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Reversal of the Kynurenine Pathway of Tryptophan Catabolism May Improve Depression in ART-treated HIV-infected Ugandans

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Abstract

Background—Major depressive disorder is highly prevalent among HIV-infected persons, and depression symptom severity improves during the course of HIV antiretroviral therapy (ART). The potential biologic pathways explaining these phenomena remain unclear. We investigated the extent to which ART-mediated suppression of the kynurenine pathway of tryptophan catabolism (via indoleamine 2,3-dioxygenase-1 and potentially other sources) may correlate with improvements in depression symptom severity in this setting.

Method—We used the first year of data from the Uganda AIDS Rural Treatment Outcomes Study, a prospective cohort of 504 HIV-infected individuals initiating their first ART regimen in rural Uganda. We fitted random-effects regression models to estimate the associations between plasma tryptophan, plasma kynurenine, dietary diversity, and self-reported depression symptom severity.

Results—Greater depressive symptoms were associated with both lower plasma tryptophan and higher plasma kynurenine/tryptophan (KT) ratio over 12-month follow-up. In multivariable-adjusted models, declines in KT ratio and increases in plasma tryptophan levels partially explained ART-mediated improvements in depressive symptom severity. The association between KT ratio and depression symptom severity was stronger among persons with protein-deficient diets than among those with protein-rich diets.

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Conclusions—IDO-mediated tryptophan catabolism may contribute to depression symptom severity among HIV-infected individuals, particularly among those with poor dietary protein intake. ART-mediated improvements in depressive symptom severity may also be at least partially mediated by immunologic mechanisms. Interventions to reduce immune activation, and dietary protein supplementation, may be promising strategies to further reduce depression in this setting.

Introduction

Depression is highly prevalent among HIV-infected individuals. In a U.S. national study of HIV-infected individuals receiving medical care, the 12-month prevalence of major depressive disorder was 36 percent,[1] much higher than the 5–7 percent prevalence reported in the general population.[2] Measurement challenges notwithstanding,[3] depression is also very common among HIV-infected individuals in resource-limited settings worldwide,[4] including HIV-infected persons in Uganda.[5,6] The impact of depression on the care and management of HIV infection is also well established: depression is associated with both reduced antiretroviral therapy (ART) adherence,[7,8] delayed ART uptake,[9] accelerated disease progression,[10,11] and reduced survival.[12] Thus, understanding the determinants of depression in this population may help identify targets for interventions to improve clinical outcomes.

ART-mediated viral suppression has also been associated with reduced depression symptom severity in HIV-infected individuals.[13–16] The improvement of depression on ART is often attributed to psychosocial and lifestyle factors such as improved social support, living situation, and overall health status.[15,17,18] While biological mechanisms may also contribute to improvements in depression on ART,[19,20] these mechanisms remain poorly understood.

One key biologic pathway may result from the HIV-associated induction of indoleamine 2,3-dioxygenase-1 (IDO). IDO is induced by microbial products and both Type I and II interferons in HIV infection,[21,22] and results in catabolism of the essential amino acid tryptophan, which is required for serotonin synthesis, into kynurenine and several other downstream immunologically active catabolites.[19] IDO induction in the immediate postpartum period has long been implicated as one of the mechanisms in the pathogenesis of postpartum depression in HIV-uninfected women, presumably due to serotonin depletion in the central nervous system.[20–23] Increased activity of the kynurenine pathway of tryptophan catabolism (as assessed by the ratio of kynurenine to tryptophan in plasma, KT ratio) has also been associated with progressive AIDS,[24,25] and ART-mediated viral suppression decreases activation of the kynurenine pathway.[24] Poor dietary protein intake may also contribute to lower plasma tryptophan levels,[25] which may further lower serotonin levels and contribute to the heightened prevalence of depression among HIV-infected individuals in resource-poor settings.[26,27]

For these reasons, we hypothesized that the kynurenine pathway of tryptophan catabolism contributes to depression in HIV-infected individuals, and that ART-mediated reductions in the kynurenine pathway may explain some of the reductions in depression severity observed among HIV-infected individuals on ART in prior studies. We also hypothesized that the impact of the kynurenine pathway on depression would be greatest among individuals with low dietary protein intake and that increased dietary protein intake would be associated with improved depression severity. To examine these hypotheses, we conducted a longitudinal study of changes in depression symptom severity and tryptophan catabolism among treatment-naive HIV-infected individuals initiating ART in rural Uganda.

Methods

Participants

Participants were sampled from the Uganda AIDS Rural Treatment Outcomes (UARTO) Study, an ongoing cohort of 504 ART-naïve HIV-infected individuals initiating free ART at the Mbarara Immune Suppression Syndrome (ISS) Clinic in Mbarara, Uganda. Clinic patients were eligible for participation if they were newly initiating ART, were 18 years of age or older, and lived within 20 km of the clinic. Participants undergo structured interviews every 3 to 4 months, blood draws to determine CD4+ T cell count and plasma HIV RNA levels, and biologic specimen archiving. All participants with available pre-ART plasma were assessed in the current analysis.

This study was approved by the Committee on Human Research, University of California at San Francisco; the Partners Human Research Committee, Massachusetts General Hospital; and the Institutional Ethical Review Committee, Mbarara University of Science and Technology. All participants provided written informed consent.

Measurements

Cryopreserved plasma was assessed at pre-ART baseline and at months 6 and 12 of ART for tryptophan and kynurenine levels using liquid chromatography -tandem mass spectrometry (LC-MS/MS) as previously described.[28] Kynurenine pathway activity was assessed as the ratio of plasma kynurenine concentration to plasma tryptophan concentration (KT ratio). All plasma samples were drawn in the morning before 9:30am, prior to receipt of a complimentary snack voucher. However, fasting peripheral blood measures were not planned *a priori* during cohort enrollment, and participants were not required to have been fasting prior to their scheduled blood draws. Plasma HIV RNA levels and CD4+ T cell counts were measured at each visit at a CAP-certified laboratory in Kampala, Uganda.

To measure depression symptom severity we used a modified version of the Hopkins Symptom Checklist for Depression (HSCL-D).[29] This version was developed and previously used among HIV-infected individuals in Uganda[30,31] and contains an additional item, “Feeling like I don’t care about my health” and deletes the item “feeling trapped or caught”. We removed three items addressing somatic symptoms of depression based on evidence that the inclusion of these items may inflate depression scores among HIV-infected individuals due to overlap between symptoms of depression and symptoms of HIV.[32,33] The total HSCL-D score was calculated by averaging across the remaining 12 cognitive-affective items. The conventional threshold of 1.75 or greater was used to indicate probable depression,[34] consistent with the majority of studies conducted in Sub-Saharan Africa that employed the HSCL-D.[35,36] The HSCL-D has shown excellent reliability and construct validity among HIV-infected persons in rural Uganda.[16,37,38] At baseline, the Cronbach’s alpha for the modified HSCL-D was 0.83.

Dietary protein intake was assessed using the Dietary Diversity Scale, which assesses consumption of food in 12 different food groups in a 24-hour reference period.[39] Based on the distribution of the data, we constructed a dichotomous variable representing two or more (vs. one or fewer) sources of dietary protein. Potential sources of dietary protein included beef, eggs, fish, beans, and/or cheese. The non-protein sources elicited in the Dietary Diversity Scale were bread, Irish potatoes, vegetables, fruits, oil, sugar/honey, and condiments.

Participants were weighed at each study visit. We determined participants’ heights at study enrollment. Using these quarterly weight measurements and the participant’s height, we calculated body mass index (BMI) as the ratio of weight to height squared.

Baseline socio-demographic variables included age, marital status, educational attainment, household asset wealth, and alcohol use. The wealth index was generated using principal components analysis applied to data from a 25-item questionnaire inquiring about household assets and housing characteristics, with higher values indicating greater household wealth.[40] Heavy drinking was defined as a positive screen based on the three-item consumption subset of the Alcohol Use Disorders Identification Test (AUDIT-C).[41,42]

Statistical analyses

Correlations between continuous variables were assessed with Spearman's rank order correlation coefficients. Associations between continuous and categorical variables were assessed with the Kolmogorov-Smirnov test. We used random-effects linear regression models to estimate the association between depression symptom severity and duration of ART; these models included both fixed effects and a random effect, where the "fixed effects" are the covariates and the "random effect" is the random intercept. We created a linear spline of duration on ART with a knot at six months in order to account for potentially non-linear changes. To determine whether ART-associated changes in depression were potentially mediated by tryptophan levels, we added this variable to the regression model and then reassessed the statistical significance of the duration terms. The models were further adjusted for baseline age, gender, marital status, educational attainment, household asset wealth, and AUDIT-C positive screen; and time-varying BMI and CD4+ T cell count. No variables were removed as part of model selection. Plasma HIV RNA level was not considered as a potential confounder as it is likely to be both a primary cause and a consequence of IDO induction. We fit similar models replacing tryptophan with KT ratio as the explanatory variable.

We also used random-effects linear regression models to assess the relationship between dietary protein intake and plasma tryptophan levels. These regression models were restricted to participants who were recruited after the dietary protein assessment was incorporated into the survey instrument in 2007. Interaction terms were constructed to assess the extent to which dietary protein intake modified the association between KT ratio and depression severity.

Results

Participants were enrolled from July 2005 through September 2010. Most participants were women (318 [63.1%]), median age was 34, and most had AIDS with a median CD4 count of 138 cells/mm^3 and high median viral load of 4.97 $\log_{10}$ copies/ml at baseline (Table 1). At baseline, the median depression score was 1.42 (interquartile range [IQR], 1.17–1.92), and 157 (31.2%) had scores consistent with the screening threshold for probable depression. At pre-ART baseline, the median depression score was greater among women than men (1.71 vs. 1.41, P<0.001). Greater depression symptom severity was also associated with lower household asset wealth (rho = −0.11, P=0.03), lower plasma tryptophan (rho = −0.16; P<0.001), and higher plasma KT ratio (rho= 0.18, P<0.001).

We next evaluated the impact of ART-mediated viral suppression on both depression severity and tryptophan levels. Among those contributing data at months 6 and 12 of ART, 402 of 430 (93.5%) and 330 of 360 (91.7%) participants, respectively, had a plasma HIV RNA level ≤ 400 copies/mL. Over the 12-month study period, depression scores declined to a median of 1.08 (P<0.001), and 28 of 353 (7.9%) participants met screening criteria for probable depression (P<0.001). The change in depressive symptoms was non-linear over the 12 month period, with the greatest rate of improvement in HSCL-D score observed in the first 6 months (−0.05 points per month, P<0.001) and a somewhat slower rate of

improvement observed between months 6 and 12 (−0.02 points per month, P<0.001) (Figure 1A).

The median plasma KT ratio decreased from 122 nM/μM to 60 nM/μM over the 12-month study period (P<0.001). This decrease was also non-linear, paralleling the decline in depression severity (Figure 1B). KT ratio was associated with level of depression symptom severity (+0.02 for each 10 nM/μM increase in KT ratio, P<0.001). The median plasma tryptophan level increased from 3710 ng/ml to 5280 ng/ml during the 12-month study period (P<0.001). This increase was also non-linear, mirroring the changes observed in depression severity (Figure 1C). Plasma tryptophan level was associated with level of depressive symptom severity (−0.07 for each 1000 ng/ml increase in tryptophan level, P<0.001) (Table 2).

After adjustment for age, gender, marital status, educational attainment, BMI, household asset wealth, AUDIT positive screen and CD4+ T cell count, the association between tryptophan level and depression symptom severity remained statistically significant (b= −0.05; 95% confidence interval [CI], −0.07 to −0.03; P<0.001) as did the association between KT ratio and depression (b=0.01; 95% CI, 0.004 to 0.02; P=0.004). Because IDO induction may partially mediate the associations between gender and depression and between CD4 count and depression (i.e., these factors might not appropriately be considered confounders), we conducted sensitivity analyses excluding these variables from the regression model. We also re-fit the regression models while limiting the sample to the 305 participants who had achieved viral suppression at 6 and 12 months. The estimates from these sensitivity models were qualitatively similar to our main adjusted findings (Table 2).

We next assessed the degree to which ART-mediated changes in tryptophan levels and KT ratio may have explained the observed declines in depression symptom severity. Inclusion of tryptophan in the regression model attenuated the association between duration of ART and depression symptom severity (Table 3): the z-score corresponding to the level difference in depression symptom severity during the first six months on ART was reduced by 17.7%. Similarly, upon the addition of KT ratio to the regression model, the z-score for the first six months on ART was reduced by 28.1%. In both models, the duration of ART variable remained statistically significant.

At the time of the first dietary diversity assessment, the median number of self-reported dietary protein sources was 2 (range, 0 to 5), with 99 participants (37.5%) reporting very few (0–1) protein sources. The median number of non-protein sources was 4 (range, 0 to 7). In the multivariable regression models, each additional dietary protein source was associated with a mean 188 ng/ml greater tryptophan level (P=0.01) while the number of non-protein sources was not (36 ng/ml of tryptophan per non-protein source, P=0.44). A lower number of dietary protein sources was also associated with depression symptom severity after adjustment for covariates (b=−0.05; 95% CI, −0.08 to −0.01; p=0.01).

Since poor dietary protein intake could plausibly exacerbate the effect of the kynurenine pathway of tryptophan catabolism on depression, we next assessed whether the relationship between KT ratio and depression was modified by self-reported dietary protein intake. As hypothesized, KT ratio tended to be more strongly associated with depression symptom severity among participants reporting 0–1 dietary protein sources (b=0.02 for each 10 nM/μM increase in KT ratio; 95% CI, 0.01–0.03; P<0.001) than among those reporting two or more dietary protein sources (b=0.01; 95% CI, −0.004 to −0.017; p=0.27), but the formal test for interaction was not statistically significant (P=0.08).

Discussion

It has long been recognized that depression is more common among HIV-infected individuals than in the general population and that ART leads to improved depression symptom severity.[13–16] While these observations have often been attributed to changes in psychosocial and general improvements in health,[18] our study has identified a potential biologic mechanism that may at least partially explain these observed findings. In this longitudinal study of HIV-infected individuals initiating ART in rural Uganda, we found baseline levels of tryptophan catabolism (through the kynurenine pathway) approximately 2 fold higher compared to HIV negative control populations,[29,30] and higher tryptophan catabolism and lower plasma tryptophan level were associated with greater depression symptom severity both before and during ART. We confirmed earlier reports finding that depressive symptoms are common among HIV-infected persons in Uganda,[5,6] and that symptoms improve during early ART,[15,17,18] and demonstrated that at least part of the ART-associated improvements in depression symptom severity may be mediated by increased plasma tryptophan levels. In ancillary analyses, we found that having few dietary protein sources was associated with low tryptophan level and increased depression symptom severity. Furthermore, the association between kynurenine pathway activity and depression symptom severity tended to be stronger among those with protein-deficient diets.

Our findings suggest that the immunologic changes associated with HIV infection and its treatment may at least partly explain the greater prevalence of depression observed among HIV-infected persons, as well as improvements in depressed mood observed during ART. IDO has long been recognized as an important immunoregulatory enzyme induced in activated dendritic cells and monocytes in response to several inflammatory diseases, cancers, and infections including HIV,[24,43–46] IDO induces the catabolism of tryptophan into several downstream immunologically active catabolites that decrease T cell proliferation and suppress Th17 cells, effects that appear to be important in the prevention of fetal allograft rejection during pregnancy, the evasion of many cancers from the host immune response, and in HIV pathogenesis.[47–50] However, the kynurenine pathway of tryptophan catabolism can also have important psychological effects.[19] Tryptophan is required for serotonin synthesis, and the relative depletion of serotonin in the CNS has been implicated in the pathogenesis of depression.[51] Furthermore, some downstream tryptophan catabolites, including quinolinic acid, can be neurotoxic and could contribute to cognitive impairment or mood disorders in this setting.[52] Indeed, the increase in IDO activity observed among women after giving birth is thought to be one potential biologic mechanism explaining postpartum depression among HIV-uninfected women.[20–23] Our finding that HIV-associated IDO induction of tryptophan depletion is associated with increased depression symptom severity both before and during ART is consistent with this earlier body of work and may provide unique insights into the biologic basis for depression in HIV infection.

This hypothesis is further supported through several of our ancillary analyses. Having few dietary protein sources was associated with low levels of tryptophan and greater depression symptom severity. Also, while the formal test for statistical interaction was not statistically significant, the association between kynurenine pathway activity and depression symptom severity was stronger among those with a protein-deficient diet. This suggests, but is not proven in our study, that the kynurenine pathway is causally related to depressive symptoms in this setting and not simply a marker for an alternative immunologic mechanism. Moreover, the observations may also partially explain the high prevalence of depression among HIV-infected individuals in resource-limited settings where food insecurity is common,[53] and may suggest a greater likelihood of observing an “anti-depressant” effect of ART in these settings compared to the resource-rich settings where these findings were first

noted.[13,18] If true, then dietary protein supplementation would be expected to have beneficial effects on depression among HIV-infected individuals with protein-limited diets, a hypothesis that is potentially testable in randomized controlled trials.

Our findings that higher tryptophan catabolism through the kynurenine pathway, and lower plasma tryptophan levels, were significantly associated with greater depression symptom severity during ART may also explain the observation that depression is associated with more rapid disease progression and death in both treated and untreated HIV-infected individuals.[10–12] HIV-associated immune activation may cause more rapid disease progression and death, but it may also lead to greater IDO-mediated depletion of tryptophan and, therefore, increased depressive symptom severity.

It is important to highlight that the correlations between KT ratio, tryptophan levels and depressive symptoms, while statistically significant, were modest in magnitude and that duration of ART retained a statistically significant association with depressive symptoms even after adjustment for tryptophan level and/or KT ratio. This suggests that factors other than tryptophan level and IDO induction are likely contributing to the apparently beneficial effect of ART on depression. Indeed, social integration, food insecurity and overall health status typically improve during ART,[54–58] and each of these factors likely contributed to decreased depressive symptoms as well. It is also relevant to acknowledge the possibility that both depression and kynurenine pathway induction may be less severe in patients starting ART at earlier disease stages. While we did not find evidence of interaction by CD4+ T cell count (data not shown), we cannot exclude the possibility that the estimated association between KT ratio and depression would be less strong in HIV-infected patients at earlier stages of disease.

There are several limitations to this analysis. First, we did not have access to formal DSM-IV diagnoses of major depressive disorder, so there may have been some misclassification of depression in this study. Second, depression may itself increase the risk of HIV acquisition[59] and thereby have independent effects on the immune system. Since our measures of IDO activity were concurrent with measures of depression, and since we do not have plasma samples and depression measures obtained prior to the participants' acquisition of HIV infection, we cannot confirm the causal direction of these relationships. Third, IDO induction and poor protein intake may simply be a consequence of poor overall health status that may drive depression through independent mechanisms. Fourth, our measure of dietary diversity is an imperfect measure of dietary protein intake (i.e., a persons who eats a large amount of a single type of protein may have greater total protein intake than one who eats small amounts of multiple protein sources). Yet, this is likely to have biased the association between tryptophan level and the number of dietary protein sources toward the null. Fifth, the tryptophan and kynurenine determinations were based on plasma specimens that were not confirmed to be fasting, which may have made associations more difficult to detect. Recent protein intake transiently increases both plasma tryptophan level and KT ratio, but this effect is likely modest relative to the wide distribution of levels observed in HIV-infected individuals[60] and, if anything, also would have biased the association between these measures and depression toward the null. Sixth, we did not have measurements of peripheral serotonin, which would have allowed us to observe more directly the link between depression and plasma tryptophan. Finally, tryptophan 2,3-Dioxygenase (TDO) may also contribute to tryptophan catabolism via the kynurenine pathway. Unlike IDO, TDO is not inducible and mainly expressed in the liver, such that the dramatic changes in kynurenine pathway activity seen in HIV infection and with ART are much more likely to be driven by changes in IDO then TDO expression[61]. HIV-mediated changes in the composition of the gut microbiome may also contribute to systemic kynurenine levels, even in the setting of ART-mediated viral suppression[62]. Thus, other factors beyond host IDO activity may

contribute to kynurenine levels, and their role in the biologic mechanisms underlying depression in HIV should be considered in future studies.

In summary, we identified the kynurenine pathway of tryptophan catabolism as a biologic mechanism that may partially explain why HIV-infected individuals have an increased risk of depression and why ART appears to decrease depression symptom severity. These data suggest that interventions designed to further reduce the inflammatory state and kynurenine pathway activity during ART may also have beneficial effects on depressive symptoms and that protein supplementation may also have beneficial effects on depression in resource-poor settings. Both of these hypotheses are testable in randomized clinical trials.

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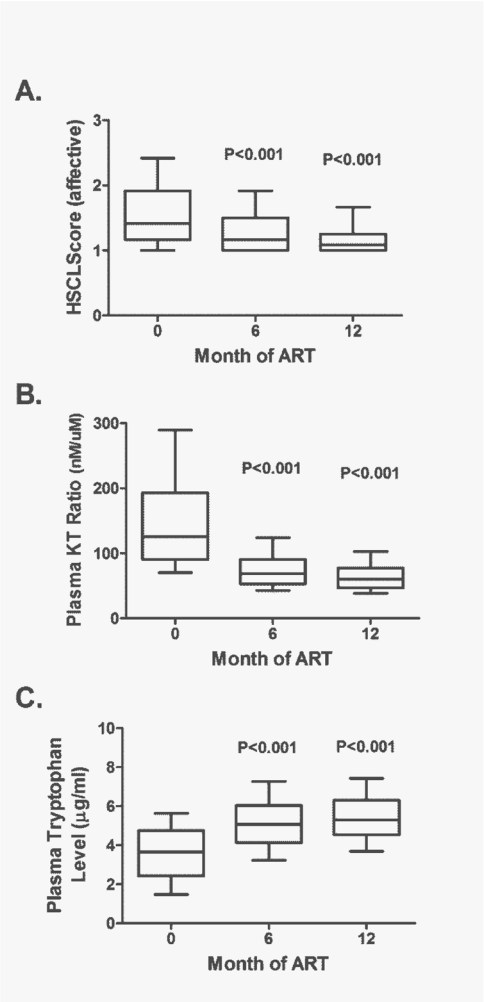

Figure 1.

Changes in Depression Symptom Severity, KT Ratio, and Tryptophan Levels during ART. HSCL-D score (A), plasma KT ratio (B), and tryptophan levels (C) are plotted at baseline (pre-ART), and at months 6 and 12 of ART in HIV-infected Ugandans. Horizontal lines represent medians, the boxes span the 25th and 75th percentile values, and the error bars span the 10th and 90th percentile values. P values represent change from baseline from random effects models.

Table 1

Selected pre-ART baseline characteristics of HIV-infected Ugandans

Characteristic	Total (n=504)
	Median (IQR) or No. (%)
Age, years	34 (29 to 39)
Female	318 (63.1)
Married	194 (38.5)
Achieved secondary education	104 (20.6)
Assets index	−0.26 (−1.6 to 1.43)
AUDIT-C positive	96 (19.1)
CD4+ count (cells/mm^3)	138 (80 to 213)
HIV RNA level (copies/ml)	4.97 (4.42 to 5.52)
BMI	21.0 (19.3 to 23.6)
Tryptophan [ng/ml]	3710 (2535 to 4810)
Kynurenine to tryptophan ratio(nM/uM)	122.2 (87.6 to 186.4)
Few (0 or 1) protein sources	99 (37.5)
HSCL depression core	1.42 (1.17 to 1.92)
Probable Depression (HSCL-D>1.75)	157 (31.2)

Table 2

Unadjusted and adjusted pooled associations between tryptophan level and depression symptom level, and KT ratio and depression symptom level among HIV-infected Ugandans initiating ART

	All participants, regardless of viral suppression		Participants who achieved viral suppression at 6 and 12 months
	Unadjusted b coefficient (95% CI; P-value)	**Adjusted* b coefficient (95% CI; P-value)**	**Adjusted* b coefficient (95% CI; P-value)**
Tryptophan level, per 1000 ng/ml increase	−0.07 (−0.09 to −0.06; 0.000)	−0.05 (−0.07 to −0.03; 0.000)	−0.07 (−0.091 to −0.048; 0.000)
KT ratio level, per 10 nM/ uM increase	0.02 (0.01 to 0.02; 0.000)	0.01 (0.004 to 0.02; 0.004)	0.01 (0.004 to 0.025; 0.005)

*Adjusted for age, gender, marital status, educational attainment, BMI, household asset wealth, AUDIT positive screen and CD4+ T cell count

Table 3

Random effects pooled regression estimates for associations of time on ART on depression symptom severity controlling for tryptophan and KT ratio separately

Independent variables	0–6 months		6–12 months	
	Adjusted coefficient (95% CI)	Z-score % change	Adjusted coefficient (95% CI)	Z-score % change
Duration on ART only	−0.051 (−0.060 to −0.041)	-	−0.016 (−0.024 to −0.007)	-
Duration on ART adjusted for Tryptophan	−0.046 (−0.056 to −0.036)	17.7	−0.015 (−0.023 to −0.006)	7.7
Duration of ART adjusted for KT ratio	−0.045 (−0.056 to −0.033)	28.1	−0.015 (−0.023 to −0.006)	5.8