlight the importance of the time after receiving an HIV-positive diagnosis for individuals' mental health. Post-test counseling is therefore an important tool, which should include an assessment of the presence of underlying mental health problems [38]. Our results additionally suggest that the high burden of mental health problems among HIV-infected populations are more likely to emerge in the time period following a diagnosis, which would necessitate extensive longitudinal mental health evaluation after HIV diagnostic services. One example of possible post-test interventions can be found in Project Accept (HPTN 043), which had a cadre of interventions that patients could access including information sharing group sessions, psychosocial support groups, crisis counseling, coping effectiveness training workshops, and stigma reduction workshops [39]. Integrating ongoing mental health services into HIV care may provide better care overall, though research on this topic is limited [40].

We did not find an association between pre-test psychiatric comorbidity, with respect to unipolar depression, anxiety, and trauma disorders, and linkage to care or number of follow-up clinic appointments. Several studies in the United States have found that psychiatric comorbidity is related to worse HIV outcomes, including a greater number of symptoms [3], prolonged time to ART initiation [9], and poorer ART adherence [7]. Although we examined a different HIV outcome, we expected a similar pattern to emerge. It is interesting to note that in this study, the subgroup with psychiatric comorbidity had a linkage to care rate of 15 percentage points greater than those without any psychiatric disorder. Although this was not statistically significant, it is possible that individuals with psychiatric disorders were already linked to care for other physical health concerns, given the physical symptoms that occur alongside, or as part of, psychiatric disorders [41, 42].

Relatedly, all individuals in the study received their HIV test while accessing care at a primary care clinic, as opposed to home-based testing, for example. Already being linked to a healthcare system may have reduced the burden of linkage for HIV care. These ideas fit with the population framework put forth by Cholera and colleagues, who suggest that where a patient is in the HIV care continuum (unaware of HIV status through retention in care) matters in terms of how mental health problems affect patient behavior [15]. A longer prospective study, ideally studying individuals in the community before they have accessed care, is needed to clarify the role of intervening variables that might influence psychiatric comorbidity from the time of HIV diagnosis through viral suppression in South Africa. The current research builds on these previous studies by being the first study in sub-Saharan Africa to examine the influence of psychiatric comorbidity on linkage to care for HIV-positive individuals.

One major difference between the current investigation and previous studies on this topic is that patients in the current study completed their psychiatric assessment immediately prior to being diagnosed with HIV. Since previous investigations have studied patients who were already aware of their HIV status, it suggests a different population under investigation. The newly diagnosed patients in this study may not yet have experienced the unique social stressors associated with HIV (e.g., stigma and discrimination, loss of social support), which may explain why the underlying psychiatric comorbidity, with respect to unipolar mood, anxiety, and trauma disorders, was not associated with linkage to care. It is possible that the psychiatric comorbidity that develops or is maintained after an HIV diagnosis is the important variable, rather than pre-test psychiatric comorbidity. Furthermore, the study assessed linkage to care using a standard definition of returning to the clinic for a CD4 staging visit within 3 months. However, this approach does not capture patients who are higher functioning at the time of diagnosis and may return to care after a longer period of time (i.e., when they become sick) or patients who transferred HIV care to another clinic, which occurs in 5–55% of patients who are believed to be lost to follow-up [43].

Overall, this study is the first to examine psychiatric comorbidity among people undergoing HIV testing

in sub-Saharan Africa. This investigation has several strengths including use of the gold standard diagnostic measure for assessing psychiatric disorders, use of an HIV-negative control group to compare prevalence of psychiatric disorders and comorbidity, and longitudinal data to create temporal precedence when assessing HIV outcomes. The results suggest that HIV-infected and uninfected people in a generalized HIV epidemic setting have a similar psychiatric profile before becoming aware of their HIV status and that psychiatric comorbidity, with respect to unipolar mood, anxiety, and trauma disorders, is not predictive of linkage to care. Study findings should be viewed as preliminary and future studies with larger samples should replicate these results. The findings suggest that other intervening factors after diagnosis may influence the development of greater psychiatric burden typically observed in HIV-positive people. This study lays the groundwork for future research to determine the development and trajectory of psychiatric comorbidity over time in HIV-positive individuals living in sub-Saharan Africa.

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Compliance with Ethical Standards

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

Research Involving in Human and Animal Rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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