

Risk Factors for Viral Non-Suppression among People Living with HIV and Major Depressive Disorder in Uganda

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Abstract

Background: Several studies indicate that depression is associated with non-viral suppression among persons living with HIV (PLWH) using antiretroviral therapy (ART) worldwide. However, among PLWH with major depressive disorder, factors associated with non-viral suppression remain uncertain. We determined the prevalence and identified the factors associated with viral non-suppression among PLWH with major depressive disorder using ART in Northern Uganda. **Method:** A total of 30 primary care HIV clinics across three northern districts (Gulu, Kitgum, Pader) participated in the study. Using baseline data from the SEEK-GSP study, a cluster-randomized trial in northern Uganda (2016-2019) that involved 1140 PLWH with mild to moderate major depressive disorder; we examined the demographic, clinical, and psychosocial factors using standardized questionnaires. Data on viral load was abstracted from clinic records and dichotomized into suppressed (<1000



viral copies/mL) and non-suppressed (≥ 1000 viral copies/mL). We used generalized linear regression models to evaluate the factors associated with non-viral suppression. **Results:** We recruited 1140 PLWH. The viral non-suppression prevalence was 12.2%. In multivariable analysis, the only baseline psychosocial variable independently associated with non-viral suppression was suicide risk (PRR = 1.56, 95% CI: 1.05 - 2.32, p-value = 0.029). The prevalence odds for non-viral suppression were 56% higher among depressed PLWH with moderate to high suicide risk than those with low suicide risk. Among clinical variables, duration on ART ≥ 4 years was independently associated with non-viral suppression (PRR = 1.62, 95% CI: 1.09 - 2.32, p-value = 0.015). **Conclusions:** Suicide risk and longer duration on ART are associated with non-viral suppression among anti-retroviral therapy users with mild to moderate major depressive disorder in Uganda. As ART is scaled up across Sub-Saharan Africa, first-line psychological care for depression and its complications is urgently needed in established HIV treatment centers.

Keywords

Depression, Suicide Risk, Anti-Retroviral Therapy, Viral Suppression, Uganda

1. Introduction

The number of persons living with HIV (PLWH) accessing anti-retroviral therapy has rapidly increased over time in Sub-Saharan Africa. [1]. The revision of the ART eligibility criteria in 2015 by the World Health Organization (WHO) recommends treatment initiation for all the HIV-infected, regardless of their immunological status (dubbed “universal test and treat”). Furthermore, it facilitated the increase in the number of persons accessing ART [2]. In Uganda, the number of PLWH accessing ART increased by more than 100,000 annually, from 313,117 in 2011 to 570,486 by late 2013 then 1,140,550 in 2018 [3]. Uganda has an estimated 1.3 million persons living with HIV (PLWH) translating to a 6.2% prevalence of the general population.

The rising numbers of patients accessing ART call for the sustainability of the treatment success and limits treatment development failure through monitoring patients once on treatment and this allows timely detection of treatment failures. WHO in July 2013 recommended viral load testing usage as the gold standard to monitor patients’ responses to ART [4]. Since the introduction of universal viral load testing in Africa, several countries including Uganda have embraced the recommendation.

According to the WHO, persons with ≥ 1000 copies/mL of plasma are regarded as virologically non-suppressed while those with < 1000 copies/mL of plasma are virologically suppressed [4] [5]. Additionally, during 2014 the Joint United Nations Programme on HIV/AIDS (UNAIDS) set new ambitious targets

towards the elimination of HIV that included a 90% diagnosis of HIV infected individuals with access for treatment to the same and with a 90% viral suppression to the treatment initiates [6].

Several studies have documented a strong association between depression and poor HIV treatment outcomes, particularly, ART adherence and viral non-suppression [7] [8]. Systematic reviews of published studies on prevalence of depression among ART users in Sub-Saharan Africa report estimates of 20% - 30% and indicate that depression is associated with poor ART adherence [9] [10].

However, studies of PLWH with depression are limited worldwide. In this sub-group of PLWH, we are uncertain of those factors that are associated with poor HIV treatment outcomes. In this paper, we determine the prevalence and factors associated with viral non-suppression among PLWH with major depressive disorder and on ART in northern Uganda.

2. Methods

Study Design, Population, and Setting

We conducted a cross-sectional analysis of 1140 PLWH who enrolled into the Social Emotional & Economic Empowerment through Knowledge of Group Support Psychotherapy (SEEK-GSP) trial (2016-2019) from primary care HIV clinics. To be eligible for the study, PLWH participants had to be ≥ 19 years, diagnosed with major depression as assessed with the Mini International Neuropsychiatric Interview (MINI) depression module [11], antidepressant naïve, and using ART. We excluded those with psychotic symptoms, high suicide risk, severe medical disorders such as pneumonia or active tuberculosis, hearing, and visual impairment.

The HIV clinics involved in the study were situated in three post-conflict northern districts (Gulu, Pader and Kitgum). Most clinics initiated their ART programs in 2005 and provide ART care free of charge. Viral load monitoring was introduced in the region in August 2014.

Recruitment Process

We used study teams that reflected the ethnicity of the target community at each of the participating primary health centers. The study teams worked with the trained lay health workers (LHWs), who are the first level of health care delivery in the country, to spread information about the study by word of mouth in villages within the study region. The study team conducted presentations in the community to explain study purpose and procedures to facilitate community understanding of the trial activities.

Data Collection

Trained research assistants worked with HIV care providers at each participating clinic to give health talks on depression to clients in the waiting area. Clients who felt that they had experienced depression symptoms as per the health talk were then invited for further evaluations using the Luo version of the 20-item self-reporting questionnaire [12] and the MINI depression module. Clients

diagnosed with major depression were approached by research assistants who explained study procedures, determined eligibility, and then obtained informed consent. Each client who gave informed consent received baseline assessments with a standardized questionnaire.

Study Measures

Socio-demographic variables were assessed using a demographic questionnaire that asked about descriptive information including age, gender, number of children, education, and relationship and employment status. Employment status was categorized into “unemployed”, “employed”, and “peasant farmer”. Relationship status was categorized into “never married,” “married/living with a partner”, “divorced/separated”, or “widowed”. Education status was categorized into “primary/no formal education” and “secondary and above”.

Depression symptoms were assessed using the SRQ-20 [12]. Cross-cultural adaptation and validation of the SRQ-20 in PLWH in southern Uganda showed that an optimum cut-off point of six or higher had a sensitivity of 84% and a specificity of 93% for current depression. In this study sample, SRQ scores were modeled as a continuous variable with a Cronbach alpha reliability coefficient of 0.80.

The SAD PERSONS scale was used to assess the suicide risk [13]. The total score ranges from 0 to 10. Scores of <4 indicate low risk; scores of 5 - 7 indicate moderate risk; and scores of 8 - 10 indicate high risk. Post-traumatic stress symptoms were assessed using the locally adapted Harvard Trauma Questionnaire (HTQ) [14]. The total score ranges from 16 to 64 and a total score ≥ 36 is indicative of post-traumatic stress disorder.

Alcohol use was assessed using the 10-item alcohol use disorders identification test (AUDIT) [15]. The total score ranges from 0 to 40 and a score of ≥ 8 is indicative of hazardous use. AUDIT scores were modelled as a continuous variable. In this study population, the measure attained a Cronbach α of 0.95.

We used the modified coping inventory to assess a broad range of both positive and negative coping responses which establish how the study participants responded when they were confronted with difficult or stressful events in their lives [16]. Each coping strategy is assessed by a set of two questions. Responses were based on a four-point scale. For each coping strategy, the scores range from two to eight, with higher scores indicating frequent use of the coping strategy. A binary variable was created whereby frequent use of 1 or more coping skills was coded 1 while non-use was coded 0.

To measure internalized stigma, we used the brief AIDS-related stigma scale [17]. Responses were based on a four-point Likert scale. The scores ranged from 8 to 32 with high scores indicating higher levels of internalized stigma.

Adherence to antiretroviral therapy was assessed using one question “During the past week, how many days have you missed taking all your medication doses?” Adherence was calculated as the percent of days in the week the person missed all medications. Adherence “scores” were treated as a dichotomous vari-

able. Those with $\geq 95\%$ adherence were regarded as adherent (coded 1) while those with $< 95\%$ adherence were regarded as non-adherent (coded 0) to simplify their interpretation for the descriptive analyses

HIV clinics routinely assess viral load of clients once a year. Measures of viral load were obtained from the medical charts of study participants but the actual assay used to measure viral load in the laboratory was not recorded. Viral load was treated as a categorical variable indicating suppression (coded 1) or non-suppression of viral load (coded 0).

HIV clinics routinely screen for tuberculosis. Medical charts were reviewed to determine whether or not study participants had received a diagnosis of Tuberculosis.

Statistical Analysis

We used STATA version 15 for analysis. We performed descriptive statistics to describe the demographic, clinical, and psychosocial characteristics of the study population. Due to violations of normality in the dependent variable, we opted to use generalized linear models with Poisson regression to evaluate bivariate and multivariate associations between non-viral suppression and other study variables. Statistical significance was considered at two-tailed $p \leq 0.05$.

Regulatory Approvals

We sought and obtained approval from both the Makerere University College of Health Sciences Research Ethics Committee and the Uganda National Council of Science and Technology. The study protocol is also registered in the Pan African Clinical Trials Registry (PACTR201608001738234).

3. Results

Socio-demographic and clinical characteristics of study participants

A total of 1473 PLWH were screened and 1140 were recruited. Female participants (612/1140, 54%) were slightly more than males (528/1140, 46%). Participants' age ranged from 19 to 80 years, with a mean of 38.5 (SD 10.9) years. The majority (622/1140, 55%) earned a living as peasant farmers and had a primary level education or less (983/1140, 86%). Most participants met criteria for major depression (1105/1140, 97%) at baseline, and reported moderate suicide risk (599/1140, 53%). The prevalence of viral non-suppression was 12%.

Risk factors for viral non-suppression

At bivariate analysis, long duration on ART (PRR = 1.65, 95% CI: 1.15 - 2.38, p -value = 0.007) and moderate to high suicide risk (PRR_{crude} = 1.58, 95% CI: 1.07 - 2.32, p -value = 0.022) increased the prevalence odds for virological non-suppression. Sex, age-group, employment status, education level, marital status, adherence to ART, history of TB infection and treatment, hazardous alcohol use, post-traumatic stress disorder (PTSD), enacted stigma, negative coping skills, and social support were not statistically associated with viral non-suppression (**Table 1**).

Table 1. Risk factors for viral non-suppression among HIV patients with major depressive disorder in Gulu, Pader, and Kitgum districts, Northern Uganda (2016-2019).

Variable	Non-viral suppressed (%)	Suppressed (%)	PRR _{Crude} (95% CI)	PRR _{Adjusted} (95% CI)
Socio-demographic characteristics				
Sex				
Female	89 (64)	523 (52)	-	
Male	50 (36)	478 (48)	0.77 (0.49 - 1.19)	0.75 (0.46 - 1.24)
Age-group				
>25	120 (86)	896 (90)	-	-
≤25	19 (14)	105 (10)	1.2 (0.68 - 1.94)	
Employment status				
Unemployed	36 (26)	369 (37)	-	
Employed*	103 (74)	632 (63)	1.43 (0.96 - 2.13)	1.41 (0.91 - 2.18)
Education status				
≤Primary	129 (93)	854 (85)	-	-
≥Secondary	10 (7)	147 (15)	0.51 (0.09 - 0.23)	
Marital status				
Single	24 (17)	127 (13)	-	-
Married	99 (71)	717 (72)	0.71 (0.20 - 0.42)	0.76 (0.49 - 1.18)
Divorced	7 (5)	80 (8)	0.57 (0.29 - 0.19)	0.56 (0.26 - 1.31)
Widowed	9 (7)	77 (7)	0.69 (0.31 - 0.34)	0.58 (1.09 - 2.38)
Clinical characteristics				
Adherence to ART				
<95%	22 (16)	238 (24)	-	-
≥95%	117 (84)	763 (76)	1.10 (0.58 - 2.1)	
Duration on ART				
≤4 Years	107 (77)	853 (85)	-	
>4 Years	32 (23)	148 (15)	1.65 (1.15 - 2.38)	1.62 (1.09 - 2.32)
History of tuberculosis infection and treatment				
No	122 (88)	891 (89)	-	
Yes	17 (12)	110 (11)	1.28 (0.69 - 2.35)	1.41 (0.78 - 2.58)
Psychosocial characteristics				
Hazardous alcohol use				
No	102 (73)	713 (71)	-	-
Yes	37 (27)	288 (29)	0.85 (0.55 - 1.32)	

Continued

PTSD				
No probable PTSD	33 (24)	265 (27)	-	-
Has probable PTSD	106 (76)	736 (74)	1.12 (0.72 - 1.75)	
Suicide risk				
Low	46 (33)	443 (44)	-	
Moderate-High	93 (67)	558 (56)	1.58 (1.07 - 2.32)	1.56 (1.05 - 2.32)
Enacted stigma				
Reported low level	100 (72)	723 (72)	-	
Reported high level	39 (28)	278 (28)	0.95 (0.61 - 1.49)	-
Negative copying skills				
Using few	52 (37)	463 (46)	-	
Using high number	87 (63)	538 (54)	1.31 (0.93 - 1.84)	1.19 (0.84 - 1.67)
Social support				
Low level	68 (49)	535 (53)	-	-
Moderate to high	71 (51)	466 (47)	1.13 (0.68 - 1.89)	

*Either has a job or earns from peasant farming.

In a multivariate analysis, suicide risk emerged as the only psychosocial variable independently associated with non-viral suppression (PRR = 1.56, 95% CI: 1.05 - 2.32, p-value = 0.029). The prevalence odds for non-viral suppression were 56% higher among depressed PLWH with moderate to high suicide risk than those with low suicide risk. Among clinical variables, only duration of ART use > 4 years was independently associated with non-viral suppression (PRR = 1.62, 95% CI: 1.09 - 2.32). The prevalence odds for non-viral suppression were 62% higher among depressed PLWH who had used ART for >4 years than those who has used ART for ≤4 years.

4. Discussion

We found the prevalence of viral non-suppression at 12% among PLWH with major depressive disorder and on ART. The prevalence odds of viral non-suppression were higher among PLWH with moderate to high suicide risk and those who had used ART for a long duration of ≥4 years.

Although depression in PLWH has been associated with a lower likelihood of adherence to ART probably leading to viral non-suppression, our study revealed a relatively low viral non-suppression prevalence which is also similar to the national prevalence of 13% among the general population of PLWH as indicated in the Ugandan study based on routinely generated viral load monitoring program data from the entire country [18].

Factors that increase the suicide risk include male gender, young age (15 - 24

years), previous suicide attempt, alcohol and drug use, depression, presence of psychoses, lack of social support and presence of chronic illness [19]. Accumulation of these factors raises the risk of suicide. None of these factors by themselves was associated with viral suppression in our study. But, when combined in a suicide risk score [13], we found that the higher the suicide risk score the higher the prevalence odds for non-viral suppression.

This finding is in keeping with prior research in high income countries. López *et al.* studied 648 PLWH and found that individuals who endorsed suicidality were more likely to have unsuppressed viral loads [20]. Similarly, Durham *et al.* conducted a cross-sectional survey of 6706 PLWH in the United States and found that increased risk for suicide was associated with unsuppressed viral load [21]. Also, Quinlivan *et al.* conducted a cross-sectional analysis among 4099 PLWH in the United States and found an association between moderate to high suicide risk and unsuppressed viral loads [22]. To our knowledge, this study is the first to demonstrate the association between suicide risk and unsuppressed viral load in Sub-Saharan Africa.

An accumulation of suicide risk factors indicates severer depressive disorder [22]. Given that there is no mental healthcare in HIV treatment centers in northern Uganda, it's possible that depression progressed to severer states over time. This and other factors such as anti-retroviral drug resistance may explain why study participants with a longer duration on ART were also more likely to have non-viral suppression. This finding is not unique to our study.

Some studies of viral suppression in other HIV populations have also reported an association between long duration of ART and non-viral suppression [23] [24]. In Uganda, a study based on routinely generated viral load monitoring program data from the entire country reported a similar association [17]. On the contrary, a study conducted in South Africa found that a shorter duration on ART was associated with viral non-suppression [25]. An elevated viral load may indicate either poor adherence or drug resistance [26] [27]. In our study sample, adherence rates were quite high at 78% and ART adherence was not associated with viral non-suppression. Severe depression symptoms or drug resistance may be playing a role in viral non-suppression.

In our study, it is possible that our patients were experiencing treatment resistance, given that they had been on ART for a long duration. This finding calls for Ministry of health to consider adopting resistance testing for patients with elevated viral load.

Although stigma, hazardous alcohol usage, adherence to ART have been widely documented to influence viral non-suppression [28] [29], there was no statistically significant relationship between each of these three factors and viral non-suppression. This could be explained by the low burden of these factors in this population of depressed PLWH. Further, substantial resources have been invested into the post-conflict districts to allow livelihood recovery. The government of Uganda, through the peace, recovery, and development plan for North-

ern Uganda has made several investments in the region [30]. The livelihood programs might have had an impact on the overall wellbeing of the entire community including PLWH.

Clinical implications

Our findings call for critical need for investment into mental health care services in Uganda with more focus on the post-conflict districts of Northern Uganda to ensure routine assessment of depression and suicide risk among PLWH. Increased prevalence odds of viral non-suppression among chronic ART users with major depressive disorder requires additional investment into the viral load testing program to allow routine assessment for treatment resistance.

Limitations

We assess viral non-suppression based on routinely generated HIV/AIDS care program data at health care facilities. Although we were able to access the patients' medical charts to obtain viral load testing results, the charts did not indicate the specific assay used to derive the results. According to the Uganda MOH viral load monitoring guidelines, viral non-suppression is defined as having ≥ 1000 copies of viral RNA/ml of blood for plasma. However, studies have shown that this is a conservative threshold to define viral non-suppression that can lead to an underestimation of those who experiencing ART failure [31] [32].

5. Conclusion

Suicide risk and long-term ART usage are associated with viral non-suppression among anti-retroviral therapy users with mild to moderate major depressive disorder in Uganda. As ART is scaled up across Sub-Saharan Africa, greater attention must be paid to integrating first-line psychological interventions for depression treatment into routine HIV care.

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Contributors

EN-M, JDN, JO, SM, SN, RM, JB, EM, and JN conceptualized the study and EN-M sought and obtained funding. EM and OH conducted statistical analyses. FS and CM conducted the cost-effectiveness analyses. EN-M and JO managed the literature searches. EN-M and LB wrote the initial manuscript. SM, RM, HM, ME, EM, and JN revised the manuscript critically for important intellectual content. All authors contributed to the final manuscript.

Conflicts of Interest

EN-M holds copyright for group support psychotherapy manual. Other authors have nothing to disclose.

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