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Depression and ART initiation among HIV serodiscordant couples in Kenya and Uganda

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Abstract

Background—Depression is a known barrier for antiretroviral therapy (ART) adherence, but less is understood about its effects on ART initiation.

Methods—We followed 1,013 HIV-infected individuals participating in the Partners Demonstration Project, an open-label study of integrated pre-exposure prophylaxis (PrEP) and ART delivery for HIV serodiscordant couples in Kenya and Uganda. Associations between depression, measured annually with the Hopkins Symptoms Checklist-Depression (HSCL-D), and ART initiation were assessed with Cox proportional hazards regression.

Results—At enrollment, 162 participants (16.0%) reported symptoms consistent with probable depression, defined by a HSCL-D mean score >1.75, and this proportion decreased during study follow-up (6.7% and 3.6% at 12- and 24-months, respectively; p-value <0.001). Greater depressive symptom severity was associated with a greater likelihood of ART initiation overall (adjusted hazard ratio [aHR] 1.32, 95% CI:1.01–1.73) and among participants with CD4 count <350 cells/μl

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COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of potential conflicts of interest: All authors declare no conflicts of interest.

Research involving human participants and/or animals: All procedures performed were in accordance with the ethical standards of the institutional review boards at the University of Washington and collaborating institutions in Kenya and Uganda, national research ethics committees for each study site, 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.

(aHR 1.30, 95% CI:1.01–1.67). Depression decreased six months after ART initiation (adjusted odds ratio [aOR] 0.34, 95% CI:0.23–0.51).

Discussion—Among East African HIV-infected persons in HIV serodiscordant couples, depression was not a barrier to ART initiation. ART initiation was associated with improved depressive symptoms in this setting.

Keywords

Depression; HIV; Antiretroviral therapy initiation; Africa

INTRODUCTION

Major depressive disorder affects an estimated 10–60% of HIV-infected adults in sub-Saharan Africa and is approximately 3–4 times more prevalent among people living with HIV than in the general adult population (1–8). Higher levels of depressive symptoms often are associated with reduced engagement in HIV care and adherence to antiretroviral therapy (ART) and accelerated viral progression (1,9–11). In sub-Saharan Africa, HIV-infected individuals with severe depression are approximately 40% less likely to adhere to ART regimens than those without depression (1,9,10,12). This association may have broad consequences for the potential clinical and prevention benefits of ART, as high rates of untreated depression are common worldwide and particularly in settings where HIV is prevalent (13). Women are more likely to report depressive symptoms and have approximately twice the risk of experiencing major depressive disorder in their lifetimes than men (7,14).

While associations between depression and ART adherence have been well-established, less research has been done to understand the impact of depression on ART initiation. Early initiation of ART to suppress HIV viremia is critical to optimize clinical benefits and reduce infectiousness (15,16). A new HIV diagnosis is a significant risk factor for depression and the period after initial diagnosis is particularly important for linkage into HIV care services (17,18). Prior research in sub-Saharan Africa has shown that individuals with depression are less likely to attend their initial HIV clinic appointments after diagnosis and that symptoms of “psychological distress” are associated with ART delay (17,19). However, recent work in South Africa found that depression did not impair linkage to care and ART initiation among individuals presenting to primary care clinics for HIV testing, potentially because this patient population was already motivated to seek healthcare despite their depressive symptoms (18). In addition, while research in the United States has demonstrated that depression is a risk factor for poor engagement with the healthcare system, a cross-sectional study in Uganda suggested that major depressive disorder was associated with a greater number of visits to a healthcare facility (17,20). The uncertain potential for depression to impact success with ART use in sub-Saharan Africa highlights an important gap for programmatic delivery of ART and whether there is a role for mental health assessment and treatment to impact ART programs (18).

To contribute information to this gap, we evaluated the association between depression and ART initiation among a cohort of 1,013 HIV-infected individuals participating in a study of

ART and pre-exposure prophylaxis (PrEP) use in Kenya and Uganda. In this unique study population, participants were all in stable partnerships, had mutually disclosed their HIV status to their partner prior to enrollment, and completed up to two years of follow-up to assess uptake and adherence to ART and PrEP. We hypothesized that: 1) participants with greater depressive symptom severity would be less likely to initiate ART than those with less severe symptoms and 2) the odds of depression would be lower for participants during periods when they were on ART compared with periods when they were not on ART.

METHODS

Study population

The Partners Demonstration Project was an open-label implementation study to evaluate integrated delivery of ART and PrEP for HIV prevention among high-risk, HIV serodiscordant couples (21). The study was implemented between November 2012 and June 2016 among 1,013 couples from four sites: Thika and Kisumu, Kenya and Kampala and Kabwohe, Uganda. Eligible participants were aged 18 years or older, planned to remain in their relationships for at least one year, and the HIV-infected members of the couples were not using ART at enrollment. Couples were followed for up to 24 months to assess their use of ART and PrEP as an integrated HIV prevention strategy. In this model, PrEP was offered to HIV-uninfected participants prior to ART initiation by their HIV-infected partners and through the first six months of sustained ART use, at which point PrEP discontinuation was encouraged. A majority of HIV-infected participants initiated ART (93%) and were virally suppressed 12 months after initiation (91%), indicating very high levels of ART initiation and adherence in this cohort (22). Participants were also assessed for depression at enrollment and annual follow-up visits, and those who screened positive were referred to local specialists for mental health care.

Data collection procedures

HIV-infected participants attended study visits on a quarterly basis with their HIV-uninfected study partner and were provided with couples-based HIV prevention counseling at each visit. Standardized questionnaires were administered by interviewers in the participant's preferred language to collect sociodemographic, sexual risk behavior, perceived risk of HIV transmission, and contraceptive use information. For HIV-infected participants, CD4 counts and plasma HIV-1 RNA viral loads were measured at enrollment and each six-month visit, and participants eligible for ART according to national guidelines for serodiscordant couples were either offered medications on-site or given referrals to local HIV-1 care clinics, according to participant preference. During the first two years of the study (2012–2013), the national guidelines recommended ART initiation for individuals with a CD4 count ≤ 350 cells/ μ l or symptomatic HIV disease. These guidelines were changed in 2014 to recommend ART initiation for all HIV-infected individuals in serodiscordant relationships, regardless of CD4 cell count.

At baseline and annual follow-up visits, HIV-infected participants were assessed for depression, internalized stigma, perceived social support, and problem alcohol use with validated questionnaires. Depression was measured using the 16-item version of the Hopkins

Symptoms Checklist for Depression (HSCL-D), which was validated and used previously in Uganda (23–25). Total scores were calculated as a mean value (from zero to four), with a value closer to four indicating higher depression symptom severity. We also calculated a binary measure of “probable depression” with a cutoff value >1.75 indicative of probable depression (26). Depression was analyzed as a time-dependent exposure and participants were assumed to have the same HSCL-D score and “probable depression” classification during the 12 months that elapsed between study visits. In sensitivity analyses, the scale’s five somatic items were removed, as these items could be related to progression of HIV infection rather than clinical depression (25,27).

Stigma was measured by summing scores from the six-item validated Internalized AIDS-Related Stigma Scale (28), with a value closer to six indicating greater internalized stigma. Problem alcohol use was indicated if participants responded “yes” to any of four items about harmful and hazardous drinking behavior. Social support was measured by calculating a mean score from the 10-item Functional Social Support Questionnaire (29,30), with a score closer to four indicating greater perceived social support. Stigma, alcohol use, and social support were also all analyzed as time-dependent covariates with scores carried forward between annual visits.

Statistical analyses

The primary outcome of interest was initiation of ART among HIV-infected study participants, not including short-course or single agent antiretroviral prophylaxis by pregnant women for the prevention of perinatal HIV transmission. Participants were excluded from the sample if they: were using ART at enrollment ($n=3$); did not attend follow-up visits to receive ART initiation counseling and information about their ART eligibility ($n=28$); or received ART initiation counseling at the final visit and did not have a subsequent visit to assess ART initiation ($n=9$). Follow-up time was measured from the initial study visit during which participants were eligible and received a recommendation from the study clinician to start ART based on the national guidelines, until either the date that they reported starting a three-drug ART regimen or until the date of the last study visit attended (for those who did not initiate ART).

We compared participant characteristics during periods of probable depression and those without probable depression using generalized estimating equations extension to logistic regression. The cumulative probability of ART initiation was estimated using Kaplan-Meier methods. To assess the effect of depressive symptom severity on ART initiation, we used Cox proportional hazards regression with robust standard error estimates to account for repeated measurements within subjects (31). In this model, study site, gender, and time-dependent measures of internalized stigma and social support were included based on *a priori* knowledge that 1) women are more likely to experience depression and initiate ART than men, 2) internalized stigma and social support are frequently predictive of depression, and 3) individuals with higher levels of stigma and lower levels of social support are less likely to use ART (32–36). We also assessed several additional covariates for confounding including age, education, income, marital status, partnership duration, time known to be in an HIV-1 serodiscordant relationship, and parity (all measured at enrollment), as well as

time-dependent measures of sexual behavior (number of sex acts, proportion of unprotected sex acts, number of partners), perceived risk of HIV transmission, STI symptoms, pregnancy, abuse, alcohol use, plasma HIV-1 RNA viral load ($\log_{10}$ copies/mL), and CD4 count (cells/ μ L). Of these covariates, any that resulted in a substantial change in the effect estimate ($>10\%$) were included in the multivariable model. We examined the presence of effect modification by CD4 count at enrollment (<350 cells/ μ L versus >350 cells/ μ L) using a likelihood ratio test since prior studies among cohorts with low median CD4 cell counts have shown significant associations between depression and linkage to HIV care but these associations have not been present among cohorts with higher median CD4 cell counts (17,18,37).

Finally, since depressive symptoms have been shown to decrease one year after ART initiation, we examined odds of probable depression at enrollment versus the study visit six and 12 months after ART initiation within participants using conditional logistic regression and the same adjustment factors as specified in the proportional hazards model (38,39). All analyses were conducted using SAS 9.4 (Cary, North Carolina, USA).

Ethical statement

Protocols were approved by ethical review boards at the University of Washington and collaborating institutions in Kenya and Uganda. All participants provided written informed consent.

RESULTS

Participant characteristics

Of the 1,013 HIV-infected participants followed in the Partners Demonstration Project, 679 were female (67.0%) and the median age at enrollment was 28 years (interquartile range [IQR] 23, 35 years) (21). The median reported duration of partnership was 3.1 years (IQR 1.0, 8.0 years). Most participants discovered that they were in an HIV serodiscordant relationship shortly before study enrollment (median time since learning their HIV serodiscordant results was 1.2 months before enrollment; IQR 1.2, 3.6 months). A majority ($n=643$; 63.5%) had at least one condomless sex act with their partner in the month prior to enrollment. The median CD4 count at enrollment was 436 cells/ μ L (IQR 272, 638) and the median plasma HIV-1 RNA concentration was 4.6 $\log_{10}$ copies/mL (IQR 3.9, 5.0). During the two-year study period, all 1,013 HIV-infected participants became eligible for ART based on the national guidelines (described in the Methods). After excluding those who were lost to follow-up or on ART at enrollment, 982 participants (96.9%) received counseling that they were eligible for ART. In this sample, 481 (49.0%) participants were eligible for ART at enrollment, 725 (73.8%) were eligible by their 6-month visit, and 894 (91.0%) were eligible by their 12-month visit.

At enrollment, 162 participants (16.0%) had probable depression as measured by the HSCL-D scale, which had high internal consistency in the baseline sample (Cronbach's $\alpha=0.90$; Table 1). The majority were women ($n=126$; 77.8% of those with probable depression), and 18.6% of all women in the study had probable depression at enrollment compared with

10.8% of men. The most commonly reported depressive symptoms included: feeling low in energy (53.1% of 1,013 participants at enrollment); loss of sexual interest or pleasure (48.8%); poor appetite (38.5%); worrying too much about things (35.5%); and feeling sad (35.0%). Participants with probable depression had higher baseline levels of internalized stigma than those without probable depression (median score of 4.0 versus 2.0, respectively; p -value <0.001). Levels of social support (median score of 3.4 for those with probable depression and 3.7 for those without depression) and frequency of problem alcohol use (20.4% for those with probable depression and 16.8% for those without probable depression) were similar for both groups at enrollment.

Associations between depression and participant characteristics during follow-up

The proportion of participants with probable depression decreased during study follow-up (6.7% and 3.6% of participants were classified as having probable depression at 12- and 24-month visits, respectively; p -value for trend <0.001). There was also evidence of decreasing HIV-related stigma and increasing social support between enrollment and annual follow-up visits (p -value <0.001 for both). Women had a higher prevalence of probable depression than men during follow-up (adjusted odds ratio [aOR] 1.64, 95% CI 1.11–2.42; Table 2).

Reporting verbal, physical, or emotional abuse from a study partner (aOR 2.26, 95% CI 1.11–4.62) and having CD4 counts ≤ 350 cells/ μ l (aOR 1.73, 95% CI 1.26–2.38) were also associated with probable depression during enrollment and follow-up visits. Additionally, participants were less likely to be using ART (aOR 0.65, 95% CI 0.48–0.87) at visits when they had probable depression, either because they never initiated ART or because they stopped ART after initiating. Higher levels of internalized stigma (aOR 1.46, 95% CI 1.33–1.61), greater frequency of problem alcohol use (aOR 2.02, 95% CI 1.32–3.11), and lower levels of social support from others (aOR 0.52, 95% CI 0.38–0.71) were more likely during periods with probable depression than during periods without probable depression. Other participants characteristics, including age, marital status, partnership duration, and sexual behavior, were not significantly associated with probable depression during follow-up.

Depression and ART initiation

A total of 973 participants were included in the analysis of depression and ART initiation. Rates of ART initiation were higher in participants with greater depressive symptom severity, after adjusting for study site, gender, stigma, social support, CD4 count, and viral load. A one-unit higher mean depressive symptom score (e.g. a score of 4.0 vs. 3.0) was associated with a 32% increase in ART initiation (adjusted hazard ratio [aHR] 1.32, 95% CI 1.01–1.73; Table 3). Sensitivity analyses removing somatic items from the depression symptom scale produced results that were not substantially different (aHR 1.20, 95% CI 1.02–1.37). The effect of depressive symptoms on ART initiation differed by baseline CD4 count ($p_{\text{interaction}} = 0.02$): among participants with a baseline CD4 count ≤ 350 cells/ μ l, greater depressive symptom severity was associated with ART initiation (aHR 1.30, 95% CI 1.01–1.67, Figure 1) but this association was not significant for those with a CD4 count >350 cells/ μ l.

For participants who initiated ART during study follow-up and had data for a study visit six months after ART initiation ($n=884$), the odds of probable depression were 66% lower when

comparing their enrollment visit with their visit six months after ART initiation (aOR= 0.34, 95% CI 0.23–0.51), after adjustment for internalized stigma, social support, problem alcohol use, CD4 count, and HIV-1 viral load (Table 4). Similar results were obtained in analyses of probable depression at 12 months after ART initiation (aOR=0.22, 95% CI 0.14–0.36), although fewer participants had sufficient time in the study to contribute data 12 months after ART initiation (n=786).

DISCUSSION

In this prospective cohort study of HIV-infected individuals in mutually disclosed HIV serodiscordant partnerships in East Africa, a minority (16.0%) reported probable depression at enrollment. The prevalence of probable depression decreased during follow-up, which may be related to continued involvement in a research study that increased participants' instrumental and emotional support and access to HIV care and treatment services (40). During follow-up, probable depression was more likely among women and participants experiencing social harm, internalized HIV-related stigma, problem alcohol use, less social support, and CD4 cell counts < 350 cells/ μ l. Participants with more severe depressive symptoms initiated ART earlier than those with less severe symptoms, a relationship that was strongest among those who had CD4 cell counts < 350 cells/ μ l. Given that most participants reported discovering they were in an HIV serodiscordant relationship shortly before study enrollment, depressive symptoms measured in this cohort may be primarily related to worry, fear, or concern about HIV status and transmission (18). This could explain the positive association found between depressive symptom severity and ART initiation, particularly among participants with lower CD4 cell counts.

Our findings are consistent with recent research in South Africa and Uganda which showed that depressive symptoms were not significantly associated with delayed ART initiation or poor healthcare engagement among adults in the primary care setting (18,20). In addition, while other studies in sub-Saharan Africa have also found reductions in depressive symptoms at 12-months after ART initiation, our findings demonstrate a more rapid change in depressive symptoms as well as a decline in HIV-related stigma and an increase in social support during study follow-up (39,41,42). ART use may mitigate depressive symptoms by acting through psychological, behavioral, or biological pathways (39,41–45). For example, regular ART use can result in lower HIV RNA viral loads and higher CD4 counts, improved physical health and quality of life, and reduced general distress, which may in turn lead to less severe depression (39,43,45). Prior research on the association between ART use and depression has largely been conducted in cohorts with more advanced HIV disease than this cohort. Our findings are novel in demonstrating an effect of ART use on depressive symptoms in a generally healthy cohort with a relatively high median CD4 cell count at enrollment. Future research is needed to more thoroughly understand the mechanism by which ART use can impact depression, particularly for patients with higher CD4 counts prior to ART initiation.

We classified probable depression using the HSCL-D, which includes items assessing both cognitive and somatic depressive symptoms. In HIV-infected populations, somatic scale items may actually capture HIV symptoms or ART side effects rather than depressive

symptoms (27). However, depression is often expressed more somatically in sub-Saharan Africa than in Western settings and we maintained the scale's somatic items in our primary analysis (25,27,46). We repeated our analyses after excluding the five somatic items and found similar results. The most commonly endorsed non-somatic item was "worrying too much about things", and this feeling may have motivated participants with more severe depressive symptoms to initiate ART. Depressive symptoms may influence ART initiation differently than ART adherence and these findings highlight the complex relationship between depression and ART use (1,18).

The strengths of this study included the large, prospective cohort with participants from four different African settings, the diverse mix of rural and urban HIV clinics where participants were counseled and received ART, and the use of a depressive symptom scale previously adapted for sub-Saharan Africa (24,25). Retention rates were high in the sample (only 28 participants did not attend any follow-up visits) and there did not appear to be a difference in depressive symptom severity between those who completely dropped out of the study and those who remained in follow-up long enough to receive counseling on ART initiation. Limitations of this study included annual depression measurement, which reduced our ability to detect more frequent changes in depression status during study follow-up. We carried forward depressive symptom scores between annual visits; however, prior research suggests that depressive symptoms may resolve themselves by about six months of study follow-up (47,48). The HSCL-D scale was interviewer-administered and report of depressive symptoms could have been influenced by social desirability bias. Interviews were conducted with trained counselors in order to mitigate this issue. In addition, there may be some misclassification of probable depression and we did not validate the cut-off score in our cohort. However, this misclassification is likely non-differential with respect to ART initiation and would be expected to attenuate our hazard ratio estimates. We did not have information on the date of initial HIV diagnosis so we were unable to adjust for length of time living with HIV, which could significantly impact both depressive symptoms and ART initiation. Instead, we used time known to be in a serodiscordant relationship, which may only be an approximate proxy measure given that disclosure is challenging and participants could have delayed disclosing to their partners for a time after diagnosis (49,50). We also did not ascertain history of mental illness and it is unclear if depressive symptoms preceded HIV diagnosis (potentially indicative of longer-term depressive disorder) or if they were a result of recent HIV diagnosis (indicative of adjustment disorder with depressive symptoms). Results of our conditional logistic regression analysis are likely confounded by time in the study, as participants initiated ART at different lengths of time after enrollment. Finally, participants were all in stable HIV serodiscordant relationships at enrollment and this cohort included both newly diagnosed individuals as well as people who were living with HIV for a number of years, so our findings may not be widely generalizable to other populations.

In conclusion, depressive symptoms did not appear to negatively impact ART initiation among HIV-infected individuals in HIV serodiscordant relationships and may have actually resulted in more rapid ART initiation among participants with CD4 counts ≥ 350 cells/ μ l. These findings indicate that such symptoms should not serve as a barrier to clinical administration of ART in the treatment-as-prevention era, although future research is necessary to confirm or refute our results. Furthermore, receipt of ART and HIV care

services may help to mitigate depressive symptoms in resource-limited settings. Our study supports the importance of offering ART to HIV-infected persons with depression and providing integrated mental health care to HIV serodiscordant couples, which has the potential to reach depressed individuals initiating ART, promote long-term engagement in HIV care, and reduce the burden of depression among people living with HIV.

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Figure I.

The cumulative probability of ART initiation by probable depression and CD4 cell count at enrollment (n=973)

Table I

Participant characteristics, by probable depression status at enrollment (n=1,013)

	Probable depression at enrollment ^I (n=162)	No probable depression at enrollment ^I (n=851)	p-value ²
Demographic characteristics			
Gender			
Male	36 (22.2%)	298 (35.1%)	0.002
Female	126 (77.8%)	553 (65.0%)	
Age, years	27.0 (23.0–35.0)	28.0 (23.0–36.0)	0.72
Any income reported	114 (70.4%)	625 (73.4%)	0.42
Education, years	8.0 (6.0–12.0)	8.0 (6.0–11.0)	0.18
Couple characteristics			
Married	152 (93.8%)	813 (95.5%)	0.35
Partnership duration, years	2.4 (1.0–6.4)	3.3 (1.1–8.2)	0.12
Number of children with study partner	1.0 (0.0–3.0)	2.0 (1.0–3.0)	0.13
Time known discordant, years	0.1 (0.0–0.1)	0.1 (0.1–0.3)	<0.001
Pregnant at enrollment	32 (25.4%)	106 (19.2%)	0.12
Sexual behavior, month before enrollment			
Number of sex acts with study partner	5.0 (3.0–10.0)	5.0 (3.0–10.0)	0.80
Any unprotected sex with study partner	111 (68.5%)	532 (62.5%)	0.15
Any sex with outside partner	7 (4.3%)	32 (3.8%)	0.73
STI symptoms	21 (13.0%)	59 (6.9%)	0.009
Circumcised (men only)	22 (61.1)	128 (43.0)	0.04
HIV-related characteristics			
Plasma HIV-1 RNA (log ₁₀ copies per mL)	4.5 (3.5–5.0)	4.5 (3.8–5.0)	0.50
CD4 count (cells per µl)	430.0 (210.0–587.0)	437.0 (278.0–645.0)	0.05
Eligible for ART	81 (50.0%)	400 (47.0%)	0.98
Perceived risk of transmitting HIV			
High risk	21 (15.4%)	109 (15.2%)	
Moderate risk	8 (5.9%)	94 (13.1%)	0.13
Low risk	55 (40.4%)	264 (36.7%)	
No risk	52 (38.2%)	252 (35.1%)	
Psychosocial and behavioral characteristics			
Internalized stigma ³	4.0 (2.0–5.0)	2.0 (1.0–4.0)	<0.001
Problem alcohol use ⁴	33 (20.4%)	143 (16.8%)	0.27
Social support ⁵	3.4 (2.9–3.9)	3.7 (3.3–4.0)	<0.001
Reported abuse	0 (0.0%)	2 (0.2%)	0.54

Data are number (%) or median (IQR). ART=Antiretroviral Therapy

^I Cognitive, behavioral disengagement, and somatic depressive symptoms were assessed with a Likert response scale ranging from 1 (“Not at all”) to 4 (“Extremely”). A mean score >1.75 was indicative of “probable depression”.

² p-values are based on the Wilcoxon rank sum test for continuous variables and χ^2 tests for categorical variables.

³ Internalized stigma was assessed with six items, scored as 1 (“Strongly agree or agree”) or 0 (“Strongly disagree or disagree”). Item scores were summed to calculate the total score.

⁴ Alcohol use was assessed with questions about guilt and forgetfulness after drinking, failure to meet expectations because of drinking, and desires to drink. An answer of “yes” to any item was indicative of problem alcohol use.

⁵ Both instrumental and emotional social support were assessed. Responses ranged from 1 (“I never receive this support”) to 4 (“I receive as much of this support as I would like”) and mean scores were calculated.

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Table II

Associations between probable depression and participant characteristics during study follow-up (n=1,013)

	Frequency of visits ^I		Factors associated with probable depression			
	Probable depression ²	No probable depression	Univariable OR (95% CI)	p-value	Multivariable OR ³ (95% CI)	p-value
Demographic characteristics						
Female	861/1109 (77.6)	5884/8927 (65.9)	1.62 (1.12–1.34)	0.01	1.64 (1.11–2.42)	0.01
Age, years	27.0 (23.0–35.0)	28.0 (23.0–35.0)	1.00 (0.98–1.01)	0.64	.	.
Any income	755/1109 (68.1)	6563/8927 (73.5)	0.81 (0.57–1.14)	0.23	.	.
Education, years	8.0 (6.0–12.0)	8.0 (6.0–11.0)	0.99 (0.94–1.04)	0.71	.	.
Couple characteristics						
Married	1038/1109 (93.6)	8525/8927 (95.5)	0.63 (0.31–1.26)	0.19	.	.
Partnership duration, years	2.15 (0.87–5.78)	3.27 (1.05–8.15)	0.99 (0.96–1.02)	0.36	.	.
Number of children	1.0 (0.0–3.0)	2.0 (1.0–3.0)	0.99 (0.91–1.06)	0.71	.	.
Time known to be discordant, years	0.1 (0.0–0.1)	0.1 (0.1–0.3)	0.79 (0.61–1.02)	0.07	.	.
Pregnant (women)	166/862 (19.3)	680/5884 (11.6)	1.59 (1.07–2.37)	0.02	1.32 (0.92–1.90)	0.13
Sexual behavior						
Number of sex acts with study partner	4.0 (1.0–8.0)	3.0 (1.0–8.0)	1.00 (0.98–1.01)	0.62	.	.
Any unprotected sex acts with study partner	263/908 (29.0)	2266/8003 (28.3)	1.07 (0.87–1.32)	0.53	.	.
Any sex with outside partner	49/908 (5.4)	534/8003 (6.7)	0.91 (0.52–1.57)	0.73	.	.
STI symptoms	160/1109 (14.4)	627/8927 (7.02)	1.43 (0.85–2.41)	0.18	.	.
HIV-related characteristics						
Plasma HIV-1 RNA (log10 copies/mL)	3.8 (1.6–4.7)	2.3 (1.5–4.4)	1.22 (1.12–1.32)	<0.001	1.01 (0.91–1.13)	0.82
CD4 count 350 (cell/μl)	400/1109 (36.1)	2249/8927 (25.2)	1.59 (1.14–2.08)	0.005	1.73 (1.26–2.38)	0.001
Using ART	518/1109 (46.7)	5505/8927 (61.7)	0.67 (0.53–0.84)	0.001	0.65 (0.48–0.87)	0.004
Psychosocial and behavioral characteristics						
Internalized stigma	4.0 (2.0–5.0)	2.0 (1.0–3.0)	1.53 (1.39–1.68)	<0.001	1.46 (1.33–1.61)	<0.001
Problem alcohol use	256/1109 (23.1)	1372/8927 (15.4)	1.91 (1.25–2.91)	0.003	2.02 (1.32–3.11)	0.001
Social support	3.4 (2.8–3.9)	3.7 (3.4–4.0)	0.45 (0.34–0.60)	<0.001	0.52 (0.38–0.71)	0.004
Any abuse reported	19/902 (2.1)	52/7972 (0.7)	2.77 (1.56–4.90)	<0.001	2.26 (1.11–4.62)	0.03

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OR=Odds Ratio; CI=Confidence Interval

¹Data are n/N(%) or median (IQR). The number of data points assessed is total number of visits with each characteristic during study follow-up, stratified by depression status.

²A mean HSCL-D score ≥ 1.75 was indicative of "probable depression".

³Multivariable models adjusted for study site and all other factors associated with probable depression in the univariable models.

Table III

Associations between depressive symptom severity and ART initiation among HIV-infected participants (n=973)

	Unadjusted		Adjusted ^I	
	HR (95% CI)	Wald p-value	aHR (95% CI)	Wald p-value
Depressive symptoms ²	1.35 (1.06–1.71)	0.01	1.32 (1.01–1.73)	0.04
Among those with CD4 Count ≤ 350	1.39 (1.10–1.77)	0.01	1.30 (1.01–1.67)	0.04
Among those with CD4 Count >350	0.91 (0.68–1.22)	0.53	1.08 (0.79–1.48)	0.63

HR=Hazard Ratio; aHR= adjusted Hazard Ratio; CI= Confidence Interval

^IModel adjusted for study site, gender, and time-varying internalized HIV-related stigma, social support, CD4 count, and viral load.

²Depressive symptoms are measured as the continuous mean score on the HSCL-D scale (range 1–4).

Table IV

Odds of probable depression before and after ART initiation

	N(%) of visits with probable depression ¹	OR (95% CI) p-value	Adjusted OR (95% CI) ² p-value
6 months after ART initiation (n=884)			
Visits 6 months after ART initiation	100 (11.3)	0.14 (0.06–0.35) <0.001	0.34 (0.23–0.51) <0.001
Enrollment visits before initiating ART	131 (14.8)	Reference	Reference
12 months after ART initiation (n=786)			
Visits 12 months after ART initiation	42 (5.3)	0.13 (0.03–0.64) 0.01	0.22 (0.14–0.36) <0.001
Enrollment visits before initiating ART	112 (14.2)	Reference	Reference

OR=Odds Ratio; CI=Confidence Interval

¹ A mean HSCL-D score >1.75 was indicative of “probable depression”.² Model adjusted for internalized HIV-related stigma, social support, problem alcohol use, CD4 count, and viral load.