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ORIGINAL RESEARCH

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Neurocognitive decline as a major predictor of nonadherence to antiretroviral therapy among adults living with HIV in Dodoma region, central Tanzania

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Abstract

Background: The survival of people living with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome largely depends on good adherence to antiretroviral medications. Neuropsychiatric conditions such as major depressive disorders (MDDs) and neurocognitive disorders, in particular, are common in the HIV population and attributed to suboptimal adherence to antiretroviral treatment and overall poor clinical outcomes. This study aimed to determine the association between neurocognitive disorders and nonadherence to antiretroviral therapy (ART) in the Dodoma region's adult population living with HIV.

Methods: The study was conducted in Dodoma Regional Referral Hospital using a cross-sectional design to assess 397 participants through a systematic sampling approach. Montreal Cognitive Assessment was used to determine neurocognitive function, while the Simplified Medical Adherence Questionnaire was used to assess nonadherence to ART. Logistic regression analysis was computed to determine the association between cognitive decline and nonadherence to ART while controlling for sociodemographic and clinical confounders.

Results: Out of the 397 recruited participants, 266 (67.00%) and 41 (10.33%) met the criteria for neurocognitive decline and nonadherence to ART. Participants with cognitive impairment had a significantly poorer adherence rate than those without, even after controlling for confounders adjusted odds ratio (aOR): 2.183 (95% confidence interval [CI]: 1.031, 4.630, $p = 0.0413$). MDD was the only additional factor that remained significantly associated with ART nonadherence (aOR: 4.332, 95% CI: 1.634, 11.485, $p = 0.0032$).

Conclusion: Neurocognitive disorders are strong predictor of suboptimal adherence to ART; a comorbid neuropsychiatric condition such as MDD may further compromise the ART adherence rate leading to poor HIV care and poor clinical outcome. Further research with systematic and more robust studies in the field will provide a baseline to design and integrate appropriate care models to maximize ART adherence in HIV care. Integration of psychiatric services in HIV care can benefit the overall patient outcome.

KEYWORDS
ART nonadherence, HIV/AIDS, neurocognitive decline

1 | INTRODUCTION

Nonadherence to antiretroviral therapy (ART) and poor retention in human immunodeficiency virus (HIV) care are linked to virologic failure, increased chance of HIV transmission,[1] and poor survival.[2] Neuropsychiatric conditions, including neurocognitive disorders, may act as a significant barrier in the HIV treatment cascade leading to higher rates of nonadherence and overall poorer health outcomes.[3,4]

The introduction and the widespread use of highly active antiretroviral therapy have significantly lowered the prevalence of HIV-associated neurocognitive disorders (HAND), particularly the most severe form known as HIV-associated dementia (HAD).[5–8] However, the overall prevalence of HAND and associated morbidity remain at approximately 50%, with the majority presenting with less severe forms as either asymptomatic neurocognitive impairment (ANI) or mild cognitive impairment (MND).[9–12] From the onset of HIV infection, central nervous system (CNS) acts as a reservoir where the HIV is accommodated and induces a cascade of inflammatory reactions leading to HIV encephalitis that could be responsible for cognitive impairment even among those with undetectable viral load and good immune markers.[9–14] Compared to cognitively intact adults, HIV patients with cognitive deficits have significantly higher risks for poor adherence to ARTs.[15–17] Psychiatric disorders, including depression and bipolar disorders, may also negatively impact adherence to ART and retention in HIV care.[4,18,19] Along with psychiatric disorders, substance use and dependence, such as stimulants and alcohol, may adversely impact adherence and retention in HIV-care.[20–22]

Although there is increased access to ART, nonadherence to ART remains a significant obstacle in HIV care in sub-Saharan Africa. Due to the lack of routine screening, there is a paucity of data on the prevalence of neurocognitive decline in the Tanzanian population[23]; furthermore, the effect of cognitive impairment on ART nonadherence is largely unknown. Therefore, the study aims to determine the association between neurocognitive decline in HIV and nonadherence to ART among adults with HIV in Dodoma.

2 | MATERIALS AND METHODS

2.1 | Study design

The study was a cross-sectional analytical design.

2.2 | Study settings

The study was conducted in Dodoma Regional and Referral Hospital, the main referral hospital in the Dodoma region, the capital city of Tanzania, with about 410,956 people as per the 2012 census.[24] The hospital also conducts comprehensive treatment and care (CTC) services 5 days a week and attends about 50–100 patients, most of whom coming from the city while a few come from the outer district of Dodoma and outside the Dodoma region. The CTC offers a wide range of services, including ART medications, counseling services, routine investigations such as viral load count, blood parameters, general medical care, and referrals in case of need.

2.3 | Study population and sampling

The participants were derived from the 10,288 enrolled patients on ART attending the CTC, of whom 3708 were available for participation during the study period. A calculated sample size of 384 using the Kish Leslie formula for single proportions, $n = Z^2p\,(1-p)/d2$. p Was estimated at 0.5. Once the inclusion and exclusion criteria were applied, we followed a systematic sampling approach using the daily attendance list of the registered patients, whereby every third participant was directed for the interview until a targeted sample of 397 was obtained over 45 working days between March and June 2020.

2.4 | Inclusion/exclusion criteria

The study included patients at least 18 years of age with a minimum of 6 months on ART, able to provide informed consent, with adequate hearing, vision, articulation, and without disability of any of the upper limbs for assessment of neurocognitive functions. Those who cannot read and write in Swahili and English' were excluded from the present study. Those with active CNS infection, known complications of past CNS infection, neurological disorders, and an acute and active phase of a psychotic episode were excluded.

2.5 | Data collection, variables, and measurements

2.5.1 | Outcome variable

Nonadherence to ART was assessed using the *Simplified Medical Adherence Questionnaire*, a reliable instrument for assessing adherence in HIV-infected patients and may be applied in most clinical settings with a sensitivity of 72% and specificity of 91%.[25] The tool has six questions, four of which are qualitative, with a yes or no response to identifying whether or not one has forgotten or missed taking the medications. The other two are quantitative questions that aim to determine the number of days one did not take the medications in the past 2 weeks and 3 months. Nonadherence was defined as a positive response to any qualitative questions; if more than two doses were missed over the past week or over 2 days of total nonmedication during the past 3 months.

2.5.2 | Independent variables

Neurocognitive function: A Swahili-translated Montreal Cognitive Assessment (MoCA) was used to assess neurocognitive performance under the study's operation definition for the neurocognitive decline to be defined as a score of <23 on MoCA. Although mostly used at a cutoff point of 26, a meta-analysis has shown that MoCA at a cutoff point of 23/30 displays better diagnostic accuracy across all domains, especially in a less-educated population.[26] The tool assesses key neurocognitive domains: visuospatial-executive (clock drawing, trail making B task, and three-dimension cube copy) having five points maximum; naming of unfamiliar animals for three points maximum; for a maximum of three points language was assessed on phonetic fluency task and sentence; delayed recall of words was used to determine short-term memory which had a maximum of five points; for a maximum of two points verbal abstraction was assessed; attention and calculation were assessed using serial 7s subtraction, target detection using tapping and digits forward and backward for a maximum of six points; and orientation for space and time had a maximum of six points.[27] Widely used across the globe, MoCA has demonstrated its practicability as a screening tool for bot symptomatic and asymptomatic HIV-related cognitive impairment with the area under the curve of 0.71 under the receiver operating curve.[28,29]

Major depressive disorders and substance use and related disorders: MINI International Neuropsychiatry Interview Schedule (MINI) was used to assess major depressive disorder (MDD) and substance use disorders. MINI has acceptably high reliability and validity, administered at a relatively short time of mean duration of mean 18.7 ± 11.6min and a median of 15 min after a brief training session; both clinicians and lay interviewers can use it, although the latter may need more extensive training.[30] The main reason to only use the subscale of MDD and substance use disorders in the MINI is because of their direct influence on cognitive function even in the HIV population.[20,21,31,32]

Other explanatory variables included were gender, age (in years), marital status, level of formal education (attained in years), occupational status (formal employment or no formal employment), living arrangement, current viral load (detectable at a cutoff point of ≥40 copies/ml), most recent CD4+ count (cells/mm^3), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection screening, HIV/acquired immunodeficiency syndrome (AIDS) clinical staging as per World Health Organization (WHO) criteria, type of ART regimen, duration of ART use (in years), and hemoglobin (HB) concentration in (mmol/L) and body mass index (BMI measured in kg/m^2.

2.6 | Collection of data and analysis procedure

A researcher-designed, evidence-based questionnaire collected sociodemographic and baseline clinical profiles of interest. MoCA was translated to Swahili by two different bilingual groups and then back-translated to English to ensure that similar meaning was closely maintained. Medical doctors were trained as research assistants who conducted the interviews and other assessment procedures for all 397 participants. Psychiatric diagnoses were assessed using MINI. Data analysis was computed using SAS version 9.4, where descriptive statistics, including frequency and percentage, were summarized as categorical variables. In contrast, mean and standard deviation (SD) or median and interquartile ranges (IQRs) summarized the continuous variables and presented them as figures and tables where appropriate.

Unadjusted binary logistic regression was done for preliminary analysis of factors associated with nonadherence to ART. After that, adjusted for variables that reached an overall significance level of <20% ($p < 0.2$). A χ^2 test was computed to determine the association between Nonadherence to ART and neurocognitive decline. Since almost all participants were negative for HBV/HCV and were on the same ART regimen, these variables were not included in the logistic analysis. Except for the duration of ART use, age, and HB concentration, which were continuous independent variables, and WHO clinical staging, which was an ordinal variable, the rest of the independent variables were categorical. In light of this, linear and ordinal logistic regression were computed for continuous and ordinal independent variables.

2.7 | Ethical considerations and concerns

Participants were provided with accurate information about the study by the trained research assistants who were medical doctors at the registrar level. If a participant had a psychiatric, neurological, or any other medical disorder requiring treatment were referred to CTC clinicians, neurologists, or mental health clinicians according to locally agreed protocols. Where participants could not consent due to cognitive impairment or any other reason, assent was sought from a custodian who had to be a close relative could provide the assent.

3 | RESULTS

3.1 | Sociodemographic characteristics of the participants

Out of 397 study participants, the mean age of the population was 41.95 ± 12.61 years, and females constituted 276 (69.52%) of the participants. The majority, 270 (68.01%), attended primary education, while 30 (7.56%) had no formal education, and 24.23% attained postprimary education. A significant minority of 163 (40.81%) were married, with the rest being either never married, 80 (20.15%), widowed, 66 (16.62%), or divorced, 89 (22.42%), (Table 1).

TABLE 1 Sociodemographic characteristics, *N* (397)

Variable	Frequency (%)	Percentage
Age of the respondent		
Mean (SD)	41.95 (12.61)	
≤24	43	10.83
25–34	65	16.37
35–44	104	26.20
45–54	117	29.47
≥55	68	17.13
Gender		
Male	121	30.48
Female	276	69.52
Marital status		
Married/cohabiting	162	40.81
Never married	80	20.15
Divorced/separated	89	22.42
Widowed	66	16.62
Level of education (in years)		
No formal education	30	7.56
Primary incomplete	25	6.29
Primary complete (7 years)	245	61.71
8–11 years (O-level)	70	17.63
11–13 years (A-level/more)	27	6.80
Occupation status		
No formal employment	350	88.16
Formal employment	47	11.84
Living arrangement		
Lives alone	88	22.17
Lives with caregiver/nursing staff	71	17.88
Lives with spouse	150	37.78
Lives with friends/other	88	22.17

3.2 | Baseline clinical characteristics of the study population

Two hundred and sixty-six (67%) had neurocognitive decline or impairment, while 22 (5.51%) had MDD. Forty-five (11.28%) met the criteria for substance use or related disorders, and clinical stages II and III had the highest proportion of 38.85% and 28.82%, respectively. The mean duration of ART use was 6.1 years, and the mean HB concentration was 12.40 mmol/L (SD: 2.57). Most participants 344 (87%) had CD4+ count of ≥200 cells/mm^3, while only 88 (22.17%) had detectable viral load with median of 349.5 (IQR: 306.5) copies/ml, (Table 2).

TABLE 2 Baseline clinical characteristics of the study population, *N* (397)

Variable	Frequency	Percentage
Neurocognitive status		
Neurocognitive decline	266	67.00
No neurocognitive decline	131	33.00
Major depressive disorder		
No	275	94.49
Yes	22	5.51
Substance use or disorder		
Yes	45	11.34
No	352	89.66
WHO clinical staging		
I	84	21.16
II	153	38.54
III	115	28.97
IV	45	11.34
Hepatitis B virus		
Negative	391	98.48
Positive	6	1.52
Hepatitis C virus		
Negative	396	99.75
Positive	1	0.25
ART regime		
TDF + 3TC + DTG	382	96.22
Others	15	3.78
Most recent CD4 count		
Median (IQR): 295 (400)		
<200	53	13.35
200–499	148	37.28
≥500	196	49.37
Current viral load (*n* = 88)		
Median (IQR): 349.5 (306.5)		
Undetected	309	77.83
Detected	88	22.17
Duration of ART use, mean (SD): 6.13 years (4.61)		
Hemoglobin level, mean (SD): 12.40 mmol/L (2.57)		

Abbreviation: ART, antiretroviral therapy; IQR, interquartile range; WHO, World Health Organization.

3.3 | Prevalence of ART nonadherence and association with neurocognitive decline, *N* (397)

Forty-one (10.33%) out of 397 participants met the criteria for nonadherence to ART, of whom there was a significant disproportionate

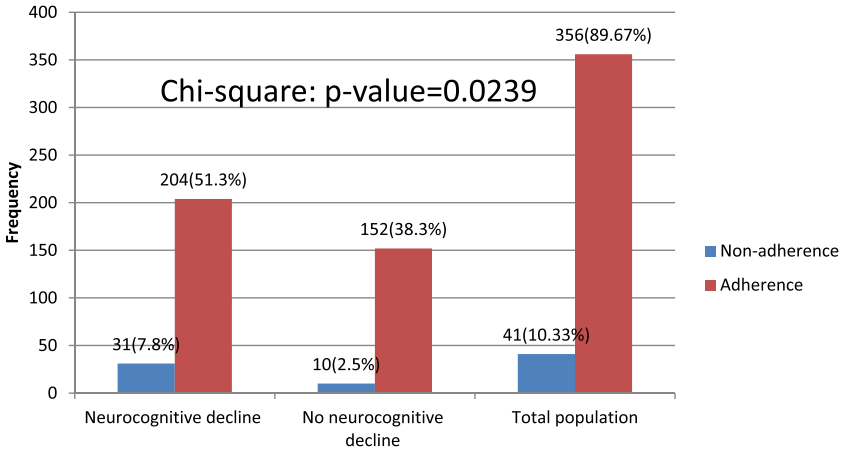

FIGURE 1 Prevalence of ART-nonadherence and association with neurocognitive status. ART, antiretroviral therapy.

TABLE 3 Factors associated with nonadherence to ART, *N* (397)

	Unadjusted		Adjusted	
Variable	**OR [95% CI]**	***p*-value**	**a OR [95% CI]**	***p*-value**
Neuorocognitive decline				
Yes	2.257 [1.099, 4.854]	0.0272	2.183 [1.031, 4.630]	0.0413
No	Reference			
MDD				
Yes	4.681 [1.785, 12.27]	0.0017	4.332 [1.634, 11.485]	0.0032
No	Reference			
Education		0.4647		
No formal education	Reference			
Primary incomplete	2.192 [0.684, 7.022]	0.1866		
Primary complete	1.066 [0.436, 2.607]	0.8893		
8–11 years (O-level)	1.224 [0.452, 3.316]	0.6909		
≥11 years	1.643 [0.513, 5.265]	0.4033		
Occupation				
Unemployed/self-employed	Reference			
Employed	1.207 [0.618, 2.358]	0.5808		
Gender				
Male	Reference			
Female	1.066 [0.525, 2.168]	0.8589		
Marital status		0.4301		
Married/cohabiting	Reference			
Never married	2.023 [0.877, 4.664]	0.0984		
Divorced/separated	1.289 [0.528, 3.147]	0.5766		
Widowed	1.360 [0.517, 3.577]	0.5333		
Living arrangement		0.9967		
Lives alone	Reference			
Lives with nursing staff/ caregiver	1.033 [0.508, 2.09]	0.9293		

(Continues)

TABLE 3 (Continued)

Variable	Unadjusted OR [95% CI]	*p*-value	Adjusted a OR [95% CI]	*p*-value
Lives with spouse	0.993 [0.545, 1.808]	0.9815		
Lives with friends/other	1.060 [0.543, 2.067]	0.8647		
BMI		0.6218		
Underweight	Reference			
Normal	2.008 [0.448, 8.996]	0.3621		
Overweight	2.494 [0.532, 11.695]	0.2464		
Obese	2.691 [0.541, 13.387]	0.2266		
Current viral load				
Undetected	Reference			
Detected	0.573 [0.233, 1.410]	0.2252		
Substance use/disorder				
Yes	1.394 [0.551, 3.525]	0.4827		
No	Reference			
Current CD4 count		0.7363		
<200	Reference			
200–499	1.382 [0.437, 4.366]	0.5819		
500+	1.549 [0.510, 4.707]	0.4404		
Haemoglobin concentration	0.933 [0.814, 1.069]	0.3167		
Duration of ART use (in years)	1.014 [0.946, 1.087]	0.6917		
Current WHO clinical staging	1.160 [0.820, 1.642]	0.4015		
Age (in years)	0.988 [0.963, 1.014]	0.3528		

Note: Where necessary, linear and ordinal logistic regression were computed for continuous and ordinal variables. Unadjusted logistic regression was set at $p < 0.2$, while adjusted analysis was set at a $p < 0.05$ significance level.

Abbreviations: aOR, adjusted odds ratio; ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; HAND, HIV-associated neurocognitive disorder; MDD, major depressive disorder; OR, odds ratio; WHO, World Health Organization.

over-representation of 31 (75.6%) who met the criteria for neurocognitive impairment being in the ART nonadherence population compared to just 10 (24.4%) who did not meet the criteria, ($p = 0.00239$), see Figure 1. Under adjusted logistic regression, only neurocognitive decline (adjusted odds ratio [aOR]: 2.183 [1.0299, 4.629]; $p = 0.0413$) and MDD aOR: 4.332 (1.634, 11.485; $p = 0.0032$) remained significantly associated with poor adherence to ART. Except for not being married, which had a <10% significance level at unadjusted analysis, the rest of the independent variables did not reach a 20% significance level for suboptimal adherence to ART (see Table 3).

4 | DISCUSSION

The main aim of this study was to determine the association between neurocognitive decline and nonadherence to ART; this study's findings revealed that although there were just 41 (10.33%) of the participants who had poor (suboptimal) adherence to ART, this population disproportionately constituted the majority of those with neurocognitive decline 31/41(76%) compared to 10/41(24%) of those without neurocognitive decline, $p = 0.0329$. Indeed, even after adjusting for other confounding variables in multivariable logistic regression, neurocognitive decline remained significantly associated with poor adherence to ART.

The impact of cognitive impairment on adherence to ART has been reported in the HIV era. Hinkin et al. showed that deficits in executive function, memory, and attention are associated with poor adherence to ART, although more so among those prescribed complex dosing regimens.[32] Specifically, deficits in prospective memory functioning, particularly on the index of time-based prospective memory, are linked to an increased risk of medication nonadherence independent of general cognitive impairment and psychiatric comorbidity.[17,33]

In addition to poor cognitive functioning, the other major culprits for poor adherence to ART are neuropsychiatric conditions, including MDD and substance-related disorders. Studies have demonstrated an aggregate interactive effect of cognitive disorders, substance use/disorder, and MDD towards poor adherence to ART.[33-35] In this study, despite that just 5.5% of the participants had MDD, the ART adherence rate of these patients was significantly poorer compared to those without MDD, even after adjusting for confounders. Similarly, a prospective observational study in Tanzania showed that depression, especially in severe form, is a significant predictor of ART nonadherence at baseline and 12-month follow-up visits and is inversely associated with favorable clinical outcomes.[36] Another 12-month observational study in Uganda showed that alleviation of depressive symptoms improves both ART adherence and overall clinic attendance.[37] The impact of depression on ART adherence could directly or indirectly be linked to cognitive decline that impacts medication adherence. A published study using the same data showed that even a small prevalence of MDD has an overall negative impact on cognitive function.[38] Specific cognitive domains whose impairment could be linked to suboptimal adherence were also affected, thus worsening cognitive function in an already cognitively comprised HIV population.[38]

The 10.32% prevalence of suboptimal adherence to ART corresponds to an 89.68% adherence rate which is lower than the national recommended ART adherence target of ≥95%.[39] The diversity in nonadherence rates is reported elsewhere in Sub-Saharan Africa; for example, 9.4% ART nonadherence rate was reported in an AIDS indicator survey in Kenya,[34] 14.4% in Batu town Ethiopia,[40] 18.8% in Addis Ababa Ethiopia[41] and 17.02% in Sudan[35]: Interestingly, a much higher suboptimal adherence of 48% and 39.7% are reported in Nairobi, Kenya, and Benishangul-Gumuz in Ethiopia, respectively.[42] A relatively better adherence rate observed in this study could partly be explained by specific programs within the study population that target improving adherence and use of the CTC services. These programs utilize the designated team leaders who follow up and trace members and address challenges that affect their medication adherence and retention in HIV care.

While depression was significant for poor adherence to ART, substance use did not significantly associate with suboptimal adherence to ART. However, participants with a substance use/disorder had at least 39% higher odds of poor adherence to ART. One possible explanation is that a small sample of poor adherence to ART had to be computed against another small sample of substance use/disorder and controlled against multiple confounders. In this case, the impact of each substance on ART nonadherence could be diluted by other covariates under multivariable regression, thus dissipating the statistical association; therefore, the lack of association observed could be a reflection of statistical but not necessarily clinical association.

Our study sample was disproportionately over-represented by females, who were about two-thirds of the population; in one way, reflecting a 6.2% national HIV prevalence for females compared to a 3.1% for males in the Tanzanian population aged 15–49 within which our study's mean age of 41.95 (SD: 12.61) years is included.[43] However, previous studies have suggested that gender inequalities in access to HIV care could contribute to suboptimal ART adherence among females in sub-Saharan Africa.[44–48] Moreover, having the support group mentioned earlier, the members showing missing appointments are traced by team leaders, and the specific challenges related to suboptimal adherence and poor retention in HIV care are addressed.

While our study demonstrated that cognitive decline and depressive symptoms negatively influenced adherence to ART, all other variables, including gender, BMI, current viral load, CD4+ count, duration of ART use, and HB concentration, were not significantly associated with ART nonadherence. However, under an unadjusted analysis set at a significance level of <20%, participants who were never married had significantly higher rates of nonadherence compared to those who were married or living with a partner. This observation suggests that being in a stable relationship that involves living with a spouse may offer a protective effect from the support of the loved one and may also be a proxy indication of stability and a higher level of functioning manifest as better adherence and outcome.

The main strength of this study is that, to the best of our knowledge, this is the first published study in Tanzania attempting to elicit the impact of cognitive decline on ART adherence in the HIV population. In contrast, previous studies have mainly focused on the overall prevalence of ART adherence. Furthermore, psychiatric comorbidities, including MDD and substance abuse, were assessed using MINI, which has better diagnostic accuracy than the screening tools used in most other studies.

As for limitations, being a cross-sectional design, the study cannot adequately inform the causal relationship between the outcome and explanatory variables. The specific cognitive measures provided by a comprehensive neuropsychological battery that offers HAND categories ANI, MND, and HAD were not done; instead, the neurocognitive function was assessed using a screening tool (MoCA). Despite being highly recommended for cognitive screening, MoCA is sensitive to the cultural and educational background; nonetheless, MoCA can assess specific cognitive domains affected by HIV and has demonstrated good reliability in the HIV population when a comprehensive neuropsychological battery is not available.[29] Given that the instrument used to assess depressive symptoms could only dichotomize the presence or absence of MDD, it was impossible to study the impact of the severity of depressive symptoms on ART adherence rate.

In conclusion, neurocognitive disorders in the HIV population play a significant role in ART adherence, coupled with MDD; the interaction could further worsen the adherence rate and complicate overall treatment outcomes. Therefore, it is essential to integrate psychiatric care by screening common neuropsychiatric morbidity and providing specialized management. Further research should offer a better understanding and provide the platform to design and optimize future care models (Tables 1-3). There should be result section for factors associated non adherence to ART before the discussion section and intext cited with Table 3

AUTHOR CONTRIBUTIONS

Azan Nyundo: conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; resources; writing – original draft; writing – review and editing.

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ETHICS STATEMENT

Ethical approval was granted by the local IRB of the Dodoma University Ethical and Research Committee with reference UDOM/DRP/134/VOL V/91.

TRANSPARENCY STATEMENT

The author affirms that this manuscript is an honest, accurate and transparent account of the study have not been ommited.

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