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ORIGINAL PAPER

Depressive Symptoms Before and After Antiretroviral Therapy Initiation Among Older-Aged Individuals in Rural Uganda

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Abstract

This study aims to characterize associations between depression symptom severity and HIV infection, both prior to and in years after ART initiation, among older adults. The Ugandan Non-Communicable Diseases & Aging Cohort Study (UGANDAC) is a study of 154 PLWH on ART and 142 community-based, HIV-negative controls. The Hopkins Checklist (HSCL), a 15-item depression scale, was used to screen for depression. We estimate differences in depressive symptoms by HIV and ART status and use multivariable log binomial regression to quantify differences in probable depression between PLWH on ART. HIV-infected and HIV-uninfected participants had a similar age (mean 52.0 vs. 51.9, p = 0.854) and sex distribution (47.4 vs. 47.9% female, p = 0.934). PLWH on ART had lower depression symptom severity than HIV-uninfected controls (mean score: 1.50 vs. 1.60, p = 0.006) and a lower prevalence of probable depression (21.4 vs. 33.8%, p = 0.017). Among 102 PLWH with pre-ART depression screening scores available, their mean depression symptom severity was similar to HIV-uninfected participants (mean 1.56 vs. 1.60, p = 0.512). In adjusted models, PLWH on ART had a lower prevalence of probable depression than HIV-negative controls [adjusted prevalence ratio: 0.68 (95% CI 0.47–0.99)]. In an observational cohort of PLWH over 40 on long-term ART and matched, community-based HIV-uninfected controls in rural Uganda, we found a lower prevalence of self-reported depression among aging PLWH on ART.

Keywords Depression · Antiretroviral therapy · Aging

Introduction

In the era of widespread availability of antiretroviral therapy (ART), HIV-positive people are living to older ages in sub-Saharan Africa [1]. There is a growing recognition of the role of mental health conditions as an important source of comorbidity among people living with HIV (PLWH) [2]. For instance, a recent meta-analysis of PLWH, including both those prior to and on ART, estimated a pooled prevalence of depression ranged between 9 and 32%, with substantial variability across geographic contexts, and measurement approaches [3, 4].

Depression and other mental health disorders have complex and potentially far reaching implications for health and well-being, including risk of disease acquisition and engagement in care for chronic conditions such as HIV [5, 6]. The relationship between depression and engagement in HIV care has been demonstrated in several low- and middle-income settings [7, 8]. In PLWH, depressive symptoms are an important barrier to HIV self-care and

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adherence to ART [7, 9, 10]. In a large systematic review of studies from across sub-Saharan Africa, depression was significantly associated with ART non-adherence (OR 2.54, 95% CI 1.65–3.91) [6]. In a second multi-country study, over 2400 participants across 6 countries in sub-Saharan Africa reported depression as a barrier to ART adherence [11]. These findings are likely related to both biological and social determinants of depression among PLWH, as HIV remains heavily stigmatized throughout sub-Saharan Africa and the stigma attached to HIV remains a significant structural barrier to treatment adherence [12–14]. Given these findings, the ability to diagnose and treat depression may be an important element in efforts to improve adherence and outcomes for HIV or other chronic diseases.

Depression has also been linked to a number of deleterious health behaviors in low- and middle-income countries (LMICs) [15]. A study in South Africa showed that symptoms of depression at baseline were associated with increased risk of high-risk sexual behavior, including transactional sex in both men (aOR = 1.48, 95% CI 1.01–2.17) and women (aOR = 2.60, 95% CI 1.37, 4.92) and lower odds of correct condom use at last sex (aOR = 0.50, 95% CI 0.32–0.78) [16]. A similar study in Uganda also demonstrated a relationship between depression and high-risk sexual behavior in women and several studies have shown relationships between depression, alcohol or other substance use and high-risk sexual behavior in sub-Saharan Africa [17, 18]. These data provide increasing support for efforts to diagnose and effectively treat depression among PLWH, both for the direct health benefits and downstream effects on health-related behaviors, including HIV transmission [19].

Uganda is a low-income country in sub-Saharan Africa with a generalized HIV epidemic and large expansion of ART services in recent years. The prevalence of depressive symptoms among PLWH in Uganda has been estimated to range from 14 to 54%, and is notably elevated among HIV-positive women [15, 20–23]. However, few studies have compared rates of depressive symptoms between PLWH and community-based uninfected comparators. One prior study showed that older adults with HIV not on ART may have greater rates of depression than HIV-negative comparators but did not have a sufficient sample size to address the difference between PLWH who are stable on ART and HIV-negative people [24]. Moreover, as HIV treatment programs have expanded, there have been limited data on how ART might contribute to ameliorating depression in this population [25]. This study aims to characterize associations between HIV infection, both before and after ART use, and depressive symptoms in a mixed cohort of aging PLWH and sex and age-matched, population-based, HIV-negative comparators.

Methods

Data Collection

We used data from the Ugandan Non-Communicable Diseases & Aging Cohort Study UGANDAC (NCT02445079). UGANDAC is an observational cohort study of aging PLWH in ambulatory HIV care and a group of age and sex-similar uninfected comparators enrolled from the community in the catchment area of the clinic. The design is based on similar mixed cohorts in the US [26, 27]. PLWH were selected using convenience sampling from the Mbarara Regional Referral Hospital immune suppression syndrome (ISS) clinic [28]. Eligibility criteria for participation included (1) in ambulatory care at the Immune Suppression Syndrome Clinic at Mbarara Regional Referral Hospital, (2) age ≥ 40 years and (3) duration of ART use ≥ 3 years [29]. We consecutively selected participants who met these criteria. After enrolling the PLWH, we selected HIV-uninfected controls through selective matching. These participants were enrolled from their homes in Nyakabare Parish, a community located about 20 km from the clinic site [30]. In brief, we stratified the sample of PLWH by sex, then by quartiles of age within sex strata. Using a complete census conducted as part of a community-based study within this clinic catchment area [31], we then recruited HIV-uninfected comparators of similar numbers within each sex/age stratum. Of 205 eligible HIV-uninfected individuals approached for enrollment, 164 (80%) consented and 154 (75%) were ultimately enrolled in the study.

The study's objective was to test hypotheses related to the impact of HIV on non-communicable diseases, including cardiovascular and pulmonary disease, mental health and geriatric syndromes. Participants are seen annually for NCD data collection. A subset of the PLWH (n = 102) were previously enrolled in a study of long-term ART adherence (Uganda AIDS Rural Treatment Outcomes Study [UARTO], funded by U.S. National Institutes of Health R01 MH54907 and P30AI27763). During each study visit, data on demographic, health and socioeconomic characteristics were collected. HIV serostatus was confirmed by HIV testing of all HIV-uninfected comparators on the day of study procedures prior to each annual study visit. In addition, for PLWH, HIV viral load (VL), and CD4 + T cell counts were obtained from the clinical record. In this study, virologic suppression was defined as a VL below the limit of detection of the assay (plasma specimens: < 40 copies/μL; dried blood spots: < 550 copies/μL) [28].

The outcome of interest in this study is probable depression, as measured by a modified version of the Hopkins

Symptom Checklist for Depression (HSCL) [32]. All participants were administered this scale at their baseline or first follow-up visit. In this study, we use the first available HSCL measurement from the UGANDAC study for each participant. The HSCL is a 15-item scale that quantifies depression symptom severity and has previously been validated in East African populations [4, 30]. Those who score greater than 1.75 on the HSCL are categorized as having probable depression. Finally, in a subset of PLWH (n = 102), an HSCL score was also available from just before ART initiation, collected during a prior study [23]. Among PLWH who were previously enrolled in the long term adherence study, one pre-ART depression score measurement was available, collected on the day of ART initiation.

Statistical Analyses

We first described the cohort by comparing sociodemographic and clinical characteristics between PLWH on ART and HIV-uninfected comparators. We then estimated crude differences in depressive symptoms and prevalence between these two groups by comparing both the difference in the mean HSCL with a student's t-test and the difference in the proportion of participants in each group with an HSCL > 1.75 with a Z-test of proportions. We repeated these estimates comparing PLWH prior to ART with HIV-uninfected individuals, and between PLWH prior to after ART, using a matched pairs analysis for the latter.

We next sought to identify adjusted correlates of probable depression by fitting multivariable log binomial regression models, including HIV status (comparing PLWH on ART and HIV-uninfected comparators), age, sex, educational attainment and household wealth [33]. Household wealth was quantified based on a 21-item series of questions about assets and housing conditions. This summary variable was generated using a principal components analysis and then divided into quartiles to allow within-cohort comparisons of wealth. All statistical analyses were conducted in Stata version 14 (College Station, TX).

Ethics

This study was approved by the Partners Healthcare (2014P001928) and Mbarara University of Science and Technology (06/04-14) human studies ethics committees. All participants gave written informed consent. Participants were informed that both UGANDAC and UARTO were observational cohort studies, and that the questionnaires were not being used for clinical purposes.

Results

The study included 154 PLWH and 142 community-based, HIV-negative controls. There were no differences in mean age, sex, or the prevalence of hypertension or diabetes between HIV-negative participants and PLWH on ART (Table 1). PLWH on ART were more likely to be in the highest wealth quartile by an asset index (13.6 vs. 35.1, p < 0.001). In our sample, PLWH on ART had a mean duration of ART of 8 years, a mean CD4 cell count of 510 and a mean CD4 nadir of 136 (95% CI 121–136). The most common ART regimens were zidovudine, lamivudine and nevirapine (60%), zidovudine, lamivudine, and efavirenz (19%) and tenofovir, lamivudine and efavirenz (8%). Viral load data were available for 94% (145/154) of PLWH on ART; among these, 90% (131/145) were virally suppressed.

PLWH on ART had lower depression symptom scores than HIV-uninfected controls (mean score: 1.50 vs. 1.60, p = 0.006) and a lower prevalence of probable depression (21.4 vs. 33.8%, p = 0.017). The full distribution of HSCL scores in the HIV-negative and PLWH on ART are shown in Fig. 1. The distribution of HSCL scores was significantly different for PLWH on ART as compared to the HIV-negative participants in six domains. These included blaming oneself, no desire for sex, difficulty falling asleep, feeling hopeless, feeling unhappy and worrying. In each of these domains, PLWH on ART were more likely to report the absence of symptoms (i.e. "not at all") over the past 7 days, as compared to their HIV-negative counterparts (blaming oneself: 63% vs.

Table 1 Demographic & health characteristics of participants in UGANDAC, by HIV status

	HIV-negative	HIV-positive	p
Total	142	154	–
Age (mean)	51.9	52.0	0.854
Female (%)	47.9	47.4	0.934
Asset Index (% in top quartile)	13.6	35.1	< 0.001
Depression Screen (Mean + 95% CI)	1.60 (1.54–1.67)	1.50 (1.44–1.57)	0.036
Depressed (%)	33.8	21.4	0.017
Not happy (%)	17.6	13.0	0.487
Hypertension (%)	25.4	16.9	0.074
Diabetes (%)	2.9	5.2	0.312

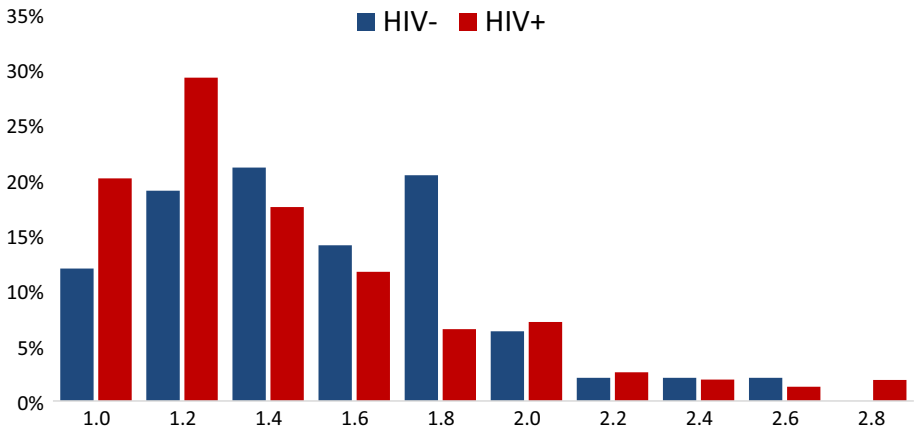

Fig. 1 Distribution of mean depression screening scores by HIV status in UGANDAC

45%, p = 0.011; no desire for sex: 57% vs. 38%, p < 0.001; difficulty falling asleep 64% vs. 47%, p = 0.018; felt hopeless: 87% vs. 73%, p < 0.006; felt unhappy: 70% vs. 52% p = 0.002; worrying: 66% vs. 44%, p = 0.050). These differences by study group are further detailed in the supplemental appendix (Table S1).

In a sub-analysis of 102 PLWH in whom both pre-ART and post-ART depression screening scores were available, the mean depression score prior to ART was lower in magnitude but not significantly different from the mean score in the HIV-negative group (1.56 vs. 1.60, p = 0.5121). The difference in the mean score between the HIV + - Pre-ART and HIV + - Post-ART groups was significant (1.56 vs. 1.42, p = 0.035). The same proportion of participants was depressed in each of these two groups (13%). The mean HSCL and significance testing for all three pairwise comparisons is provided in the supplemental appendix (Table S2) (Fig. 2).

In unadjusted analyses, PLWH on ART [prevalence ratio (PR): 0.63, 95% CI 0.43–0.94] and those falling in the highest wealth quartile (PR: 0.47, 95% CI 0.24–0.93) had a lower prevalence of probable depression while women had a significantly higher prevalence of probable depression (PR: 1.77, 95% CI 1.19–2.65). These relationships were preserved in multivariable log binomial regression models in which PLWH on ART had a lower prevalence of probable depression than HIV-negative controls [adjusted prevalence ratio (aPR): 0.69 (95% CI 0.47–0.99)]. Those participants in the highest wealth quartile as measured by an asset index had a lower prevalence of probable depression as compared to those in the lowest wealth quartile (aPR: 0.39, 95% CI 0.18–0.87). In addition, women had a higher

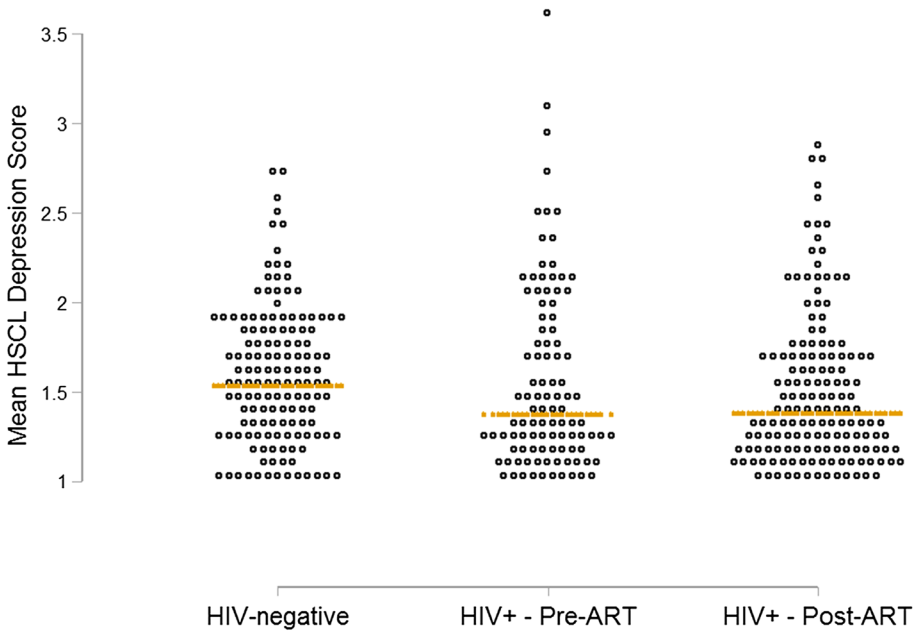

Fig. 2 Mean HSCL Depression Score among HIV-negative, HIV-positive/Pre-ART and HIV-positive/Post-ART participants in UGANDAC

prevalence of probable depression than men (aPR: 2.02, 95% CI 1.35–3.02) (Table 2).

Discussion

Our study found that PLWH on ART had a lower prevalence of probable depression, as compared with age- and sex-matched, population-based HIV-negative comparators, after adjustment for key demographic characteristics such as educational attainment and household wealth. Furthermore, depressive symptoms were similar among pre-treatment PLWH and HIV-negative comparators; however, after enrollment in ART care, symptoms of probable depression declined among PLWH. These data add to a growing body of literature demonstrating improved physical and mental health indicators among PLWH on ART in sub-Saharan Africa, compared to people without HIV [34].

The mechanisms responsible for this so-called 'ART advantage' require further study, but may include direct effects of ART on HIV replication, inflammation and downstream disease pathophysiology [35]; a survivorship bias among those with HIV who link to and remain in care; greater community support and resilience among PLWH who link to care; and positive spillover effects of ART programs in the form of increased access to primary care or psychosocial support services, leading to earlier recognition and management of depression and comorbid health conditions [34, 36, 37]. Longitudinal and qualitative data have also shown that increasing duration of ART is associated with declines in internalized stigma, which could also contribute to the observed declines in depression symptom severity [38, 39]. There may also be a normalization of knowledge of one's HIV-positive status that contributes to this decline as well. Alternatively, the benefits of ART might be mediated via reductions in inflammatory pathways that affect depression risk, such as the kynurenine pathway of tryptophan catabolism, which is reduced by use of ART [40]. Finally, evidence is emerging from both Uganda and South Africa that there is improved control of other chronic co-morbidities, such as hypertension and diabetes, among people with HIV on ART, compared to uninfected, community based controls in this region [34, 41].

Table 2 Regression analyses of the association between positive baseline depression screen, HIV infection and other key chronic diseases in UGANDAC

	Univariable		Multivariable	
	PR (95% CI)	*p-value*	*aPR (95% CI)*	*p-value*
Age (years)	0.99 (0.98–1.02)	0.939	1.01 (0.99–1.03)	0.441
Female	1.77 (1.19–2.65)	0.005	2.02 (1.35–3.03)	0.001
Education				
0–1 Years	REF	REF	REF	REF
2–5 Years	0.77 (0.49–1.21)	0.255	0.79 (0.51–1.24)	0.313
6 + Years	0.80 (0.51–1.25)	0.319	0.76 (0.52–1.12)	0.169
Wealth quintile				
Quantile 1	REF	REF	REF	REF
Quantile 2	0.81 (0.51–1.28)	0.362	0.75 (0.48–1.16)	0.193
Quantile 3	0.86 (0.55–1.34)	0.499	0.87 (0.58–1.29)	0.479
Quantile 4	0.47 (0.24–0.93)	0.030	0.39 (0.18–0.88)	0.023
HIV+	0.63 (0.43–0.94)	0.022	0.69 (0.48–0.99)	0.049
Diabetes	1.22 (0.56–2.67)	0.618	–	–
Hypertension	1.16 (0.76–1.76)	0.500	–	–
BMI				
Overweight	0.78 (0.43–1.41)	0.417	–	–
Obesity	1.35 (0.86–2.10)	0.192	–	–

Our results offer an interesting contrast to recent evidence from high-income countries. For instance, in a study of quality of life of participants in the in the AGEHIV Cohort Study in the Netherlands, PLWH on ART reported significantly worse physical and mental health-related quality of life and had a higher prevalence of depression than HIV-uninfected individuals [42]. In adjusted models, PLWH on ART had a 1.60 times increased odds of depression compared to HIV-negative participants ($p = 0.002$) [42]. In the United States, a similar study showed a prevalence ratio of 2.90 for depression in multivariable adjusted models comparing PLWH on ART to the general population [43]. This may suggest context-specific differences in the drivers of depression—including the role of engagement in HIV care—among those with and without HIV, especially when comparing low- and middle-income settings to high-income settings. Specifically, ART programs may offer a degree of social and health system support that, paradoxically, may advantage PLWH in certain ways compared to the HIV-negative population in LMICs. In contrast, our finding that the mean depression score was significantly lower in PLWH after ART initiation as compared to pre-ART initiation seems to be consistent with findings in high-income settings. For instance, a recent retrospective analysis of data from 281 PLWH initiating ART in the United States showed a significant decrease in depression as measured by the PHQ-9 over the period from just prior to ART initiated to 12 months after ART initiation [44].

While the difference between PLWH and HIV-negative participants was a primary focus of this analysis, we also highlight the high prevalence of probable depression in our study population. We find that probable depression is more prevalent than hypertension or diabetes in both PLWH and HIV-negative comparators. This finding reinforces the large burden of depression in sub-Saharan Africa that has been highlighted in other recent epidemiological studies [45]. Our finding suggests an urgent need to strengthen diagnostic and therapeutic mental health care services in the region. This

finding is also consistent with previous studies that have also demonstrated a need for greater investment in mental health services in Uganda, especially in its rural regions [46].

Secondary findings of this analysis include that women both with and without HIV are twice as likely as men to report depressive symptoms, a finding consistent with prior work in several sub-Saharan African contexts, as well as in studies of sex differences in depression outside this region [16, 23, 47]. The drivers of this relationship are poorly understood but are important given that depression is in turn associated with other negative health outcomes [18]. Moreover, this study also identified a relationship between wealth and depression, as those who fell into the highest wealth quartile had a significantly lower prevalence of probable depression. The inverse relationship between depression and wealth is one that has been described in the literature previously [24, 48, 49].

Limitations

This study should be considered in the context of important limitations. First, we defined probable depression on the basis of a positive screen on a validated symptom survey rather than on the basis of a structured diagnostic interview. In studies of PLWH in sub-Saharan Africa, screening instruments tend to over-estimate the prevalence of major depressive disorder by a factor of two to three compared with structured diagnostic interviews [4]. Whereas there is little consensus about the most appropriate depression scales to use for measuring depression among PLWH in African settings, we used the HSCL, which has been validated in this population [30]. In addition, our study was limited to PLWH who had survived to the time of presentation to care and completion of at least 3 years of ART. Therefore our findings should be interpreted as comparing PLWH who are stably in care with uninfected comparators. This study is generalizable only to aging PLWH who have been stable on ART, and should not be generalized to the global population of PLWH prior to achieving long-term retention in care, including younger adults. Third, we adjusted for those confounding factors that were measured in the study and which we hypothesized may be relevant to this analysis. However, it is possible that there are residual, unmeasured confounding factors that we were unable to account for in this analysis and which might partially explain the differences observed between people with and without HIV. For instance, it is possible that levels of social support could confound the relationship between HIV infection and depression in this context, though this study did not routinely collect these data. In addition, greater information about differential access to psychosocial support services or antidepressant medications would have been useful to further characterize the association we identify in this analysis. Fourth, we did not have longitudinal data among HIV-negative controls that could be used to better support a causal analysis or exclude the possibility that some members of the cohort experienced spontaneous remission of their depression. Finally, this study took place at an HIV clinic and in a region where availability of depression treatment is limited.

In summary, this study suggests for the first time that older PLWH on ART in Uganda might have a lower prevalence of probable depression than a comparable HIV-negative group. Our results add to data about relatively improved health indicators among aging PLWH on ART vs HIV-negative people in sub-Saharan Africa. Further research is needed to elucidate the underlying mechanisms for these findings and whether the role of primary care provision for PLWH can be expanded to other chronic diseases in the region.

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Compliance with Ethical Standards

Conflict of interest All authors declare no conflicts of interest.

Ethical Approval 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.

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

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