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Likely Clinical Depression and HIV-Related Decline in ART Untreated Women who Seroconverted During Participation in Microbicide Trials in Sub-Saharan Africa

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Abstract

Depression worsens HIV outcomes in populations treated with antiretroviral (ART) medications. Data are limited on the relationship between depression and HIV in untreated populations in sub-Saharan Africa. We aimed to identify associations between likely clinical depression, alcohol use, social support by partners, and HIV VL among ART untreated women who recently became HIV positive and enrolled in the Microbicide Trials Network (MTN)-015 study. Analyses used cross-

sectional data collected at baseline in MTN-015. Participants in this analysis (N=190) enrolled from other MTN trials, were not receiving ART, and provided data on their HIV disclosure status to their husband or male partner and alcohol use behavior. The dependent variable, VL, was categorized as: low (≤400 RNA copies/ml; 9.1% of participants), medium (401–20,000 RNA copies/ml; 48.8%), and high (>20,000 RNA copies/ml; 42.0%). Depression was assessed using eight-items from Hopkins Symptom Checklist; a cutoff of ≥1.75 indicated likely clinical depression. Independent variables with a significance of $p \leq 0.05$ in unadjusted regressions were included in a regression adjusted for age, education, and time since seroconversion. Depressive symptoms were positively associated with high VL, in the adjusted regression [OR=1.80; 95%CI=1.07–3.01]. Results suggest that likely having clinical depression may have a biological relationship with HIV disease progression.

Introduction:

Depression is the most common neuropsychological condition diagnosed in people living with HIV/AIDS (PLWHA) (1), and may be especially common in women living with HIV/AIDS (WLWHA)(2). The prevalence of depressive symptoms among WLWHA is estimated to be up to 81.0% in the limited parts of sub-Saharan Africa where data are available (3). While depression can be a risk (4) and a consequence (5) of HIV infection, it is highly likely that depressive disorders occur during all phases of disease progression (1). It is especially important to examine depression in WLWHA in sub-Saharan Africa, where more than 70% of the world's HIV infections are concentrated (6) and 56% of new adult HIV infections are diagnosed in women (7). Among WLWHA who are engaged in care, depression has been associated with poorer adherence to antiretroviral therapy (ART), lower quality of life and functionality, and worse outcomes related to disease trajectory through HIV-associated neuroinflammation pathways (1, 5, 8). However, we know little about how depression is related to measures of HIV progression (e.g., HIV viral load [VL]) in ART untreated populations in the HAART era. This is critical, since even in areas with test and treat guidelines, there are delays in ART initiation (9). Furthermore, for countries that have not optimally implemented Universal Test and Treat initiatives, access to ART at the population level could be comparatively limited (10).

Social support, and substance misuse (including alcohol), are often assessed together with depression (11). This is because substance misuse has been repeatedly shown to worsen HIV outcomes, including HIV VL, among PLWHA in sub-Saharan Africa (12, 13). On the other hand, improvements in social support may have a protective effect against depression-related HIV decline (14). The present work provides the opportunity to examine the relationship between likely clinical depression and HIV VL, while considering the impact of alcohol use and social support, without the mediating influence of medication adherence. Though these psychosocial factors are bidirectional, our approach allows us to see if there is a biologic relationship between social support, alcohol misuse, and depression on HIV VL, uninfluenced by ART adherence, a topic that is relatively unexplored. Understanding this will help providers in contexts where there is a lag between diagnosis and ART initiation to manage these psychosocial factors in the interim before patients start treatment, which could potentially have the effect of slowing disease progression.

Methods

Participants

MTN-015 was a longitudinal cohort study following women in parts of sub-Saharan Africa who became HIV positive during participation in parent Microbicide Trials Network (MTN) clinical trials (15–17). Participants in this analysis (N=190) enrolled from either the MTN-003/VOICE (a phase 2B five-arm placebo-controlled randomized trial to investigate the effectiveness of daily use of oral PrEP compared to vaginal tenofovir gel for preventing male-to-female sexual transmission of HIV) (18) or MTN-020/ASPIRE (a two-arm, placebo-controlled phase 3 study to determine whether a 30-day vaginal ring containing dapivirine is safe and effective in preventing male-to-female sexual transmission of HIV) (19) parent studies. Additionally, participants were ≥18 years old, were enrolled in MTN-015 as a "non-ART" participant (e.g., the participant was not receiving ART at the time of enrollment), and provided data on whether they had or had not disclosed their HIV status to their husband or male partner (since this analysis included a battery of questions about partners' responses to disclosure; participants who did not provide these data were excluded, since they lacked the information necessary for the present analysis). All participants were seen in "research clinics," meaning that staff were employed by the MTN and saw only study participants. All participants were offered HIV treatment, including access to ART (offered as a part of this study - MTN-015), after testing positive in MTN-003 or −020.

Procedures

The MTN-015 protocol and study materials were approved by each site's institutional review board(s), and all participants provided written informed consent. After testing positive for HIV and enrolling in MTN-015 (August 2008-February 2017), participants completed behavioral questionnaires at the enrollment visit. The behavioral assessments were conducted by face-to-face interview initially, but were changed to audio-computer-assisted self-interviews (ACASI) with an abbreviated face-to-face interview in Version 2 of the protocol, implemented in May 2013 (Table 1). It is important to note that the time from seroconversion visit in the parent study to the MTN-015 enrollment visit varied among participants, with a median time of 67.5 days. Questionnaires in the enrollment visit focused on the following themes: demographics, alcohol use, social support following HIV status disclosure, and likely clinical depression. Participants received a blood test to assess HIV VL at enrollment and each study visit thereafter. Blood specimens were placed in EDTA (ethylenediaminetetraacetic acid) tubes, and processed in local labs connected to each study site, using an FDA-approved method. Trained staff were available to help participants who reported depression or other social harms. The present analysis includes only cross-sectional data collected at baseline, since some measures included in this analysis were only collected at that visit. A power calculation was not used to determine sample size, since our sample was limited to the number of individuals who met our inclusion criteria, enrolled in MTN-015.

Measures

The primary independent variable in this study, likely clinical depression indicated, was assessed using an eight-item, depression-focused subset of the Hopkins Symptom Checklist (HSCL-25)(20). Specifically, participants were asked to indicate how often they felt specific, depression-related symptoms in the last month (e.g., “During the past month, how much would you say you have felt trapped or caught?; 1=Not at all, 4=Extremely”). Mean clinical depression screening scores were calculated for each participant, and a clinically accepted cutoff score of 1.75 was used to indicate “likely clinical depression” (21, 22). This cutoff is consistent with findings from a study examining the pooled prevalence of likely clinical depression among untreated or mixed groups of people living with HIV/AIDS (PLWHA) in sub-Saharan Africa (31.0%) (23). VL, the dependent variable, was categorized into the following groups: low HIV VL (≤400 RNA copies/ml) (24–26), medium HIV VL (401–20,000 RNA copies/ml), and high HIV VL (>20,000 RNA copies/ml) (26). We selected these HIV VL categories because these are what were used in preceding studies of untreated populations after the advent of HAART.

Self-reported demographic data were treated as independent variables and included participant age (years), education level, if they currently had a sexual partner, if they were married or cohabitating with that partner, and if their husband or partner was HIV positive. Time since seroconversion (number of days living with HIV) was calculated based on time between the recorded date of the last HIV-negative test to the recorded date of the first HIV positive test in the parent study, rather than self-report.

Additional independent variables included alcohol use, and social support from the husband/partner after HIV-positive status disclosure. To assess alcohol use, participants responded to a single question about the average number of days per week they had consumed alcohol in the past three months. Participants were asked if they had disclosed their HIV status to their husband or partner, as applicable, in a closed-ended yes/no question (participants who answered “no” or had missing data for this question were ineligible and therefore not included). For participants who reported disclosure to their husband/partner, social support after HIV disclosure was assessed by asking about the husband/partner’s reaction to learning their HIV status.

Analyses

All statistical procedures were completed in Stata 15. Descriptive statistics summarized participant characteristics. Means were used for continuous variables and frequencies were used for categorical variables. Separate unadjusted ordered logistic regressions estimated relationships between VL and each independent variable, including demographic characteristics (age, time since seroconversion, education, having a sexual partner, husband or sexual partner is HIV positive, participant is married or cohabitating with their partner), alcohol use, social support by partner following HIV status disclosure, and likely clinical depression indicated. Each item in the measure for social support by partner following HIV disclosure was examined separately. This is because this measure is not validated, and authors felt that presenting each measure separately facilitated greater transparency, since it is not yet clear how to reliably calculate means using weighted scale items. We

planned to assess independent variables that had a significant relationship ($p \leq 0.05$) with the dependent variable, VL, for confounding in a model that contained VL and the primary independent variable (likely clinical depression) and was adjusted for age, education, and time since seroconversion. Independent variables with a significance of $p \leq 0.05$ were added to the adjusted regression. Since missing data were <6% in the adjusted regression, listwise deletion was used.

Results

Participants

Table 1 summarizes the participant characteristics. A total of N=379 women enrolled in MTN-015 in the defined time period; N=190 met our eligibility criteria and were retained in the present analysis. Participants had a median age of 24.0, were mostly from South Africa (92.6%), and over three-quarters were enrolled in MTN-015 from the MTN-003 parent study (VOICE; 76.8%). In a total of 38.7%, likely clinical depression was indicated.

Table 2 displays the unadjusted and adjusted ordered logistic regression results for the odds of having high VL, compared to the other two categories (low VL and medium VL) at the $p<0.05$ level.

In the unadjusted model, likely clinical depression was positively associated with high HIV VL, compared to the other categories [OR=2.11; 95%CI=1.17–3.82]; women with likely clincal depression had an 111% higher likelihood of falling into the high HIV VL category. In the adjusted analysis described above, likely clinical depression remained positively associated with high HIV VL, compared to the other categories [aOR=2.03; 95%CI=1.12–3.69]. Specifically, women who had likely clinical depression had an 103% higher likelihood of falling into the high HIV VL category.

We did not identify relationships between VL and alcohol use, any of the items in the social support by partner following HIV status disclosure measure, or participant demographic characteristics besides age (e.g., age was significant in unadjusted analyses only). No confounding effects were detected in this study, indicating that the relationship between likely clinical depression and HIV VL may have only operated directly in our research.

Discussion

This study explores the relationship between likely clinical depression and HIV VL in ART untreated WLWHA in sub-Saharan Africa. In adjusted analyses, likely clinical depression was positively associated with high VL. Although we were unable to identify other studies targeting this group (e.g., WLWHA who have not received HIV treatment), work with populations on antiretroviral treatment have shown a positive relationship between depression and HIV-related disease progression (20). Our findings suggest that likely experiencing clinical depression may have a clinically measurable biological relationship with HIV VL. Evidence from other studies shows that emotional states may have measurable physical outcomes. For example, pre-ART studies show that stigma directly and adversely affected clinical outcomes and disease progression – including HIV VL (27).

Furthermore, there is a mounting body of evidence that demonstrating that stress and trauma may produce a direct physiological impact on immune activation and markers of aging, such as telomere shortening (28). Other studies have noted relationships between major depression and inflammation, though it is unknown whether inflammation precedes and/or promotes depression, or vice versa (29). HIV-related studies of inflammation have shown that during acute infection stages, pro-inflammatory cytokines enhance HIV replication and CD4+ T cell loss (30). Thus, it is possible that depression could potentially have a biological relationship with HIV VL through inflammatory pathways. This may be especially relevant for WLWHA in sub-Saharan Africa where, 1) there are high rates of traumatic stress among PLWHA (~20–40%), which may compound the impact of depression (31–33), and 2) depression may be complicated by other biological and psychological stressors (e.g., food insecurity)(34), which are prevalent in this context. Further study of the biological impact of depression on HIV disease progression is needed in ART untreated populations.

On the other hand, it is possible that the relationship between likely clinical depression and HIV VL works in the other direction, since data are cross-sectional and we are unable to determine causality. Martinez et. al. (2015) found that among rural Ugandans, depression severity declined with ART-mediated viral suppression (35). This highlights the urgent need to link individuals who have an HIV positive test with treatment as quickly as possible, since it may have the effect of preventing or limiting mental health decline.

There was no relationship with HIV VL for the following independent variables: time since seroconversion, alcohol use, social support following HIV status disclosure items, and demographic characteristics. With respect to “time since seroconversion,” the lack of a relationship with the dependent variable could be due to the movement towards HIV VL stability in our sample. Specifically, acute HIV infection through sexual transmission is characterized by a massive burst of viral replication, followed by a decrease of viral load. Viral load ultimately settles to a steady “set-point” viremia that is typically stable through the chronic phase of infection (36). Since the median time since seroconversion in our study was 67.5 days, and the acute phase of HIV infection typically lasts only a few weeks or months (37), it is likely that many participants were shifting towards more stable HIV VL, and the natural characteristics of this phase would preclude a meaningful relationship with the dependent variable.

With respect to alcohol use and social support following disclosure, this could be due to low frequency of behaviors characterizing these variables reported in the sample. For instance, for the variable alcohol use, only two people (4.0%) reported using alcohol 2–6 times per week, and only one person (2.0%) reported using alcohol everyday. The distribution of responses is heavily skewed towards infrequent drinking (e.g., no drinking in the past 3 months=62.0%; drinking once per week or less=32.0%), making an association between alcohol use and HIV VL difficult to detect. Even more importantly, only n=50 participants responded to the alcohol questions, which dramatically limited our ability to detect significant associations. This may be a result of the questionnaire mostly being administered face-to-face by study nurses, that may have resulted in significant underreporting (or an unwillingness to report) this highly stigmatizing behavior. Additionally, while the limited number of responses to this scale appears to indicate that women in this study drink

infrequently, it is important to note that it is unable to identify binge drinking. This is a limitation, since other studies have found binge drinking to be a primary manifestation of alcohol abuse among women in sub-Saharan Africa (38). Future studies aiming to assess the relationship between HIV VL, depression, and alcohol use should consider measuring the quantity of alcohol consumed in one sitting (e.g., the number of drinks) in addition to the frequency of alcohol use.

Regarding social support following HIV status disclosure items, only a few participants reported that their partners exhibited some of the more severe post-disclosure behaviors (e.g., 1.3% of participants reported that their husband/partner beat them upon HIV positive status disclosure). While it is predominantly a good thing that our results suggest that women in our sample were not subjected to more extreme forms of abuse from partners upon disclosure, the effect of face-to-face interviewing may have resulted in underreporting. This skew in responses could have affected our overall results.

Limitations

Data presented in this analysis were collected as part of a larger study whose primary aims were clinical. Thus, instruments were not designed specifically to examine the aims proposed in this paper, and may have some shortcomings as a result. For instance, with respect to the social support following HIV status disclosure measure, this battery of questions was not assessed for reliability with a Cronbach's alpha (since it is designed as an index to evaluate specific partner responses). While it is important to understand the role of specific forms of partner behaviors on HIV VL, it is also meaningful to have an overall measure of social support. Future studies may consider using a similar measure that could also be scored as a scale. Additionally, it is noteworthy to mention that this study took place in a variety of diverse sites, and instruments were not adapted for use in each context, though some instruments (e.g., HSCL) have been used in a variety of diverse contexts, including sub-Saharan Africa (23).

The questionnaire was administered through a face-to-face interview by study nurses, who had repeated contact with the women during the clinical trial. This likely resulted in participants not feeling comfortable disclosing the sensitive and stigmatizing behaviors, shown in other studies done in this clinical trials program (39). For example, behaviors, such as interpersonal violence and alcohol use, are underreported when data is not collected via self-administered surveys, likely for this reason. The impact of this may be especially evident in questions about alcohol use, where there are only 50 recorded responses. This low response rate will have impacted the relationship between alcohol use and the outcome variable, and potentially missing significant associations.

Data presented here are cross-sectional, which have limitations. Specifically, this means it is difficult to determine directionality of the relationship between likely clinical depression and HIV VL. That is, we cannot tell if depression precedes increases in HIV VL, or vice versa. Furthermore, longitudinal study would have been more useful to avoid transient increases in HIV VL from other clinical causes, such as co-infection with tuberculosis or other infections. Longitudinal data would have also permitted a mediation analysis, which may

be a more meaningful way of assessing the role of alcohol use and social support on HIV VL. Moreover, we point out that the relationship between depression and HIV VL could be confounded by factors not included in our analyses, or explained by reverse temporality (e.g., in cases where people have very high viral loads and subsequently feel more physically ill, they may report more somatic symptoms on the HSCL). Furthermore, we did not conduct analyses to examine depression among those with a partner and those without, since disclosure to a partner was a part of our inclusion criteria for this analysis. Lastly, given the inclusion criteria that required participants to have disclosed their HIV-positive status to their husband or partner, the results of these analyses may have limited generalizability. Despite these study limitations, given the dearth of information on this topic, we feel that this analysis makes an important contribution to the literature on the relationship between clinical depression and HIV VL in ART untreated WLWHA.

Conclusions

Our study shows the direct relationship between likely clinical depression and HIV VL in ART untreated populations. This relationship remained, even when controlled for age, education, and time since seroconversion. Nevertheless, it is important to point out that, given the nature of cross-sectional data, it is impossible to determine if clinical depression is a precedent to increased HIV VL, or the other way around. Other studies have shown that emotional responses and/or inflammation could have an impact on HIV and other disease progression. In light of this research, our work suggests that depression may have a biological influence on HIV disease progression, potentially through HIV-related inflammatory responses, and may not simply influence this outcome through behavioral pathways (e.g., ART adherence and/or maladaptive behaviors in treated populations). Alternatively, high HIV VL may worsen depression, since feeling HIV-related symptoms may encourage declines in mental health. Either way, because depression and HIV are prevalent in sub-Saharan Africa and associated with one another, we must ensure that we identify women who are experiencing likely clinical depression, and/or living with HIV. In either case, these women must be linked with ART medications as quickly as possible, as this could prevent further mental health decline. In settings where there are lags in ART initiation, screening for depression could allow clinicians to address patients' mental health needs in a more expedient fashion, which could have the net effect of preventing worsening viral load in these individuals.

Addressing mental health and depression in WLWHA in the specific parts of sub-Saharan Africa included in this analysis may be difficult, given the dearth of mental health providers. However, it is not impossible. Increasingly, there are efforts to include mental health care in primary care settings, including South Africa and Uganda (40, 41), sites where this study took place. We suggest that in addition to primary care, these services should be embedded in HIV care. This may be feasible, since this is not a new idea, and has been proposed in some African settings (42, 43). Alternatively, some HIV prevention trials involve counselors that aim to support participants in trials product adherence (e.g., MTN-025)(44). These counselors are often formally trained in mental health care and could potentially be used in the proposed capacity as well.

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Table 1:

Characteristics of ART Untreated Women Enrolled in MTN-015 [N=190]

Variable	Median (Std. dev.)	N (%)
Descriptive characteristics of MTN-015 data collection		
Surveys collected each year		
2010		8 (4.2%)
2011		94 (49.5%)
2012		44 (23.2%)
2013		7 (3.7%)
2014		26 (13.7%)
2015		11 (5.8%)
Surveys collected by face-to-face interview		146 (76.8%)
Demographic characteristics		
Age	24.0 (4.5)	
Time since seroconversion (number of days living with HIV)	67.5 (124.2)	
Education		
Primary school not complete		79 (41.58%)
Primary school complete		6 (3.2%)
Secondary school complete		105 (55.3%)
Has a sexual partner (yes)		168 (96.0%)
Husband or sexual partner is HIV-positive (yes)		79 (73.8%)
Married or cohabitating with partner (yes)		32 (17.5%)
Country from which participant enrolled in 015		
South Africa		176 (92.6%)
Zimbabwe		9 (4.7%)
Uganda		2 (1.05%)
Malawi		3 (1.6%)
Parent protocol from which participant enrolled		
MTN-003 (VOICE)		146 (76.8%)
MTN-020 (ASPIRE)		44 (23.2%)
Alcohol use		
Frequency of alcohol consumption		
Not in the past 3 months		31 (62.0%)
Once per week or less		16 (32.0%)
2–6 times per week		2 (4.0%)
Everyday		1 (2.0%)
Social support by partner following HIV status disclosure		
Was angry (yes)		23 (12.6%)
Beaten by husband or partner (yes)		3 (1.6%)
Encouraged to see a doctor (yes)		73 (39.5%)

Variable	Median (Std. dev.)	N (%)
Stopped having sex (yes)		7 (3.8%)
Became sad (yes)		116 (62.0%)
Took another partner (yes)		3 (2.2%)
Started using condoms (yes)		127 (68.7%)
Made her leave the house (yes)		2 (1.1%)
Moved out (yes)		8 (4.4%)
Depression symptoms		
Likely clinical depression indicated (yes)		70 (38.7%)
Plasma HIV RNA (Viral load)		
Low (≤400 copies/ml)		18 (9.6%)
Medium (401–20,000 copies/ml)		90 (47.9%)
High (>20,000 copies/ml)		80 (42.6%)

Table 2:

Results of Unadjusted and Adjusted Ordered Logistic Regressions Summarizing Relationships between Having a High HIV Viral Load (VL), Compared to Other VL Categories and Independent Variables

Variable	Unadjusted OR [95% CI]	Adjusted OR [95% CI]
Demographic characteristics		
Age	0.93 [0.87–1.00] *	0.94 [0.88–1.01]
Time since seroconversion (number of days participant living with HIV)	0.09 [0.996–1.00]	0.99 [0.99–1.00]
Education level		
Primary school not complete	[REF]	[REF]
Primary school complete	0.43 [0.07–2.58]	0.60 [0.08–4.24]
Secondary school complete	0.46 [0.08–2.73]	0.62 [0.09–4.29]
Has a sexual partner (yes)	0.65 [0.14–3.04]	
Husband or sexual partner is HIV-positive (yes)	0.69 [0.30–1.59]	
Married or cohabitating with partner (yes)	1.13 [0.53–2.39]	
Alcohol use		
Frequency of alcohol consumption		
Not in the past 3 months	0.55 [0.13–2.32]	
Once per week or less	0.55 [0.13–2.32]	
2–6 times per week	[REF]	
Everyday	0	
Social support by partner following HIV status disclosure		
Disclosed HIV status to husband or partner (yes)	0.84 [0.49–1.44]	
Was angry	1.04 [0.44–2.47]	
Beaten by husband or partner (yes)	0.85 [0.11–6.82]	
Encouraged to see a doctor (yes)	0.87 [0.50–1.54]	
Stopped having sex with her (yes)	0.33 [0.08–1.38]	
Became sad (yes)	1.03 [0.58–1.82]	
Took another partner (yes)	0.95 [0.12–7.59]	
Started using condoms (yes)	0.98 [0.54–1.78]	
Made her leave the house (yes)	0.35 [0.03–3.88]	
Moved out (yes)	1.15 [0.28–4.69]	
Depression symptoms		
Likely clinical depression indicated (yes)	2.11 [1.17–3.82] *	2.03 [1.12–3.69] *

* $p<0.05$