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ORIGINAL PAPER

Depression and Viral Suppression Among Adults Living with HIV in Tanzania

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Abstract

Limited information is available on the association between depression and viral suppression among people living with HIV (PLH) in sub-Saharan Africa. We conducted a prospective cohort study of 3996 adults initiating antiretroviral therapy (ART) in Dar es Salaam, Tanzania. Log-binomial models were used to assess the association between depression and the risk of an unsuppressed viral load (> 400 copies/mL) after 6 months of ART. Women who had depression at both initiation and after 6 months of treatment had 1.94 times (95% CI 1.22, 3.09; z = 2.78, p < 0.01) the risk of an unsuppressed viral load after 6 months of treatment as compared to women who did not have depression at either time point. Men with the top tertile of depressive symptoms after 6 months of treatment had 1.58 times the risk of an unsuppressed viral load (95% CI 1.04, 2.38; z = 2.15, p = 0.03) as compared to the lowest tertile. Research should be pursued on interventions to prevent and address depression among adults initiating ART to potentially support achievement of viral suppression.

Keywords Depression · Viral suppression · Gender · Sub-Saharan Africa · Tanzania

Introduction

Globally, there are approximately 37.9 million people living with HIV of which 54% reside in Eastern and Southern Africa [1]. Emerging evidence suggests that depression, which is common among people living with HIV (PLH), may adversely affect ART effectiveness [2]. Depression is the leading cause of disability in the world and is associated with premature mortality and impaired physical health [3]. Although there is substantial heterogeneity across populations, it is estimated that globally PLH are two times more likely to meet the criteria for major depressive disorder as compared to HIV negative individuals [4]. A systematic review and meta-analysis estimated that the overall prevalence of major depressive disorder among PLH in Tanzania was 12.7% [5]. However, a study that examined depression among Tanzanian women living with HIV reported that more than half of participants had symptoms consistent with depression prior to initiating ART [6].

While the steady scale-up of antiretroviral therapy (ART) has led to a dramatic decrease in AIDS-related mortality worldwide, the mortality and morbidity of individuals on ART in this region are still high, particularly during the

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first months of treatment [7]. There is consistent evidence from both high- and low-income settings that depression is associated with reduced ART adherence [8]. A recent meta-analysis found that the likelihood of achieving good ART adherence was 42% lower among those with depressive symptoms [9]. Adherence is fundamental to ART effectiveness and a growing body of evidence, largely from high income-countries, has found an association between depressive symptoms and unsuppressed viral loads among PLH on ART [10–12]. Although the majority of PLH live in Eastern and Southern Africa, there are few studies examining the association between depression and viral load in the region. One prospective observational study conducted in Moshi, Tanzania reported an inverse relationship between depression at ART initiation and subsequent virologic failure and hypothesized that this may have been due to loss to follow-up and incomplete clinical information [13]. Less information is available on the course of depression after ART initiation and how this course relates to viral suppression. To the best of our knowledge, no study has comparatively examined the longitudinal association between depression and viral suppression in sub-Saharan Africa. In this study, we assess the prevalence of depression in men and women at ART initiation and after 6 and 12 months of treatment and then examine the association between depression and viral suppression after 6 months of treatment.

Methods

Study Population

This prospective cohort study included men and women who were enrolled in the Trial of Vitamins-4 (ToV4), an individually randomized, double-blind, placebo-controlled trial assessing the effect of vitamin D_3 (cholecalciferol) supplementation on mortality and incidence of pulmonary tuberculosis among PLH initiating ART in urban Dar es Salaam, Tanzania (ClinicalTrials.gov identifier rNCT01798680) [14]. Enrollment occurred between February 2014 and March 2017, and follow-up data collection ended in March 2018. Adult men and women aged 18 and older living with HIV were eligible to participate in the trial if they initiated ART at trial enrollment, had low vitamin D levels with a serum 25(OH)D concentration < 30 ng/mL at the time of screening, and intended to remain in Dar es Salaam for at least one year after enrollment. Pregnant women and individuals participating in other clinical trials were excluded from participation. During trial enrollment, the criteria for ART initiation changed from CD4 T cell count < 350 cells/μL or WHO HIV stage 3 or 4 disease to CD4 T cell count < 500 cells/μL or WHO HIV stage 3 or 4 disease and finally to a test-and-treat strategy [14]. All study participants received HIV treatment in accordance with Tanzanian national guidelines. The preferred first-line ART regimen during the study was Efavirenz–lamivudine–tenofovir and participants with a CD4 cell count of < 200 cells/μL received co-trimoxazole prophylaxis.

Measures

All participants completed weekly clinic visits for the first three weeks of the trial and then monthly visits from the fourth week until the completion of the trial at 12-months post ART initiation. At ART initiation, 6 months, and 12 months, participants completed a questionnaire that included data on socio-demographics, depressive symptoms, alcohol use, smoking, and social support. Depressive symptoms were assessed using the Hopkins Symptoms Checklist (HSCL-25), a 25-item screening tool for depression that includes 10 items for symptoms of anxiety and 15 items for symptoms of depression [15]. Each question has four possible response options (1 = *Not at all*, 2 = *A little*, 3 = *Quite a bit*, 4 = *Extremely*). A cutoff of 1.75 is commonly used to screen symptomatic adults [16]. The HSCL-25 has been widely used and validated across a variety of cultural and clinical settings, including a number of counties in sub-Saharan Africa [17, 18]. A validation study among pregnant adult women living with HIV in Dar es Salaam, Tanzania found that a subscale of eight items (HSCL-adapted) with a recalibrated cutoff of > 1.06 had a specificity of 89% and a sensitivity of 88% when compared to a Structured Clinical Interview for DSM-IV diagnosis of major depressive disorder [19]. We used the HSCL-adapted cut-off for both women and men to define symptoms consistent with major depressive disorder (hereafter referred to as 'depression'). To date, neither the HSCL-25 nor the HSCL-adapted has been validated among men in Tanzania. Therefore, we conducted a sensitivity analysis, using tertiles of total HSCL-25 score within the population for both men and women. We also classified participants into four categories of depression at ART initiation and after 6 months of treatment using the HSCL-adapted cut-off: no depression at ART initiation or 6 months post-initiation, depression at ART initiation but not after 6 months, depression after 6 months but not at ART initiation, and depression at both time points (sustained depression).

Social support was assessed using a modified version of the Duke University– University of North Carolina Functional Social Support Questionnaire [20] at ART initiation, 6 months, and 12 months. Following the example of Antelman et al., we created two social support variables from these responses, representing two distinct underlying constructs: instrumental support and emotional support [21]. Average scores for these two variables were divided into

tertiles, representing low, medium, and high levels of social support.

Household food expenditure was calculated by dividing the typical amount the participant's household spends on food per day by the number of people eating in the participant's household. CD4-T count was measured at the ART eligibility visit (FACSCalibur system, Becton Dickinson, San Jose, CA). HIV viral load was measured after 6 months of ART (Cobas 4800, Roche, Pleasanton, California, USA). We used a binary viral load cutoff of > 400 copies/mL to define an unsuppressed viral load. This cutoff was used for consistency with other studies and because viral loads less than 400 copies /mL have been shown to have very low to no HIV transmission risk to sexual partners [22]. At each visit participants received a full clinical examination by study physicians, including WHO HIV disease staging and TB screening, and nurses administered a questionnaire on morbidity and recorded anthropometric measurements.

Statistical Analysis

Depression prevalence was calculated at ART initiation, 6 months, and 12 months, and chi-squared tests were used to assess differences in the prevalence of depression at each time point by gender. We used log-binomial regression models to estimate risk ratios for the cross-sectional association between sociodemographic and clinical characteristics and depression at ART initiation stratified by gender. Univariate analyses were conducted to assess the associations between age, marital status, having children, education, employment status, smoking, alcohol use, wealth quintile, CD4-T cell count, WHO HIV disease stage, baseline TB status, BMI, emotional support, instrumental support and household food expenditure and depression at ART initiation. In order to create a parsimonious multivariate model, variables with a p-value < 0.20 in the univariate analysis were included in the multivariate models. We also examined the association between these baseline variables and sustained depression, which was defined as depression at both ART initiation and 6 months.

We used log-binomial regression models to assess the relationship between depression and unsuppressed viral load (> 400 copies/mL) after 6 months of ART. We defined depression and depressive symptoms in three ways (i) using the HSCL-adapted cutoff for depression at ART initiation and 6 months, (ii) comparing the top tertile of HSCL-25 scores to the lower two tertiles at ART initiation and 6 months as a sensitivity analysis, and (iii) combinations of depression defined by the HSCL-adapted cut-off at ART initiation and 6 months [no depression at either time point, depression at ART initiation but not after 6 months, depression after 6 months but not at ART initiation, and depression at both time points (sustained depression)]. Participants who died in the first 6 months (n = 364) or did not have depression and/or viral load data (n = 2054) were excluded from the viral load analysis. An additional 62 participants whose viral load was measured before depression at 6 months were also excluded in order to reduce the risk of reverse causation. In order to address the risk of selection bias, we used inverse probability (IP) weights to adjust for censoring for deaths and those without viral load data. For each participant included in the analysis, we calculated a weight inversely proportional to the estimated probability of being censored, by fitting logistic models with the following covariates: age, marital status, wealth quintile, education, alcohol use, WHO HIV disease stage, BMI, CD4 cell count, baseline pulmonary TB, emotional support, instrumental support, and randomized treatment regimen (vitamin D_3 or placebo). Censoring weights were calculated separately for participants who were censored due to death and participants who were missing data. We used stabilized weights as they typically result in narrower confidence intervals compared to non-stabilized weights [23]. Stata 15.1 (StataCorp, College Station, Texas, USA) was used to perform the analysis. Missing indicators were used to account for missing covariate data in the adjusted models.

The parent study was approved by the Harvard T. H. Chan School of Public Health Institutional Review Board (Ref. No. IRB13-0231), the Tanzanian National Health Research Ethics Sub-Committee (NatHREC) (Ref. No. NIMR/HQ/R.8a/Vol.IX/1658), and the Tanzania Medicine and Medical Devices (TMDA) (Ref No. TMDA13/CTR/0005/3).

Results

The study included 3996 adults who had depression data available at ART initiation; a flow chart of participants included in the depression analysis is shown in Supplemental Figure 1. Socio-demographic and clinical characteristics of 1264 male and 2732 female participants at ART initiation are presented in Table 1. The population of men and women had some notable differences at ART initiation. Men had a more advanced HIV disease stage than women, with 51% of men presenting with CD4-T cell counts ≤ 200 cells /mL as compared to 39% of women. Additionally, 7.4% of male participants had WHO HIV disease stage IV disease at initiation, as compared to only 3.6% of women. Of the 3996 participants who contributed depression data at ART initiation, 413 (10.3%) died within 1-year of ART-initiation; male participants had greater risk of mortality (15.5%) as compared to female participants (7.9%) ($X^2 = 53.97$, $p < 0.01$).

Table 1 Baseline demographic and clinical characteristics at ART initiation by gender (n = 3996)

Characteristic	Men (n = 1264)	Women (n = 2732)	Total (n = 3996)
Sociodemographic			
Age (years)			
< 30	136 (10.8)	620 (22.7)	756 (18.9)
≥ 30 and < 40	441 (34.9)	1108 (40.6)	1549 (38.8)
≥ 40 and < 50	457 (36.2)	728 (26.7)	1185 (29.7)
≥ 50	230 (18.2)	276 (10.1)	506 (12.7)
Marital status			
Married/cohabitating	704 (55.7)	991 (36.3)	1695 (42.4)
Single	244 (19.3)	678 (24.8)	922 (23.1)
Widowed	58 (4.6)	302 (11.1)	360 (9)
Divorced/separated	232 (18.4)	718 (26.3)	950 (23.8)
Missing	26 (2.1)	43 (1.6)	69 (1.7)
Has children			
Yes	1047 (82.8)	2292 (83.9)	3339 (84)
No	212 (16.8)	434 (15.9)	646 (16.2)
Education			
None/primary	969 (76.7)	2212 (81.0)	3181 (79.6)
Secondary plus	284 (22.5)	491 (18.0)	775 (19.4)
Employed			
Yes	727 (57.5)	678 (24.8)	1405 (36.1)
Informal	353 (27.9)	1230 (45.0)	1583 (40.7)
No	157 (12.4)	749 (27.4)	906 (23.3)
Substance use			
Smoking			
Current smoker	157 (12.4)	27 (1.0)	184 (4.6)
Not current smoker	1107 (87.6)	2705 (99)	3812 (95.4)
Alcohol use			
Drinks alcohol	194 (15.4)	302 (11.1)	496 (12.4)
Not current drinker	1070 (84.7)	2430 (89.0)	3500 (87.6)
CD4 T-cell count (cells/μL)			
≤ 200	658 (52.1)	1063 (38.9)	1721 (43.1)
201–350	260 (20.6)	639 (23.4)	899 (22.5)
351–500	137 (10.8)	494 (18.1)	631 (15.8)
> 500	137 (10.8)	422 (15.5)	559 (14.0)
Missing	72 (5.7)	114 (4.2)	186 (4.7)
WHO HIV disease stage			
I and II	370 (29.3)	1133 (41.5)	1503 (37.6)
III	801 (63.4)	1500 (54.9)	2301(57.6)
IV	93 (7.4)	99 (3.6)	192 (4.8)
Pulmonary TB			
Yes	195 (15.4)	167 (6.1)	362 (9.1)
No	1069 (84.6)	2565 (93.9)	3634 (90.9)
Body mass index (kg/m^2)			
< 18.5	359 (28.4)	485 (17.8)	844 (21.1)
≥ 18.5 and < 25.0	755 (59.8)	1343 (49.2)	2098 (52.5)
≥ 25.0	149 (11.8)	903 (33.1)	1052 (26.4)
Mean HSCL-25 score (possible range: 25–100)			
Mean (SD)	32.6 (10.7)	33.6 (11.9)	33.3 (11.5)

Prevalence of Depression at ART Initiation and at 6 Months of Treatment

Using the HSCL-adapted cutoff for depression, 49.8% of women and 45.4% of men reported symptoms consistent with depression at ART initiation. Male and female endorsement of each of the 25 HSCL items are presented in Supplemental Table 1. The most frequently endorsed item at ART initiation was 'feeling low in energy, slowed down' for both men (39.6%) and women (37.1%). The greatest difference in responses between men and women was for 'crying easily,' which was endorsed by 26.7% of women and 17.6% of men.

Figure 1 shows the prevalence of depression at ART initiation, 6 months, and 12 months of ART using the HSCL-adapted cutoff, stratified by gender. For both men and women, the prevalence of depression declined significantly ($p < 0.01$) between initiation and 6 months, and between 6 and 12 months. Among women, prevalence of depression decreased from 49.8% at ART initiation to 29.1% after 6 months ($X^2 = 202.25$, $p < 0.01$) and 20.8% at 12 months ($X^2 = 34.26$, $p < 0.01$). Among men, it similarly declined from 45.4% at ART initiation to 23.7% after 6 months ($X^2 = 100.14$, $p < 0.01$) and 13.9% at 12 months ($X^2 = 23.6$, $p < 0.01$). The prevalence of depression at both ART initiation and 6 months (sustained depression) was 12.7% for men and 15.9% for women.

Risk Factors for Depression

Risk factors for depression (HSCL-adapted cutoff) at ART initiation are presented by gender in Supplemental Table 2. In multivariate models, lower CD4 T-cell counts and more advanced WHO HIV disease stage were independently associated with greater risk of depression at ART initiation for both men and women. Additionally, working informally or being unemployed was inversely associated with risk of depression among both men ($z = -1.74$, $p = 0.08$; $z = -2.34$, $p = 0.02$, respectively) and women ($z = -5.26$, $p < 0.1$; $z = -5.56$, $p < 0.01$, respectively). Low levels of instrumental social support were associated with higher risk of depression for women ($z = -4.45$, $p < 0.01$), while low levels of emotional support were associated with higher risk of depression among men ($z = -1.87$, $p = 0.06$). Women who were in the lowest tertile of food expenditure per household member had 1.18 times the risk of depression (95% CI 1.07, 1.30 $z = 3.22$, $p < 0.01$) as compared to women in the highest tertile of food expenditures.

Risk factors for sustained depression, defined as depression at both ART initiation and at 6 months of treatment, are presented in Supplemental Table 3. In multivariate models, risk factors for sustained depression among women included having formal employment, WHO stage IV disease, and lower food expenditure per household member.

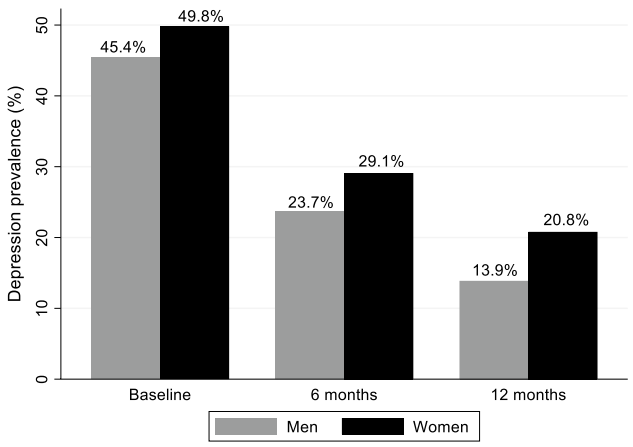

Fig. 1 Depression prevalence (HSCL-adapted) at ART initiation, 6, and 12 months of ART stratified by gender

Depression and Risk of Unsuppressed Viral Load

We present the association between depression and unsuppressed viral load after 6 months of ART using the HSCL-adapted cutoff in Table 2. Overall, 15% of the study population had an unsuppressed viral load > 400 copies/mL after 6 months; the prevalence was 18.6% and 13.5% among men and women, respectively. There was no association between depression at ART initiation with viral load > 400 copies/mL, for either men ($z = 0.74$, $p = 0.46$) or women ($z = 0.76$, $p = 0.45$). However, women with depression at 6 months had 1.56 times the risk of an unsuppressed viral load > 400 copies/mL (95% CI 1.10, 2.21; $z = 2.53$, $p = 0.01$) as compared to those without depression. Among men, there was no association between depression as defined by the HSCL-adapted cutoff at 6 months and viral suppression ($z = 1.16$; $p = 0.25$).

We then examined the association between depression at both ART initiation and 6 months with viral suppression after 6 months of treatment (Table 2). Women who had sustained depression had nearly twice the risk of a viral load over 400 copies/mL after 6 months of treatment (RR: 1.94; 95% CI 1.22, 3.09; $z = 2.78$, $p < 0.01$) as compared to those who were not depressed at either time point. There was no association between sustained depression and an unsuppressed viral load among men ($z = 0.94$, $p = 0.35$).

Table 3 presents the association between the highest tertile of HSCL-25 score and viral suppression. Being in the highest tertile of HSCL-25 score at ART initiation was not associated with having an unsuppressed viral load after 6 months for either men ($z = 0.03$, $p = 0.97$) or women ($z = 1.23$, $p = 0.22$). However, men in the highest tertile of HSCL-25 score at 6 months had 1.58 times the risk of having a viral load over 400 copies/mL (95% CI 1.04, 2.38; $z = 2.15$, $p = 0.03$) as compared to those in the lower two

Table 2 Association of depression (HSCL-adapted) and unsuppressed viral load (> 400 copies/mL) at ART initiation and after 6 months of treatment, stratified by gender

	Men (n = 447)				Women (n = 1069)			
	Viral load > 400 copies/mL (%)	IPW weighted[a] PR (95% CI)	z	p-value	Viral load > 400 copies/mL (%)	IPW weighted[a] PR (95% CI)	z	p-value
Depression at ART initiation								
Yes	39/181 (21.1)	1.17 (0.77, 1.76)	0.74	0.46	63/460 (13.7)	1.13 (0.81, 1.60)	0.76	0.45
No	42/262 (16.0)	Ref			66/609 (10.8)	Ref		
Depression after 6 months of treatment								
Yes	20/89 (22.5)	1.31 (0.83, 2.08)	1.16	0.25	46/271 (17.0)	1.56 (1.10, 2.21)	2.53	0.01
No	61/358 (17.2)	Ref			83/798 (10.4)	Ref		
Depression at ART initiation and after 6 months of treatment								
No depression at initiation or 6 months	33/219 (15.1)	Ref			45/465 (9.7)	Ref		
Depression at initiation but not after 6 months	28/139 (20.1)	1.34 (0.84, 2.14)	1.23	0.22	38/333 (11.4)	1.18 (0.72, 1.69)	0.74	0.77
Depression after 6 months but not at initiation	9/43 (20.9)	1.44 (0.74, 2.83)	1.07	0.29	21/144 (14.6)	1.32 (0.79, 2.20)	1.06	0.29
Depression at both initiation and 6 months	11/46 (23.9)	1.36 (0.72, 2.57)	0.94	0.35	25/127 (20.0)	1.94 (1.22, 3.09)	2.78	< 0.01

[a]Adjusted for age, marital status, wealth quintile, education, alcohol use, WHO HIV stage, BMI, CD4 count, pulmonary TB, emotional support, instrumental support, and regimen

Table 3 Association of top tertile of depression (HSCL-25) and unsuppressed viral load (> 400 copies/mL) at ART initiation and after 6 months of treatment, stratified by gender

	Men (n = 447)				Women (n = 1069)			
	Viral load > 400 copies/mL (%)	IPW weighted[a] PR (95% CI)	z	p-value	Viral load > 400 copies/mL (%)	IPW weighted[a] PR (95% CI)	z	p-value
Depression at ART initiation								
Top tertile	25/121 (20.7)	1.01 (0.64, 1.58)	0.03	0.97	41/287 (14.3)	1.26 (0.87, 1.81)	1.23	0.22
Lower two tertiles	56/326 (17.2)	Ref			88/782 (11.3)	Ref		
Depression after 6 months of treatment								
Top tertile	28/115 (24.4)	1.58 (1.04, 2.38)	2.15	0.03	49/282 (17.4)	1.69 (1.20, 2.38)	3.00	< 0.01
Lower two tertiles	53/332 (16.0)	Ref			80/787 (10.2)	Ref		

[a]Adjusted for age, marital status, wealth quintile, education, alcohol use, WHO HIV stage, BMI, CD4 count, pulmonary TB, emotional support, instrumental support, and regimen

tertiles. Similarly, women in highest tertile of HSLC-25 score had 1.69 times the risk (95% CI 1.20, 2.38; z = 3.00, p < 0.01) as compared to the lower two tertiles.

Discussion

In this study, we found that the prevalence of depression was nearly 50% among men and women initiating ART but was reduced to 20% or less after one year of treatment. At ART initiation, low CD4 T-cell count and advanced HIV disease stage were associated with increased risk of depression for both men and women. Additionally, low instrumental support was a risk factor for depression at among women, while low emotional support was a risk factor among men. Advanced HIV disease stage and lower food expenditures per household member were risk factors for sustained depression among women. Women with sustained depression at ART initiation and at 6 months had twice the risk of an unsuppressed viral load (> 400 copies/mL) after 6 months of treatment as compared to women who were not depressed at either time point. Further, men

in the top tertile of depressive symptoms at 6 months had an increased risk of an unsuppressed viral load after 6 months of treatment.

To the best of our knowledge, this was the first study to examine the relationship of longitudinal depressive symptoms and viral suppression for both men and women initiating ART in sub-Saharan Africa. We observed a high prevalence of depression among both men and women at ART initiation, a marked decline in prevalence for both between initiation and 6 months, and again between 6 and 12 months. Our observation that nearly half of men and women had depression at ART initiation is consistent with prior studies among PLH in Tanzania [6, 24]. While few studies have examined the longitudinal trends in depression among PLH initiating ART in the context of sub-Saharan Africa, a study conducted in Uganda also found a sharp reduction in depression prevalence from 39.3% to 4.3% over the course of 12 months of ART [25]. Given that more than half of the men and nearly 40% of the women had CD4 T-cell counts < 200 cells/mL at ART initiation in this study, we suspect that improved physical health may be a contributor to the reduction in depression prevalence over time. It is also possible that the stress associated with receiving an HIV diagnosis contributed to the high prevalence of depressive symptoms at baseline, particularly since, under the test-and-treat strategy, participants received their diagnosis shortly before completing the baseline HSCL assessment and initiating ART. We observed that individuals with HIV/TB coinfection at enrollment, whose depression was assessed at ART initiation after at least two weeks of anti-TB therapy per Tanzania standard of care, had lower prevalence of depression at initiation, suggesting that this time may have allowed for greater acceptance of their HIV status despite the presence of a serious comorbidity.

Among women, we observed a significant association between depression at 6 months and an unsuppressed viral load. We also observed that women who had sustained depression at ART initiation and at 6 months had nearly twice the risk of an unsuppressed viral load after 6 months of treatment. Low household food expenditure and employment at ART initiation were associated with sustained depression in women, suggesting that socioeconomic stress may contribute. While there has been limited research on the chronicity of depression among PLH in sub-Saharan Africa, a study conducted in the US found that a greater time spent with depression was associated with a higher number of missed clinic appointments and higher risk of an unsuppressed viral load in a dose–response manner [26]. A better understanding of the risk factors for and consequences of the cumulative burden of depression over time in this context, could provide clinicians with important information for monitoring patients and identifying patients who might benefit from additional support.

The relationship between depression and an unsuppressed viral load was not as consistent among men as compared to women. We found that men with HSCL-25 scores in the top tertile of depressive symptoms after 6 months of treatment had an increased risk of having a concurrent unsuppressed viral load. However, we found no association when using the HSCL-adapted cutoff or when looking at sustained depression at ART initiation and at 6 months. As the HSCL-adapted has only been validated among women, it may not be appropriate for use among men. Additionally, it has been suggested that prototypic depression scales may underestimate the true burden of depression among men who more strongly adhere to masculinity norms, as they are more likely to display externalizing symptoms of depression, such as irritability, anger and aggression, and substance abuse, as compared to internalizing symptoms [27]. Further research is needed on the association between depression and viral load for men, using a scale that has been locally validated for men.

Given the effectiveness of triple-drug antiretroviral therapy in reducing viral load [28], suboptimal ART adherence is likely a major contributor. However, we were unable to assess the role of adherence as we did not collect ART pill count data or other direct measures of ART adherence in our study. Previous research on ART adherence among women in resource-limited settings identified several factors associated with both depression and non-adherence in women, including intimate partner violence [29], stigma [30, 31], and food insecurity [32].

This analysis is limited by several features of the data and methodology. First, we did not have data on ART adherence and were therefore unable to evaluate non-adherence as a mediator of the relationship of depression with unsuppressed viral load. Second, as in any study of self-reported depressive symptoms, there is also a risk of misclassification due to participant misreporting and potential underestimation of the true burden of depression. This would lead to bias to the null in our study if misreporting was unrelated to viral suppression; however, this assumption cannot be confirmed. Third, adolescents and children under 18 years of age were excluded from the parent trial and therefore we were unable to evaluate younger PLH who may also be at high risk for depression. Fourth, it is difficult to untangle whether depression is a consequence or cause of an unsuppressed viral load in the cross-sectional analyses after 6 months. Specifically, somatic symptoms of depression, such as difficulty sleeping, may represent physical manifestations of HIV disease. However, this seems more likely to be the case at ART initiation as we observed a large decrease in HSCL somatic items between ART initiation and 6 months. For example, the prevalence of participants reporting difficulty sleeping was nearly halved after 6 months in our study. Additionally, depression may be either the cause or the consequence of

factors associated with poor ART adherence, including food insecurity and stigma. Fifth, the relatively small number of participants with both depression and an unsuppressed viral load could limit our ability to detect small and moderate effect sizes, particularly for men. Finally, eligibility requirement of low vitamin D levels to enroll in the parent trial may somewhat limit the generalizability of our findings. There is some evidence that vitamin D insufficiency is associated with depression [33]. However, the prevalence of depression at ART initiation in this study population was consistent with that of other studies in Tanzania [6, 24].

This study provides several implications for further research and program development. First, variation between men and women in the presence and magnitude of depression and the association of depression with viral suppression, suggest important differences related to the potential impact of depression. Further research on this topic should consider potential gender differences in symptomatology, risk factors and consequences of depression. Second, implementation research is needed on how to effectively scale up evidence-based mental health interventions and best practices for integration within with HIV care in Tanzania and similar contexts. While it is estimated that treatment gap for mental health disorders in low-income countries exceeds 90% [34], promising evidence has emerged suggesting that psychosocial support can be successfully integrated with clinical care and delivered in a treatment setting [35]. A recent stepped wedge randomized controlled trial in Tanzania found that participation in the NAMWEZA ('Yes, together we can!') psychosocial support intervention reduced levels of depression in PLH [36]. Our findings also suggest that the inclusion of social protection measures, such as cash transfers, alongside depression treatment may improve mental health particularly for women. Emerging evidence has shown that the integration of social protection packages into HIV treatment programs improved ART adherence in several sub-Saharan African settings [37, 38]. Social support groups may also be beneficial, as lower social support was a risk factor for depression for both men and women at ART initiation.

Conclusion

Depressive symptoms and depression were common among adults initiating ART in Tanzania and depression was associated with an increased risk of having an unsuppressed viral load to some degree for both men and women. Quantitative and qualitative research is needed to elucidate the mechanisms underlying this association and inform intervention design. Research should be pursued on interventions to prevent and address depression among adults initiating ART to improve their wellbeing, and potentially contribute to reaching the 95–95–95 targets for viral suppression.

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Author contributions MR and CS conceptualized the study and design. CS, FM, and WF originated the concept and obtained funding for the parent ToV4 trial. CS, FM, AM, SA, TN, NU, and WF developed and implemented data collection procedures. MR, AKY, SS, KK, and CRS developed and contributed to the statistical analysis plan. MR analyzed the data and wrote the first draft of the paper. All authors contributed important intellectual content to the manuscript and all authors approved the final submission.

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Compliance with Ethical Standards

Conflict of interest No conflict of interest are declared.

Ethics Approval The parent study was approved by the Harvard T. H. Chan School of Public Health Institutional Review Board (Ref. No. IRB13-0231), the Tanzanian National Health Research Ethics Sub-Committee (NatHREC) (Ref. No. NIMR/HQ/R.8a/Vol.IX/1658), and the Tanzania Medicine and Medical Devices (TMDA) (Ref No. TMDA13/CTR/0005/3).

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

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