Depression, adherence and attrition from care in HIV-infected adults receiving antiretroviral therapy

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ABSTRACT

Background A better understanding of the relationship between depression and HIV-related outcomes, particularly as it relates to adherence to treatment, is critical to guide effective support and treatment of individuals with HIV and depression. We examined whether depression was associated with attrition from care in a cohort of 610 HIV-infected adults in rural Rwanda and whether this relationship was mediated through suboptimal adherence to treatment.

Methods The association between depression and attrition from care was evaluated with a Cox proportional hazard model and with mediation methods that calculate the direct and indirect effects of depression on attrition and are able to account for interactions between depression and suboptimal adherence. Depression was assessed with the Hopkins Symptom Checklist-15; attrition was defined as death, treatment default, or loss to follow-up.

Results Baseline depression was significantly associated with time to attrition after adjustment for receipt of community-based accompaniment, physical functioning quality of life score, and CD4 cell count (HR=2.40, 95% CI 1.27 to 4.52, p=0.005). In multivariable mediation analysis, we found no evidence that the association between depression and attrition after 3 months was mediated by suboptimal adherence (direct effect of depression on attrition: OR=3.90 (1.26 to 12.04), p=0.02; indirect effect: OR=1.07 (0.92 to 1.25), p=0.38).

Conclusions Even in the context of high antiretroviral therapy adherence, depression may adversely influence HIV outcomes through a pathway other than suboptimal adherence. Treatment of depression is critical to achieving good mental health and retention in HIV-infected individuals with depression.

BACKGROUND

Depression is an important comorbidity among HIV-infected individuals, who may be up to five times as likely as uninfected individuals to experience depression.[1] Depression has been shown to be caused or exacerbated by HIV-related stigma and HIV-associated declines in physical health;[2 3] however, whether it accelerates disease progression or leads to worse HIV outcomes is less certain. With the increasing availability of antiretroviral therapy (ART), it is important to evaluate to what extent any observed association between depression and HIV prognosis is due to the mediating effect of suboptimal adherence to therapy, which may be more common among depressed HIV-infected patients[4–6] and is a major determinant of adverse HIV-related outcomes, including death and detectable HIV viral load.[7–9]

Several prospective studies have found significant associations between depressive symptoms and mortality after adjustment for adherence to the HIV treatment regimen.[10–12] Immunological research has also supported a biological link between depression and worse HIV prognosis. Several studies found increased cytotoxic CD8 T-cell activation and lower natural killer cell activity in HIV-infected individuals with clinical depression,[13 14] while others found a higher risk of AIDS with increasing serum cortisol levels, a steroid hormone associated with depression.[15 16] In contrast, one study in US veterans found no evidence of an association between depressive symptoms and mortality or AIDS-defining illness after adjustment for combination ART, while another, conducted prior to the availability of ART, found no association between depressive symptoms and accelerated mortality or worse medical outcome.[3 17]

A better understanding of the nature of the relationship between depression and HIV-related outcomes, as it relates to adherence to treatment, is critical to guide effective support and treatment of individuals with HIV and depression, particularly in rural, resource-poor settings. We examined whether depression was associated with attrition from care among HIV-infected adults in Rwanda and whether any relationship between depression and attrition was mediated through suboptimal adherence to treatment.

METHODS

Study setting and study population

The study population comprised 610 HIV-infected adults initiating ART for the first time between June 2006 and August 2008 at one of nine health clinics in three rural districts of Rwanda. These adults were enrolled in a prospective cohort study comparing two ART delivery models over 12 months[18 19] in which all participants received clinic-based HIV care including ART administered according to the Rwanda National Guidelines, and were encouraged to disclose their HIV status to a friend of a family member and to designate a treatment supporter.[20]

Patients from two districts additionally received community-based accompaniment, which included daily community health worker visits, directly observed ART at least once daily, nutritional support, transportation stipends, and as-needed socioeconomic support. In communities receiving community-based accompaniment, a community health worker made multiple attempts to track down patients who did not return for care. Similar

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attempts were made to locate patients living in the district without accompaniment as staffing and financial resources permitted. Details of the design of this study have been described elsewhere.[19]

Individuals without a baseline measurement for depression were excluded from this analysis. The study was approved by the Partners Human Research Committee and by the Rwanda National Ethics Committee.

Depression measurement

Depression at the time of ART initiation (ie, baseline) was assessed using the 15-item Hopkins Symptom Checklist (HSCL-15) which covers such symptoms as 'feeling low in energy' and 'feeling hopeless about the future'. Respondents are asked to rate how often they experience each symptom ('not at all', 'a little bit', 'quite a bit', and 'extremely'), and each response is assigned a score of 1–4.[21] Participants with a mean per question score greater than 1.75 were classified as depressed.[21] This scale has demonstrated good psychometric properties in Rwanda (Cronbach's α=0.87).[22]

Adherence measurement

We measured self-reported adherence at 3 months, using the Center for Adherence Support Evaluation (CASE) Adherence Index. The index has been shown to predict virological response and correlate strongly with the Adult AIDS Clinical Trials Group 3-day recall.[23] The CASE questionnaire asks individuals to recall the frequency of difficulty in taking HIV medications on time, the average number of days per week at least one dose of HIV medications was missed, and how long ago he/she missed a dose of HIV medications.[23] Composite scores from the scale range from 3–16; however, pilot data from the study population suggested that participants had difficulty distinguishing between two response categories: missing a dose an average of 'zero times per week' and 'less than once a week'. We therefore combined these response categories for a total maximum score of 15. A CASE index score of 10 or less indicates suboptimal adherence.[23]

Attrition definition

Attrition was defined as death from any cause, loss to follow-up, or treatment default during the study period. An individual was lost to follow-up or considered to have defaulted treatment if he or she did not return to the clinic or stopped treatment, respectively, for 60 consecutive days. No participant discontinued care while continuing study participation. On the basis of studies that have found that HIV-infected individuals who are lost to follow-up are often deceased,[24 25] we believed that attrition would be a good proxy for death in this cohort.

Baseline covariates

We assessed the following baseline covariates as potential confounders of associations between depression and attrition and suboptimal adherence and attrition: CD4 cell count, WHO HIV Disease Stage,[26] gender, age, marital status, body mass index, model of ART delivery (ie, community-based accompaniment vs none), travel time to the clinic, and receipt of tuberculosis therapy at the start of ART. The WHO HIV disease stage was determined by a clinician prior to ART initiation.[26]

Since greater levels of social support, quality of life, and food security have been shown to correlate with lower depression levels, higher adherence to ART, and better HIV prognosis,[6 27] we used validated survey instruments to measure these constructs: the Duke/UNC Functional Social Support Questionnaire (DUFSSQ),[28] the physical functioning quality of life subscale of the Medical Outcome Study HIV Health Survey (MOS-HIV),[29] and the Household Food Insecurity Access Scale (HFIAS).[30] Higher scores on the eight-item DUFSSQ indicate greater social support, with a maximum possible score of 40 points. The nine-question HFIAS measures the severity and frequency of problems related to household food access and permits classification of food insecurity into categories of none, mild, moderate and severe.[30] The MOS-HIV physical functioning subscale is scored on a 100-point scale, with higher scores indicating better physical functioning. The DUFSSQ and MOS-HIV physical functioning subscale demonstrated good psychometric properties in this cohort (Cronbach's α=0.91 and 0.88, respectively).[22]

Statistical analysis

We examined the association between depression and attrition from care in two ways. First, we used a Cox proportional hazard model to evaluate time to attrition. Baseline covariates shown in table 1 that were associated with depression at $p<0.20$ in univariable analysis were considered potential confounders and retained in the final multivariable model if they altered the effect estimate for depression by >10%. The DUFSSQ and MOS-HIV scores were treated as continuous variables, while the HFIAS score was treated as a categorical variable. We checked for violations of proportional hazards using Martingale residuals.

Second, we examined whether the association between depression and attrition was mediated by suboptimal adherence to ART. We constructed separate multivariable models to examine associations between baseline depression and attrition and between suboptimal adherence at 3 months and attrition. We considered confounders of the depression–attrition relationship and the adherence–attrition relationship according to the methods described for the Cox proportional hazard analysis. Analysis of these two multivariable models was operationalised using an SAS macro developed by Valeri and Vanderweele,[31] which additionally calculates the direct effect of depression on attrition and the indirect effect (ie, the effect of depression that is mediated through suboptimal adherence). The resulting ORs indicate the extent to which the overall effect of depression on HIV outcome is mediated through suboptimal adherence.[32] This approach to mediation analysis allows for incorporation of an interaction between the exposure and mediator,[33] the presence of which has been previously proposed between depression and adherence among HIV-infected individuals.[34] We fit models with and without an interaction between depression and suboptimal adherence. SEs for the ORs were estimated using the delta method. Individuals who lacked an adherence measurement at 3 months due to early attrition or early transfer out of the programme were excluded from the analysis.

In both the Cox proportional hazard and mediation analyses, to account for the small amount of missing covariate data, we performed multivariable analyses on data sets multiply imputed (N=11) using covariate and outcome data. Imputation was conducted using the Markov Chain Monte Carlo methods (SAS MI Procedure), and effect estimates were pooled across data sets. We repeated our analyses using only confirmed cases of death as the outcome.

RESULTS

Of the 610 study participants, 601 (99%) had a baseline measurement of depression and were included in the analysis. Nearly half of the participants were depressed at baseline (47%; table 1).

Table 1 Baseline characteristics of 601 HIV-infected adults in rural Rwanda

Variable (N)	
Categorical variables	**N (%)**
Depressed (N=601)	283 (47.1)
Female sex (N=601)	368 (61.2)
Marital status (N=598)	
Married	312 (52.2)
Living with partner	34 (5.7)
Never married	27 (4.5)
Widowed	165 (27.6)
Divorced	40 (6.7)
Separated	20 (3.3)
WHO HIV disease stage (N=600)	
1	114 (19.0)
2	191 (31.8)
3	280 (46.7)
4	15 (2.5)
HFIAS food insecurity category (N=600)	
Food secure	52 (8.7)
Mildly food insecure	24 (4.0)
Moderately food insecure	142 (23.7)
Severely food insecure	382 (63.7)
Tuberculosis treatment at start of ART (N=599)	23 (3.8)
ART delivery model—community-based support (N=601)	296 (49.3)
Travel time to clinic (N=546)	
Less than 30 min	128 (21.6)
30–60 min	146 (24.6)
1–2 h	182 (30.6)
2–3 h	90 (16.5)
>3 h	48 (8.1)
Continuous variables	Median (range)
Age (N=601)	38 (21–80)
Body mass index (N=597)	20.8 (13.3–31.6)
CD4 count (N=601)	214 (4–350)
DUFSSQ score (N=600)	16.6 (8–40)
MOS-HIV Quality of life: physical functioning score (N=594)	71.5 (0–100)
Cost to get to clinic, in FRw* (N=553)	742 (0–8000)

*US$1=530 FRw in 2008.
ART, antiretroviral therapy; DUFSSQ, Duke/UNC Functional Social Support Questionnaire; HFIAS, Household Food Insecurity Access Scale; MOS-HIV, Medical Outcome Study HIV Health Survey (MOS-HIV).

Relationship between depression and attrition

Forty-eight cases of attrition were observed during the 1-year follow-up period (35 deaths, 13 defaults or losses to follow-up). Depression was associated with time to attrition in a univariable Cox proportional hazard analysis (HR=2.11, 95% CI 1.17 to 3.81, p=0.01). In multivariable analysis, there was a significant association between depression and time to attrition after adjustment for the ART delivery model, physical functioning quality of life score, and CD4 cell count (HR=2.40, 95% CI 1.27 to 4.52, p=0.005). Analyses with Martingale residuals showed no violations of the proportional hazards assumption.

Mediation analysis

After excluding 1 person who transferred to a different treatment programme and 28 participants who experienced attrition prior to the 3-month adherence assessment, the mediation analysis included 572 individuals, of whom 20 experienced attrition. The 28 excluded cases of early attrition had significantly lower baseline CD4 cell counts (p<0.0001) and a more advanced WHO HIV Disease Stage (p=0.003) compared with the population included in the mediation analysis, but did not differ by age, sex, social support score, or household food insecurity. The prevalence of baseline depression in those included and excluded was 47% and 57%, respectively (p=0.28). Thirty-one individuals who were alive and still in care were missing observations for adherence at 3 months. Participants with missing adherence values were older than those without (p=0.0008).

Twelve per cent of individuals reported suboptimal adherence at 3 months. Depressed participants were more likely to be female, single (ie, not married and not living with a partner) and to have moderate or severe food insecurity and lower physical functioning quality of life scores at baseline (table 2). Depression was also more common among individuals initiating ART at a site with community-based accompaniment and in those with longer clinic travel times. Baseline disease severity, as measured by the CD4 cell count and WHO HIV Disease Stage, was comparable across patients with and without baseline depression as well as across patients with optimal versus suboptimal adherence. Individuals with depression more commonly had a low body mass index and were receiving tuberculosis treatment at the start of ART. Female sex and higher physical functioning quality of life scores were associated with suboptimal adherence at 3 months, whereas older age, receipt of community-based accompaniment, and longer travel times were inversely associated with suboptimal adherence (table 2). Prevalence of self-reported alcohol intake greater than 1 drink/week and smoking at 3 months was low (2% for both).

Consistent with our survival analysis, we observed a positive overall association between depression and attrition from care (OR=4.17, 95% CI 1.34 to 13.00, p=0.01) after adjustment for the ART delivery model, physical functioning quality of life score, and age. Nearly all of this association appeared to be independent of ART adherence at 3 months (OR for direct effect=3.90, 95% CI 1.26 to 12.04, p=0.02), and we found no evidence that the relationship between depression and attrition was mediated through suboptimal adherence (OR for indirect effect=1.07, 95% CI 0.92 to 1.25, p=0.38). Results of a complete case analysis were similar (OR for direct effect=3.53, 95% CI 1.12 to 11.15, p=0.03; OR for indirect effect=1.08, 95% CI 0.91 to 1.28, p=0.37). The interaction between depression and adherence was not statistically significant (p=0.91) and was therefore not included in the final model. In all models, analyses including only confirmed cases of death produced similar results.

DISCUSSION

The high prevalence of baseline depression in this cohort and other HIV-infected populations underscores the need for effective and accessible mental health services for HIV-infected individuals.[35] The twofold to fourfold increase in attrition observed in adults with depression, compared with those without depression, suggests that promptly identifying and effectively treating depression in HIV-infected individuals may improve treatment outcomes in addition to mental health. Results from our mediation analysis point to an association between depression and attrition that is independent of adherence to ART, suggesting that adherence support alone may be insufficient to avert adverse HIV-related outcomes among people with depression. Mental health service utilisation has previously been shown to be associated with improved treatment adherence and reduced mortality among HIV-infected patients.[12] The integration of

Table 2 Correlates of depression and suboptimal adherence

	Depression			Suboptimal adherence		
Variable	**N with data**	**OR**	**p Value**	**N with data**	**OR**	**p Value**
Female sex	572	1.90 (1.35 to 2.68)	0.0003	541	1.95 (1.08 to 3.54)	0.03
Age	572	1.01 (0.99 to 1.03)	0.39	541	0.96 (0.93 to 0.99)	0.007
Married or living with partner	570	1.45 (1.04 to 2.03)	0.03	539	1.19 (0.70 to 2.01)	0.52
Body mass index <18.5	568	1.55 (1.05 to 2.30)	0.03	538	0.51 (0.24 to 1.05)	0.07
CD4 cell count	572	1.002 (1.001 to 1.003)	0.09	541	1.00 (0.997 to 1.003)	0.79
WHO HIV disease stage	571		0.56*	540		0.91*
4		Reference			Reference	
3		1.14 (0.37 to 3.48)			0.73 (0.15 to 3.45)	
2		0.86 (0.28 to 2.67)			0.81 (0.17 to 3.87)	
1		1.03 (0.33 to 3.26)			0.63 (0.12 to 3.22)	
Residence in a district that provided community-based support	572	5.57 (3.89 to 7.99)	<0.0001		0.07 (0.03 to 0.18)	<0.0001
Travel time to clinic	567		<0.0001*	538		0.001*
Less than 30 min		Reference			Reference	
30–60 min		0.96 (0.58 to 1.61)			0.50 (0.25 to 0.99)	
1–2 h		1.58 (0.98 to 2.54)			0.43 (0.22 to 0.84)	
More than 2 h		3.43 (2.04 to 5.74)			0.15 (0.05, 0.39)	
Social support score	571	1.00 (0.98 to 1.02)	0.98	540	0.97 (0.94 to 1.01)	0.12
Food security status	571		0.0004*	540		0.19*
Food secure		Reference			Reference	
Mildly food insecure		1.94 (0.62 to 6.11)			0.90 (0.21 to 3.88)	
Moderately food insecure		4.65 (2.09 to 10.34)			0.38 (0.13 to 1.13)	
Severely food insecure		4.40 (2.07 to 9.32)			0.88 (0.37 to 2.09)	
Quality of life—physical functioning score	565	0.97 (0.96 to 0.98)	<0.0001	534	1.03 (1.01 to 1.04)	<0.0001
Receiving tuberculosis treatment at ART initiation	571	2.56 (1.03 to 6.38)	0.04	540	0.39 (0.05 to 2.96)	0.36

*Type III test.
ART, antiretroviral therapy.

HIV and mental health services is an essential step to effectively intervene on the myriad adverse effects of depression, including those related to HIV.

This study is the first, to the best of our knowledge, to examine whether suboptimal adherence mediates the relationship between depression and HIV outcomes using an approach that accounts for confounders of the association between depression and attrition and between adherence at follow-up and attrition, as well as an interaction between depression and adherence. Excluding an interaction term can result in bias.[32] Lima *et al*[34] proposed that the effect of depression on HIV outcome may be modified by adherence level, suggesting that an interaction term may be necessary in evaluating this association. While our results did not suggest that the effect of depression varies by level of adherence, our methods would have allowed us to validly estimate the effect in the presence of an interaction.

In this cohort, more than half of the attrition cases occurred soon after ART initiation and before the 3-month adherence assessment. Consistent with previous reports that early deaths in ART programmes tend to be due to more severe HIV disease, individuals who experienced early attrition were more likely to have advanced HIV disease.[24] Although excluded individuals were not significantly more likely to be depressed, if excluded depressed patients were more likely to have suboptimal adherence than included depressed patients, this could have attenuated our estimate of the mediated effect of depression on attrition.

A second limitation relates to our measure of self-reported adherence. Data from a similar population in Rwanda suggest that depression may be associated with multiday adherence lapses, which were not assessed in this study.[36] If depression leads to non-adherence not captured by the CASE Index, we may have been limited in our ability to detect an association between depression and adherence. Furthermore, the quality care received by study participants in the context of Rwanda's National HIV programme and the additional adherence support received by participants in the community-based accompaniment arm most likely facilitated the high rate of self-reported adherence at 3 months (88%) and may have obscured an association between depression and suboptimal adherence that exists in the absence of this quality care and support. This, and the small number of individuals reporting suboptimal adherence, may in part explain why we did not observe a significant association between depression and attrition that was mediated through suboptimal adherence. Finally, caution should be taken when interpreting the univariable correlates of depression and suboptimal adherence, as the distribution of some covariates differed according to the ART delivery model received. For example, the positive relationship between the CD4 cell count and depression was most likely due to the fact that individuals who received community-based accompaniment tended to have higher CD4 cell counts at the time of ART initiation and a higher baseline prevalence of depression.

Nearly three quarters of the 48 attrition cases were due to death. At the time this study was conducted, Rwanda did not have a death registry to confirm the status of patients who were lost to follow-up; however, studies conducted elsewhere in sub-Saharan Africa suggest that a large proportion of patients who are lost to follow-up are deceased.[24 25] Reassuringly, analyses using only confirmed cases of death produced similar

results. Finally, although we considered numerous potential confounders, we cannot discount the possibility of residual or unmeasured confounding of the depression–attrition relationship or the adherence–attrition relationship.

Adherence to ART is a key factor in treatment success, and effective interventions for those at high risk of suboptimal adherence will improve HIV outcomes.[37 38] While the results of this study do not suggest that additional targeted adherence support for patients with depression would have improved HIV treatment outcomes in this cohort, it is noteworthy that all patients in this study were receiving care in Rwanda's National HIV programme, the success of which has been documented.[39] Although our findings may be generalisable to other strong ART programmes with high adherence levels, in some settings adherence is most likely an important mediator between depression and attrition, and adherence-related support may represent an important intervention. Results from a small randomised study conducted in Mexico raise the possibility that treatment of depression may be a requirement for a sizeable and sustained improvement in adherence for HIV-infected adults with depression.[40] Further study of the biological mechanisms responsible for the relationship between depression and adverse ART outcomes will inform the management of patients with these two conditions.

What is already known on this subject

- While depression can be caused or exacerbated by HIV-related stigma and HIV-associated health declines, less is known about whether it in turn accelerates disease progression or leads to worse HIV outcomes.
- In an era of increasing availability of antiretroviral therapy (ART), it is important to evaluate to what extent observed associations between depression and worse HIV prognosis are due to the mediating effect of suboptimal adherence to therapy.

What this study adds

- This study of a cohort of 610 HIV-infected individuals in rural Rwanda is among the first to examine the interplay between depression, adherence and treatment outcomes in a rural setting in sub-Saharan Africa. It is also the first, to the best of our knowledge, to study whether suboptimal adherence mediates the relationship between depression and HIV outcomes using an approach that accounts for confounders of the association between depression and attrition and between adherence at follow-up and attrition from care, as well as an interaction between depression and adherence.
- The twofold to fourfold increase in attrition from care observed in adults with depression compared with those without depression suggests that promptly identifying and effectively treating depression in HIV-infected individuals may improve HIV treatment outcomes in addition to mental health.
- At the same time, the results from our mediation analysis point to an association between depression and attrition that is independent of adherence to ART, suggesting that adherence support alone may be insufficient to avert adverse HIV-related outcomes among people with depression.

The results of this study highlight the importance of integrating mental health services into existing health services for HIV-infected individuals in rural Rwanda, 1 in 10 of whom is estimated to have depression.[36] The Rwanda Ministry of Health is currently engaged in efforts to increase human resource capacity for mental health services, particularly in district hospitals and rural clinics.[41] Systematic screening for depression in the HIV primary care setting has been shown to be feasible despite challenges related to implementation.[42] Screening coupled with the effective treatment of depression in individuals diagnosed with HIV may lead to improved treatment outcomes and improved mental health. The identification of effective care delivery models for these settings is a key area of future research.

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