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Association Between High Serum Aspartate Transaminase to Alanine Transaminase Ratio and Probable HIV Dementia Among People Living With HIV on Dolutegravir-Based Antiretroviral Therapy: A Cross-Sectional Study from Central Uganda

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Abstract

Background: Probable HIV dementia (PHD) remains a significant complication among people living with HIV(PLWH), particularly in resource-limited settings where access to comprehensive neurocognitive assessment is limited**.** This study investigated the association between AST-to-ALT ratio and PHD among PLWH on Dolutegravir-based antiretroviral therapy (DTG-based ART). **Methods:** We conducted a secondary analysis using a dataset generated from hospital-based cross-sectional study that consecutively recruited 235 PLWH on DTG-based ART at St. Francis Nsambya Hospital in Kampala, Central Uganda. PHD was defined as International HIV Dementia Scale score ≤10. **Results:** PHD prevalence was 22.1% (52/235; 95% CI: 17.3–27.9) and increased across AST-to-ALT ratio tertiles (13%, 23%, and 31%; p=0.023). Participants in the second and third tertiles had higher odds of PHD (aOR=2.85, 95% CI: 1.13–7.15; p=0.026 and aOR=4.28, 95% CI: 1.75–10.45; p=0.001). Each 0.5-unit increase in the AST-to-ALT ratio increased the odds of PHD by 40% (aOR=1.40, 95% CI: 1.02–1.92; p=0.036). An AST-to-ALT ratio cutoff of 1.26 showed modest discrimination for PHD (AUC=0.622), with 73% sensitivity, 51% and specificity, 29%. **Conclusion:** A higher AST-to-ALT ratio is a potentially useful screening predictor for PHD in PLWH on DTG-based ART in resource limited settings, pending validation in larger prospective studies.

Plain Language Summary

People living with HIV are at risk of developing problems with memory, thinking, and concentration, even when they are receiving effective treatment. The most severe form of this condition is called HIV-related dementia. In many low-resource settings, such as Uganda, routine screening for these problems is limited because available tests can be expensive or difficult to use in busy clinics. This creates a need for simple and affordable ways to identify individuals at risk. This study explored

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whether a common blood test, already used in routine care, could help detect people at higher risk of HIV-related dementia. Specifically, researchers looked at the ratio between two liver enzymes, aspartate transaminase (AST) and alanine transaminase (ALT) in people living with HIV who were taking a widely used treatment called dolutegravir-based antiretroviral therapy. The study analyzed data from 235 adults receiving HIV care at a hospital in Kampala, Uganda. Each participant completed a brief screening test for dementia, and their blood samples were used to measure AST and ALT levels. The researchers then calculated the AST-to-ALT ratio and compared it with the presence of probable HIV-related dementia. About 1 in 5 participants (22%) were found to have signs of probable HIV-related dementia. The results showed that individuals with higher AST-to-ALT ratios were more likely to have dementia. In fact, the likelihood of dementia increased steadily as the ratio increased. People with the highest ratios were about four times more likely to have dementia than those with the lowest ratios. The study also found that a specific cutoff value of this ratio could help identify individuals at risk, although it correctly identifies approximately half of people without dementia as low risk. Still, because this test is simple, inexpensive, and already widely available, it could be useful as an early screening tool for HIV-associated dementia.

Keywords
aspartate transaminase, alanine transaminase, dementia, ratio, predictor

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Introduction

Probable HIV dementia (PHD), the most severe form of HIV-associated neurocognitive disorders (HAND), is a progressive subcortical syndrome characterized by impairments in memory, attention, psychomotor speed, and executive function, ultimately leading to significant functional disability.[1] The pathophysiology of HAND is complex, involving neuroinflammation, synaptic pathology, and neuronal death driven by the toxic effects of HIV viral proteins, including transactivator of transcription (Tat) and glycoprotein 120 (gp120), which compromise blood-brain barrier integrity and facilitate HIV penetration into the brain parenchyma.[2] HIV primarily infects macrophages and microglia rather than neurons, establishing reservoirs within subcortical and cortical structures,[3] with the extent of neuronal damage correlating directly with the severity of dementia. Although combination antiretroviral therapy (ART) has substantially reduced PHD incidence, the overall prevalence of neurocognitive impairment in people living with HIV (PLWH) remains high despite effective ART, with persistent low-level viral replication, HIV-related neuroinflammation, and potential Alzheimer's disease-like pathology contributing to ongoing neuronal injury.[4] Among PLWH on dolutegravir (DTG)-based regimens, metabolic complications further amplify this neurocognitive burden.[5]

The global burden of probable HIV dementia (PHD) remains substantial and disproportionately concentrated in Sub-Saharan Africa. A recent systematic review reported a global HAND prevalence of 42.6% among PLWH, with PHD accounting for a minority of cases while milder forms predominate.[6] The highest HIV prevalence globally is estimated in the African region, where approximately 1 in 25 adults are HIV-positive, accounting for over two-thirds of PLWH worldwide.[7] In Sub-Saharan Africa, the reported prevalence of HIV-related dementia ranges from 0% to 80% across studies,[8] reflecting profound heterogeneity in populations, diagnostic tools, and disease staging. In East Africa, screening for HAND among HIV clinic attendees in Tanzania identified high proportions of cognitive impairment using the International HIV Dementia Scale (IHDS).[9] In Uganda specifically, 31% of HIV-positive patients attending an ambulatory HIV clinic in Kampala were found to have HIV dementia, with advanced age and low CD4 count identified as the only significant risk factors.[10] Strikingly, a cross-sectional study of 680 HIV clinic attendees in Uganda reported a PHD prevalence of 64.4%, with increasing stress scores and psychosocial impairment as significant contributing factors.[11]

Failure to diagnose and manage PHD early carries grave clinical consequences. The gradual loss of mental clarity and physical coordination severely reduces quality of life, and without treatment, HIV-associated dementia can be fatal.[12] Unrecognized neurocognitive impairment compromises medication adherence, accelerating immunological decline and increasing the risk of opportunistic infections and mortality.[13] With the majority of PLWH being asymptomatic, screening for HAND remains extremely limited in clinical settings,[12] meaning that many patients silently deteriorate without timely intervention. In resource-limited settings such as Uganda, the downstream social and economic burden of unmanaged PHD including loss of employment, caregiver dependency, and family disintegration compounds the already significant HIV-related morbidity.

A critical research gap persists in the identification of accessible, affordable, blood-based biomarkers capable of screening, diagnosing, and predicting PHD among PLWH on ART. The neuropathogenesis of HAND is complex and identifying reliable biomarkers has been challenging.[14] Existing biomarkers such as cerebrospinal fluid neopterin, quinolinic

acid, and beta-2 microglobulin are predominantly research tools, impractical for routine clinical use in resource-constrained settings.[15] Identifying blood-based biomarkers associated with brain health is imperative for under-resourced settings and among underrepresented populations in research,[16] particularly for the early identification of at-risk individuals who could benefit from timely therapeutic and supportive interventions.

Growing evidence implicates hepatic dysfunction measurable through routine serum aminotransferase activity in cognitive decline and dementia. A systematic review and meta-analysis demonstrated that while individual ALT and AST levels were not significantly associated with cognitive impairment in pooled analysis, a higher AST to ALT ratio was significantly associated with an increased risk of cognitive impairment.[17] A longitudinal study using three clinical cohorts found that an elevated AST-to-ALT ratio was a risk factor for future cognitive impairment, with higher ratios negatively correlated with right hippocampal volume, suggesting a structural mechanism for cognitive decline.[18] Findings from the large Atherosclerosis Risk in Communities (ARIC) Study corroborate these associations, with a higher AST-to-ALT ratio linked to a higher prevalence of dementia and lower global cognition scores, attributed to liver hypometabolism, reduced brain glucose metabolism, and impaired neurotransmitter production.[19] Among community-dwelling older adults investigated for cognitive decline, patients with dementia demonstrated significantly higher AST-to-ALT ratios compared to controls ($p = 0.003$),[20] reinforcing the potential clinical utility of this routine laboratory parameter. In the HIV context, a related Ugandan study in Southwestern Uganda found that elevated AST-to-high-density lipoprotein-cholesterol ratio was significantly associated with probable dementia among PLWH on DTG-based ART,[21] suggesting that hepatic metabolic biomarkers merit targeted investigation in this population. However, to the best of our knowledge, no study in Uganda has investigated the specific association between a high serum AST:ALT ratio and probable HIV dementia among PLWH on DTG-based ART. Therefore, this study investigated the association between high serum AST-to-ALT ratio and probable HIV dementia among PLWH on DTG-based ART in Central Uganda.

Material and Methods

The reporting of this study conforms to the STROBE guidelines for observational studies.[22]

Study Design, Population, and Variables

We conducted a secondary data analysis study from January 09, 2026 to March 12, 2026 using a dataset generated from a hospital-based cross-sectional study, which investigated the Prevalence and Factors associated with Elevated serum transaminases among PLWH on Dolutegravir-based ART at St. Francis Nsambya Hospital ART clinic in Kampala, Central Uganda. This primary study was conducted from September 5, 2025 to October 30, 2025. St. Francis Nsambya Hospital ART clinic is situated in Nsambya Hill, Makindye Division, off Ggaba road, approximately 2.7 kilometers from Kampala Central Business District and operates from Monday to Friday, 8am to 4pm. The clinic has approximated 8,600 registered PLWH on ART, with a daily workday turn up of roughly 100 patients and an estimate of about 7,000 PLWH on DTG-based ART. The study population consisted of PLWH on DTG-based ART who were receiving HIV care and follow-up at St. Francis Nsambya Hospital ART clinic in Kampala, Central Uganda during the study period and who met the eligibility criteria. In the primary study, adults aged ≥18 years with confirmed HIV infection who had been receiving DTG-based ART for at least six months and provided written informed consent were eligible for inclusion. Participants were recruited using systematic sampling, whereby every eighth eligible patient attending the ART clinic during the study period was consecutively enrolled until the required sample size of 235 participants was achieved. Patients with incomplete or missing medical records, those with interrupted DTG-based ART, pregnant women, and those presenting with acute illnesses, including hepatitis B or hepatitis C infection, were excluded from the study.

The primary study used a structured researcher administered questionnaire that consisted of standard measurement tool to collect a wide range of variables which included socio-demographics (sex, age, marital status, education level, residence, religion affiliation, and employment status), clinical variables (Smoking status, Alcohol consumption, Physical activity, Sleep duration, Obstructive Sleep Apnea, Fluids and vegetables consumption per week, Milk consumption per week, Hypertension, family history of hypertension, family history of dementia, history of stroke, history of tuberculosis, history of COVD-19, Probable HIV dementia Duration on ART, and duration on DTG-based ART).

Anthropometric measurements (weight, height, waist and hip circumference), systolic and diastolic blood pressure measurements were then taken. A digital sphygmomanometer was used to measure blood pressure. Two readings were taken five minutes apart, and their average was recorded as the participant's blood pressure. Weight and height were measured using a portable weight and height scale. Waist and hip circumferences were measured using a non-stretchable SECA 201 ergonomic tape. Two measurements were taken, and when the difference between them exceeded 3 cm, a third

measurement was obtained. The final waist and hip circumference values were recorded as the mean of the two or three measurements.

After administration of the questionnaire and anthropometric measurements, phlebotomy was performed by principal investigators who are trained Medical Laboratory Technicians using a vacutainer needle with use of a tourniquet. Blood was drawn from the respondent in the seated position. About 4mL of blood in red top were drawn from each study participant. After drawing the blood, blood tubes were inverted 5-6 times to ensure mixing of the clot activator with blood. The blood samples were centrifuged to separate serum from the cells within one hour of collection. Thereafter, serum was be analyzed for alanine transaminase and aspartate transaminase using a clinical chemistry analyser (COBAS C311). This analyser was designed to perform spectrophotometric measurements of the analyte level at specific set wavelengths using specific reagents. The analyser automatically performs all reagent pipetting, incubation, photometric measurements and calculations. Quality control samples were run before patient samples were run. All laboratory measurements were performed at St. Francis Nsambya Hospital laboratory.

Main Dependent and Independent Variables in the Secondary Analysis

The primary outcome of interest was Probable HIV dementia which was measured in the primary study using the International HIV Dementia Scale.[23] This is a bed side screening tool for HIV associated dementia. It can be used in a clinic setting and only requires 2–3 minutes to complete. This tool has been validated in South Africa and Uganda and found to have good psychometric properties in African populations with sensitivity of 88% and 80% and specificity of 50% and 55% respectively at a cut off of $\leq$10.[23,24] This tool that assesses for memory impairment, motor and psychomotor speed does not require one to be proficient in English and is brief and inexpensive. Even though it is thought not to be ideal, it is one of the best for use across cultures for screening for neuro-cognitive impairment in HIV.[23]

The main independent variable in this study was the serum aspartate aminotransferase to alanine aminotransferase (AST-to-ALT ratio) ratio, calculated as the ratio of serum AST activity to ALT activity. The ratio was determined using the following formula: AST-to-ALT ratio = AST(U/L) ÷ALT(U/L). In the present study, no established clinical or epidemiological cut-off values were identified in the literature for defining "high" or "low" levels of AST-to-ALT ratio in relation to the prediction of Probable HIV dementia. In the absence of validated thresholds, data-driven approaches are frequently employed in epidemiological analyses to facilitate meaningful categorization of continuous variables. Accordingly, AST-to-ALT ratio was categorized into tertiles based on its distribution within the study population. The use of tertiles provides a balanced method for stratification, ensuring adequate sample size within each category while minimizing excessive fragmentation of the data. Additionally, tertile categorization improves interpretability by enabling comparisons across three distinct groups representing relatively low, intermediate, and high values of the respective ratios. This approach has been widely applied in observational studies where clinically validated cut-off points are not available.

Operational Definitions

Probable HIV dementia: IHDS score $\leq$10[23,24]

Hypertension: SBP $\geq$140 mmHg and/or DBP $\geq$90 mmHg[25] and being on antihypertensive medication.

Obstructive sleep apnea(OSA): Assessed using the stop bang scoring model tool and classified as low risk of OSA answering yes to less than 3 items.[26]

Physical activity: Assessed using the International Physical activity questionnaire (IPAQ) and categorized $\leq$3000 and > 3000 MET minutes per week.[27]

Sleep duration: categorized as $\leq$7, and >7hours[28]

Body Mass Index: <18.5 Kg/m^2, 18.5-24.9Kg/m^2, 25-29.9 Kg/m^2, $\geq$30 Kg/m^2[29]

Waist circumference: cut-off point for females >80 cm and >94 cm for males[30]

Waist-to-hip ratio: Considered abnormal if $\geq$ 0.90 for males or $\geq$ 0.85 for females.[30]

Waist-to-height ratio: Considered abnormal if $\geq$ 0.5[31]

Sample Size Determination

For the secondary analysis, a sample size calculation was based on the 17% (64/377) proportion of PLWH on DTG-based ART who had probable dementia in a cross-sectional study in Southwestern Uganda.[21] We used the Kish Leslie formula (1965) with a 5% margin of error and a 95% confidence interval.

$$n = 1.96^2 \text{ x } 0.17(1 - 0.17) \,/\, 0.05^2 = 217$$

Since the primary study enrolled 235 participants, this sample size was adequate for the secondary data analysis study.

Statistical Analysis

Data was analyzed using STATA Software version 17. Categorical variables were summarized using frequencies and proportions. The distribution of categorical variables between participants with Probable HIV dementia and the participants without Probable HIV dementia was compared using Chi-square test or Fishers exact test. Continuous variables were tested for normality using Shapiro-wilk normality test and all were not normally distributed(p-value<0.05). Therefore, they were all summarized using Median (IQR) and their distribution between participants with Probable HIV dementia and the participants without Probable HIV dementia compared using the Man-Whitney U test. A p-value <0.05 was considered statistically significant.

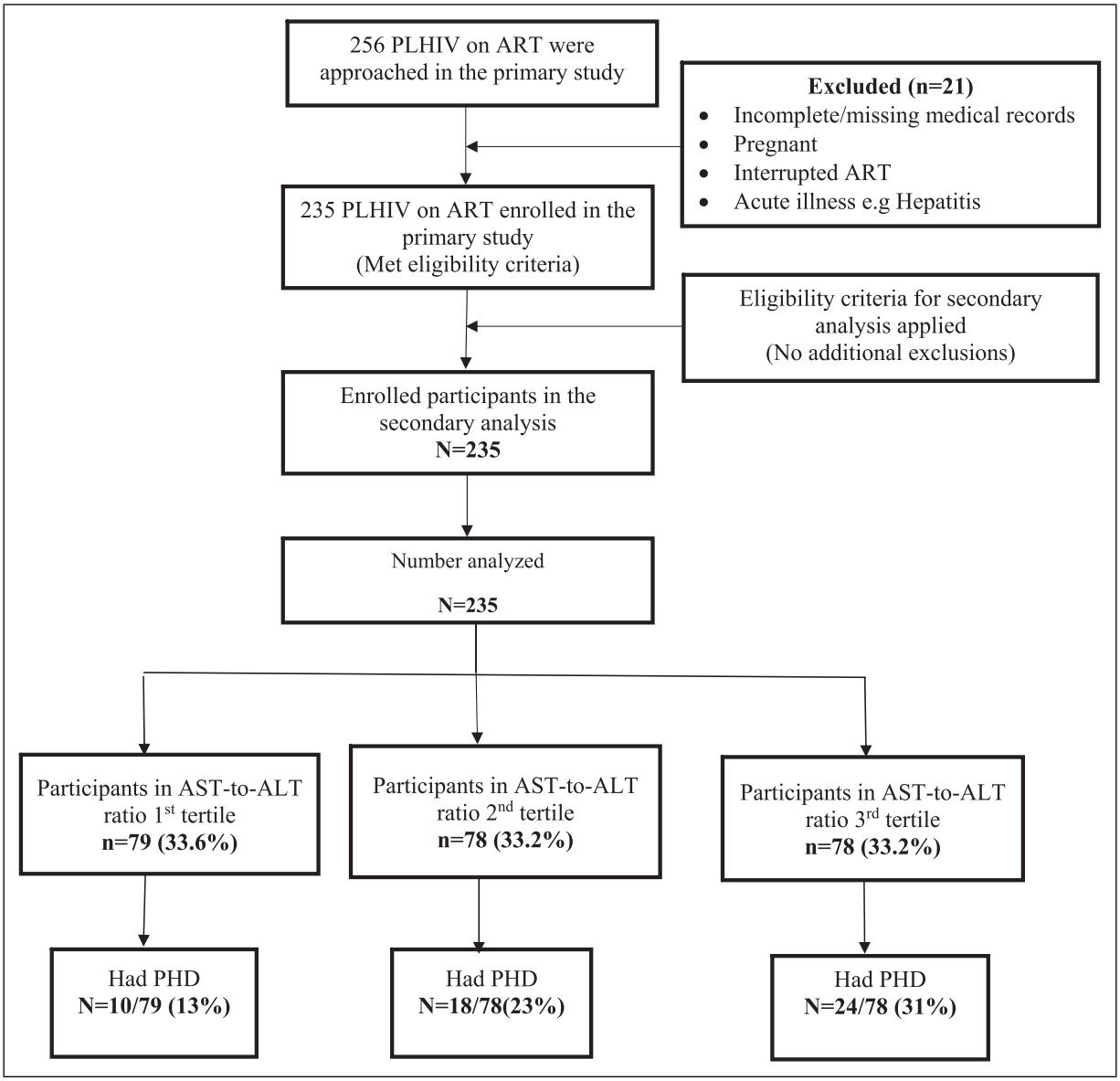


Figure 1. Study flow chart

Logistic regression was used to assess the association between major independent variable AST-to-ALT ratio and the binary dependent variable Probable HIV dementia (1=present, 0=absent). At the bivariate level, crude associations between Probable HIV dementia and each independent variable, including AST-to-ALT ratio were evaluated. Associations were quantified using crude odds ratios (ORs) with corresponding 95% confidence intervals (CIs), and statistical significance was determined at a p-value <0.2. AST-to-ALT ratio and other variables that demonstrated statistical significance at the bivariate level, along with those that were not statistically significant but were considered biologically plausible confounders were included in the multivariable model to ensure adequate adjustment for potential confounding. In an attempt to increase model precision and stability of estimates given the low number of the PHD outcome events (n=52), some variables that were not statistically significant in the full multivariate model at a p-value < 0.05 and not with a strong biological or clinical linkage to PHD were dropped to generate a reduced more parsimonious multivariate model that prioritized the primary exposure (AST-to-ALT ratio) together with the most clinically and biologically justified confounders. The variables that were initially included in the multivariate model and later dropped in an attempt to build a more parsimonious model were sex, education level, physical activity, family history of dementia, and family history of hypertension. The final model's goodness of fit was then assessed using the Hosmer-Lemeshow test, with a p-value >0.05 indicating a good fit. The final model was also tested for the absence of severe multi-collinearity. A mean Variance inflation factor (VIF) < 5 was considered acceptable. Adjusted odds ratios (aORs) with 95% CIs and p-values for the variables in the final model were reported and associations were considered significant at a p-value <0.05. As a sensitivity analysis, the AST-to-ALT ratio was modeled as a continuous variable. The assumption of linearity in the logit was assessed by adding a quadratic (squared) term for the AST:ALT ratio to the multivariable logistic regression model and testing its significance using a Wald test. A non-significant quadratic term ($p > 0.05$) was interpreted as evidence supporting a linear association.

To evaluate the predictive ability of AST-to-ALT ratio for identifying participants with Probable HIV dementia, we conducted a Receiver Operating Characteristic (ROC) curve analysis. ROC analysis was selected because it is an established method for evaluating the diagnostic or discriminative performance of a continuous biomarker in classifying a binary outcome. The area under the curve (AUC) was computed to quantify the overall discriminative performance of AST-to-ALT ratio for Probable HIV dementia. An AUC value closer to 1.0 indicates better predictive power, whereas an AUC of 0.5 suggests no better classification than chance. Predictive performance was considered statistically significant if the 95% CI for the AUC did not include the null value of 0.5. Additionally, the interpretation of AUC values is summarized as: AUC 0.90–1.00 = Excellent; 0.80–0.89 = Good; 0.70–0.79 = Fair; 0.60–0.69 = Poor; 0.50–0.59 = Failure[32]

Results

Narrative of the Study Flow Chart

A total of 256 PLWH were initially approached in the primary study. After applying the eligibility criteria, 235 participants were found to be eligible. All 235 PLWH receiving DTG-based ART who were included in the primary study met the eligibility criteria for the secondary analysis and were subsequently included in the present secondary analysis. There were no missing data for the International HIV Dementia Scale (IHDS) scores or the AST and ALT measurements among these 235 participants. Participants were divided into tertiles of AST-to-ALT ratio: first tertile (n=79), second tertile (n=78), and third tertile (n=78). PHD prevalence was 13%, 23%, and 31% across the tertiles from lowest to highest, respectively, totaling 52 PHD cases (22.1%) (Figure 1).

Socio-Demographic Characteristics of the Study Participants

A total of 235 PLWH on DTG-based ART were included in the study (Table 1). Overall, 22.1% (52/235; 95% CI: 17.3–27.9) of the participants had Probable HIV dementia. The mean age of participants was 46.47 ± 11.86 years. Participants with Probable HIV dementia were significantly older than those without dementia (50.50 vs 45.32 years; p = 0.005). Most participants were aged >50 years (39.1%), female (78.7%), single (44.7%), Catholic (40.9%), self-employed (65.5%), had primary education (54.5%), and resided in urban areas (68.5%). The prevalence of Probable HIV dementia varied across socio-demographic categories but was not statistically significant for most variables.

Clinical Characteristics of the Study Participants

Table 2 summarizes the clinical characteristics of the 235 study participants and the distribution of PHD. Most participants had never smoked (91.1%), never consumed alcohol (63.0%), and reported physical activity >3000 MET-minutes/week (58.3%). Slightly more than half slept ≤7 hours per night (53.2%), and the majority had a low risk of obstructive sleep apnea

Table 1. Distribution of Probable HIV Dementia in the Different Levels of Each of the Socio-Demographic Characteristics

Variable	Total N=235	Probable HIV dementia		p-value
		Absent N=183 77.9% (95%CI:72.1 - 82.6)	Present N=52 22.1% (95%CI:17.3 - 27.9)	
Age (Years): Mean ± SD	46.47 ± 11.86	45.32 ± 11.25	50.50 ± 13.12	**0.005***
Age groups				0.078
18-30	27 (11.5%)	22 (81%)	5 (19%)	
31-40	45 (19.1%)	34 (76%)	11 (24%)	
41-50	71 (30.2%)	62 (87%)	9 (13%)	
>50	92 (39.1%)	65 (71%)	27 (29%)	
Sex				0.43
Male	50 (21.3%)	41 (82.0%)	9 (18.0%)	
Female	185 (78.7%)	142 (76.8%)	43 (23.2%)	
Marital status				0.11
Single	105 (44.7%)	87 (82.9%)	18 (17.1%)	
Married/Cohabiting	91 (38.7%)	70 (76.9%)	21 (23.1%)	
Separated/Divorced	39 (16.6%)	26 (66.7%)	13 (33.3%)	
Religious affiliation				0.24
Catholic	96 (40.9%)	69 (72%)	27 (28%)	
Protestant	62 (26.4%)	53 (85%)	9 (15%)	
Moslem	42 (17.9%)	33 (79%)	9 (21%)	
Others	35 (14.9%)	28 (80%)	7 (20%)	
Employment status				0.75
Peasant	42 (17.9%)	31 (73.8%)	11 (26.2%)	
Self-employed	154 (65.5%)	122 (79.2%)	32 (20.8%)	
Professional	39 (16.6%)	30 (76.9%)	9 (23.1%)	
Education level				0.60**
No education	11 (4.7%)	7 (63.6%)	4 (36.4%)	
Primary	128 (54.5%)	99 (77.3%)	29 (22.7%)	
Secondary	64 (27.2%)	52 (81.3%)	12 (18.8%)	
Tertiary	32 (13.6%)	25 (78.1%)	7 (21.9%)	
Residence				0.58
Rural	74 (31.5%)	56 (75.7%)	18 (24.3%)	
Urban	161 (68.5%)	127 (78.9%)	34 (21.1%)	

*Student t-test.
**Fisher exact test; all other comparisons by chi-square test.

(82.1%). Most participants consumed fruits and vegetables ≤4 days per week (72.3%) and milk ≤4 days per week (76.6%). Hypertension was present in 14.5% of participants, while 32.3% reported a family history of hypertension and 20.4% reported a family history of dementia. A history of stroke (12.8%), tuberculosis (10.6%), and COVID-19 (6.4%) was relatively uncommon. Most participants had been on ART for >5 years (90.6%) and DTG-based ART for >2 years (90.6%). The prevalence of PHD varied across clinical characteristics but none of the differences reached statistical significance ($p > 0.05$).

Anthropometric and Biochemical Parameters of the Study Participants

Table 3 presents the anthropometric and biochemical characteristics of the 235 study participants and the distribution of PHD. Regarding anthropometric characteristics, 37.4% of participants had a body mass index (BMI) <25 kg/m^2, 36.2% had BMI 25–29.9 kg/m^2, and 26.4% were obese (BMI ≥30 kg/m^2). Although the prevalence of PHD was higher among obese participants (29%) compared with those with BMI <25 kg/m^2 (20%) and BMI 25–29.9 kg/m^2 (19%), this difference was not statistically significant ($p = 0.30$). In contrast, measures of central adiposity showed significant associations with HAD. Participants with high waist circumference had a significantly higher prevalence of PHD (27.0%) compared with those with normal waist circumference (11.1%, $p = 0.007$). Similarly, a high waist-to-hip ratio was associated with a higher prevalence of PHD (29.9%) compared with a normal ratio (11.9%, $p = 0.001$). Participants with a high waist-to-height ratio also had a significantly higher prevalence of PHD (25.8%) than those with normal values (6.7%, $p = 0.005$).

Table 2. Distribution of Probable HIV Dementia in the Different Levels of Each of the Clinical Characteristics

Variable	Total N=235	Probable HIV dementia		p-value
		Absent N=183 77.9% (95%CI:72.1 - 82.6)	Present N=52 22.1% (95%CI:17.3 - 27.9)	
Smoking status				1.00**
Never-smoked	214 (91.1%)	166 (77.6%)	48 (22.4%)	
Ever-smoked	21 (8.9%)	17 (81.0%)	4 (19.0%)	
Alcohol consumption status				0.12
Never-consumed	148 (63.0%)	120 (81.1%)	28 (18.9%)	
Ever-consumed	87 (37.0%)	63 (72.4%)	24 (27.6%)	
Physical activity (MET-minutes per week)				0.39
≤3000	98 (41.7%)	79 (80.6%)	19 (19.4%)	
>3000	137 (58.3%)	104 (75.9%)	33 (24.1%)	
Sleep duration				0.60
≤7hours	125 (53.2%)	99 (79.2%)	26 (20.8%)	
>7hours	110 (46.8%)	84 (76.4%)	26 (23.6%)	
Obstructive Sleep Apnea OSA				0.35
Low risk of OSA	193 (82.1%)	148 (76.7%)	45 (23.3%)	
High risk of OSA	42 (17.9%)	35 (83.3%)	7 (16.7%)	
Fluids and vegetables consumption per week				0.83
≤4days	170 (72.3%)	133 (78.2%)	37 (21.8%)	
>4days	65 (27.7%)	50 (76.9%)	15 (23.1%)	
Milk consumption per week				0.95
≤4days	180 (76.6%)	140 (77.8%)	40 (22.2%)	
>4days	55 (23.4%)	43 (78.2%)	12 (21.8%)	
Hypertension				0.12
No	201 (85.5%)	160 (79.6%)	41 (20.4%)	
Yes	34 (14.5%)	23 (67.6%)	11 (32.4%)	
Family history of hypertension				0.082
No	159 (67.7%)	129 (81.1%)	30 (18.9%)	
Yes	76 (32.3%)	54 (71.1%)	22 (28.9%)	
Family history of dementia				0.59
No	187 (79.6%)	147 (78.6%)	40 (21.4%)	
Yes	48 (20.4%)	36 (75.0%)	12 (25.0%)	
History of stroke				0.11
No	205 (87.2%)	163 (79.5%)	42 (20.5%)	
Yes	30 (12.8%)	20 (66.7%)	10 (33.3%)	
History of Tuberculosis				0.61**
No	210 (89.4%)	162 (77.1%)	48 (22.9%)	
Yes	25 (10.6%)	21 (84.0%)	4 (16.0%)	
History of COVID-19				0.33
No	220 (93.6%)	173 (78.6%)	47 (21.4%)	
Yes	15 (6.4%)	10 (66.7%)	5 (33.3%)	
Most recent Viral Load (RNA copies/mL of blood)				0.25**
Not detected	187 (79.6%)	149 (79.7%)	38 (20.3%)	
≤1000	46 (20.4%)	34(70.8)	14(29.2)	
>1000	2 (0.9%)	2 (100.0%)	0 (0.0%)	
Duration on ART				0.79**
≤5years	22 (9.4%)	18 (81.8%)	4 (18.2%)	
>5years	213 (90.6%)	165 (77.5%)	48 (22.5%)	
Duration on DTG-Based ART				0.54
≤2years	22 (9.4%)	16 (72.7%)	6 (27.3%)	
>2years	213 (90.6%)	167 (78.4%)	46 (21.6%)	

Limited variation in ART duration and DTG-based ART duration categories (90.6% in the longer-duration categories).
**Fisher's exact test, all other comparisons by chi-square test.

With regard to biochemical parameters, the median AST level was 23.2 U/L (IQR: 19.4–28.5) and did not differ significantly between participants with and without PHD ($p = 0.14$). However, ALT levels were significantly lower among

Table 3. Distribution of Probable HIV Dementia in the Different Levels of Each of the Anthropometric and Biochemical Parameters

Variable	Total N=235	Probable HIV dementia		p-value
		Absent N=183 77.9% (95%CI:72.1 - 82.6)	Present N=52 22.1% (95%CI:17.3 - 27.9)	
Body mass index(kg/m^2)				0.30
<25	88 (37.4%)	70 (80%)	18 (20%)	
25-29.9	85 (36.2%)	69 (81%)	16 (19%)	
≥30	62 (26.4%)	44 (71%)	18 (29%)	
Waist circumference(cm)				**0.007**
Normal	72 (30.6%)	64 (88.9%)	8 (11.1%)	
High	163 (69.4%)	119 (73.0%)	44 (27.0%)	
Waist to hip ratio				**0.001**
Normal	101 (43.0%)	89 (88.1%)	12 (11.9%)	
High	134 (57.0%)	94 (70.1%)	40 (29.9%)	
Waist to height ratio				**0.005***
Normal	45 (19.1%)	42 (93.3%)	3 (6.7%)	
High	190 (80.9%)	141 (74.2%)	49 (25.8%)	
AST(U/L)	23.2 (19.4-28.5)	23.7 (19.4-29)	21.8 (19-26.35)	0.14**
ALT(U/L)	18 (14.3-23.4)	18.9 (14.7-24.5)	15.25 (13.9-19.75)	**0.003****
AST-to-ALT ratio	1.29(1.10-1.51)	1.25(1.07-1.48)	1.42(1.22-1.60)	**0.007****
AST-to-ALT ratio tertiles				**0.023**
First	79 (33.6%)	69 (87%)	10 (13%)	
Second	78 (33.2%)	60 (77%)	18 (23%)	
Third	78 (33.2%)	54 (69%)	24 (31%)	

*Fisher's exact test, prevalence distribution in other variables was compared using Chi-square test.
**Mann-Whitney U test.

participants with PHD (15.25 U/L, IQR: 13.9–19.75) compared with those without PHD (18.9 U/L, IQR: 14.7–24.5; p = 0.003). Consequently, the AST-to-ALT ratio was significantly higher in participants with PHD (median 1.42) compared with those without PHD (median 1.25; p = 0.007). Furthermore, the prevalence of PHD increased significantly across AST-to-ALT ratio tertiles (13%, 23%, and 31% in the first, second, and third tertiles, respectively; p = 0.023).

Association Between AST-To-ALT Ratio and Probable HIV Dementia

At the bivariate analysis (Table 4), increasing AST-to-ALT ratio tertiles showed a positive association with Probable HIV dementia. Participants in the second tertile had higher odds of Probable HIV dementia compared with those in the first tertile, although this did not reach statistical significance (cOR = 2.07, 95% CI: 0.89–4.83; p = 0.092). However, individuals in the third tertile had significantly higher odds of Probable HIV dementia compared with the first tertile (cOR = 3.07, 95% CI: 1.36–6.96; p = 0.007).

Other variables significantly associated with Probable HIV dementia at the bivariate level included indicators of central obesity. Participants with a high waist circumference had nearly threefold higher odds of Probable HIV dementia compared with those with normal waist circumference (cOR = 2.96, 95% CI: 1.31–6.66; p = 0.009). Similarly, a high waist-to-hip ratio was associated with increased odds of Probable HIV dementia (cOR = 3.16, 95% CI: 1.56–6.40; p = 0.001). In addition, a high waist-to-height ratio was associated with a markedly increased likelihood of Probable HIV dementia (cOR = 4.87, 95% CI: 1.44–16.41; p = 0.011).

After adjusting for potential confounders in the multivariate logistic regression model (Table 4), the association between AST-to-ALT ratio and Probable HIV dementia became stronger. Participants in the second AST-to-ALT ratio tertile had significantly higher odds of Probable HIV dementia compared with those in the first tertile (aOR = 2.85, 95% CI: 1.13–7.15; p = 0.026). The association was even stronger for participants in the third tertile, who had higher than fourfold higher odds of Probable HIV dementia relative to those in the lowest tertile (aOR = 4.28, 95% CI: 1.75–10.45; p = 0.001). In sensitivity analysis, treating the AST:ALT ratio as a continuous variable yielded similar results. Each 0.5 unit increase in AST-to-ALT ratio was associated with 1.40 times increase in the odds of PHD; (aOR=1.40, 95% CI: 1.02-1.92; p=0.036) (Table 5), supporting the robustness of the primary tertile-based analysis. There was no statistically significant evidence that the relationship deviates from linearity (Wald test for quadratic term, p=0.082).

Table 4. Association Between AST-To-ALT Ratio Tertiles and Probable HIV Dementia

Variable	Bivariate		Multivariate	
	cOR(95%CI)	p-value	aOR(95%CI)	p-value
AST-to-ALT ratio tertiles				
First	1.00		1.00	
Second	2.07 (0.89-4.83)	0.092	**2.85 (1.13-7.15)**	**0.026**
Third	**3.07 (1.36-6.96)**	**0.007**	**4.28(1.75-10.45)**	**0.001**
Age groups				
18-30	1.00		1.00	
31-40	1.42 (0.44-4.66)	0.559	1.20 (0.32-4.49)	0.783
41-50	0.63(0.19-2.11)	0.463	0.59(0.16-2.22)	0.435
>50	1.83(0.63-5.33)	0.269	1.56(0.45-5.31)	0.476
Sex				
Male	1.00			
Female	1.38(0.62-3.06)	0.429		
Education level				
No education	1.00			
Primary	0.51(0.14-1.87)	0.312		
Secondary	0.40 (0.10-1.60)	0.198		
Tertiary	0.49 (0.11-2.17)	0.347		
Residence				
Rural	1.20(0.63-2.30)	0.583		
Urban	1.00			
Smoking status				
Never-smoked	1.00			
Ever-smoked	0.81(0.26-2.53)	0.722		
Alcohol consumption status				
Never-consumed	1.00		1.00	
Ever-consumed	1.63(0.87-3.05)	0.124	1.56 (0.76-3.18)	0.225
Physical activity (MET-minutes per week)				
≤3000	0.76 (0.40-1.43)	0.393		
>3000	1.00			
Sleep duration				
≤7hours	0.85(0.46-1.57)	0.601		
>7hours	1.00			
Obstructive Sleep Apnea(OSA)				
Low risk of OSA	1.00			
High risk of OSA	0.66(0.27-1.58)	0.349		
Fluids and vegetables consumption per week				
≤4days	0.93(0.47-1.83)	0.828		
>4days	1.00			
Milk consumption per week				
≤4days	1.02(0.49-2.12)	0.950		
>4days	1.00			
Hypertension				
No	1.00		1.00	
Yes	1.87(0.84-4.13)	0.125	1.12 (0.44-2.85)	0.818
Family history of hypertension				
No	1.00			
Yes	1.75 (0.58-2.57)	0.084		
Family history of dementia				
No	1.00			
Yes	1.23 (0.58-2.57)	0.591		
History of stroke				
No	1.00		1.00	
Yes	1.94 (0.84-4.46)	0.118	1.54 (0.59-4.01)	0.380

(continued)

Table 4. (continued)

Variable	Bivariate		Multivariate	
	cOR(95%CI)	p-value	aOR(95%CI)	p-value
History of Tuberculosis				
No	1.00			
Yes	0.64(0.21-1.96)	0.438		
History of COVID-19				
No	1.00			
Yes	1.84(0.60-5.65)	0.286		
Most recent Viral load				
Not detected	1.00		1.00	
Detected	1.61(0.79-3.31)	0.190	1.40(0.61-3.22)	0.429
Duration on ART				
≤5years	1.00			
>5years	1.31(0.42-4.05)	0.640		
Duration on DTG-Based ART				
≤2years	1.00		1.00	
>2years	0.73 (0.27-1.98)	0.543	0.82 (0.25-2.67)	0.744
Body mass index(kg/m^2)				
<25	1.00			
25-29.9	0.90 (0.43-1.91)	0.787		
≥30	1.59 (0.73-3.38)	0.228		
Waist circumference(cm)				
Normal	1.00		1.00	
High	**2.96 (1.31-6.66)**	**0.009**	1.97(0.65-6.00)	0.232
Waist to hip ratio				
Normal	1.00		1.00	
High	**3.16 (1.56-6.40)**	**0.001**	2.18 (0.93-5.09)	0.071
Waist to height ratio				
Normal			1.00	
High	**4.87(1.44-16.41)**	**0.011**	1.86 (0.39-8.93)	0.437

cOR: Crude odds ratio, aOR: adjusted odds ratio, CI: 95% confidence interval, Hosmer-Lemeshow test (p = 0.1405). Model's mean VIF= 1.81, Events-per-variable (EPV) ratio=4.

Diagnostic Performance of AST-To-ALT Ratio for Probable HIV Dementia

The AST-to-ALT ratio at an optimal cutoff of 1.26 had a significant ability (AUC=0.622, 95%CI: 0.537 - 0.707) to differentiate between participants with from those without Probable HIV dementia at a sensitivity of 73% and specificity of 51%(Figure 2). The positive predictive value (PPV) and negative predictive values (NPV) at the 1.26 optimal cutoff of the ratio were 29% and 86% respectively.

Table 5. Association Between Continuous AST-To-ALT Ratio and Probable HIV Dementia

Variable	Bivariate		Multivariate	
	cOR(95%CI)	p-value	aOR(95%CI)	p-value
AST-to-ALT ratio	1.23(0.93-1.62)	0.151	**1.40(1.02-1.92)**	**0.036**

cOR:Crude odds ratio, aOR: adjusted odds ratio, CI: 95%Confidence interval.
Adjusted model = AST-to-ALT ratio + Age+ Alcohol consumption+ Waist circumference + Waist to hip ratio+ Waist to height ratio+ Hypertension+ History of stroke+ Duration on DTG-based ART+ Most recent viral load).
Hosmer-Lemeshow test (p = 0.7315), Model's mean VIF= 1.80 and Events-per-variable (EPV) ratio=4.3.

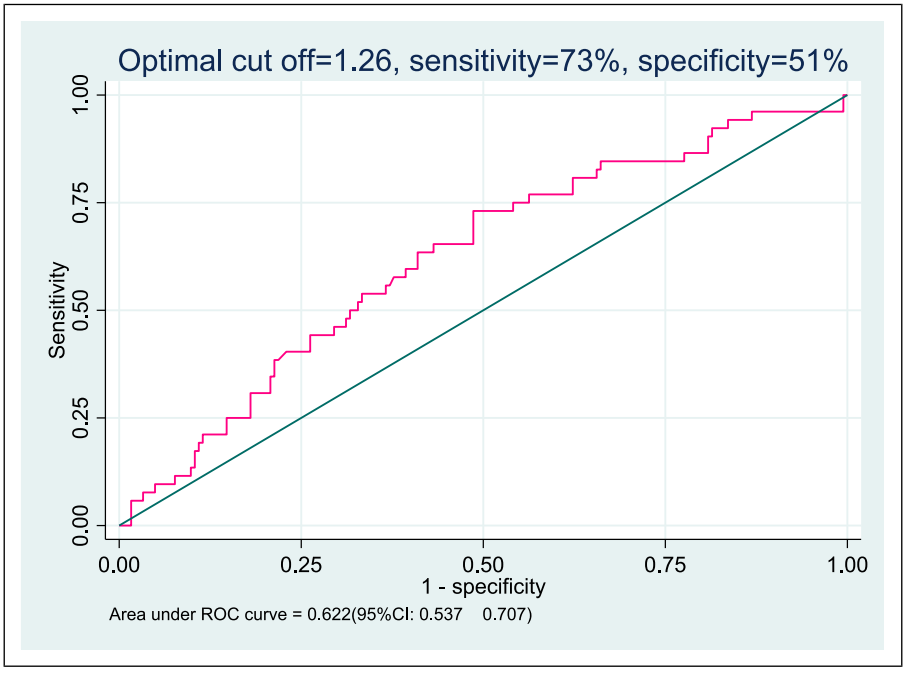


Figure 2. Receiver operating characteristic curve showing the predictive performance of AST-to-ALT ratio for Probable HIV dementia

Discussion

In this study, the overall prevalence of Probable HIV Dementia (PHD) was 22.1% among PLWH on dolutegravir-based ART in Central Uganda. This finding is clinically significant and confirms that PHD remains a substantial neurological burden in this population, even in the modern ART era. The observed prevalence is markedly higher than the estimated dementia prevalence of approximately 5–8% reported in the general HIV-uninfected older adult population worldwide,[33] underscoring the disproportionate neurocognitive vulnerability that HIV confers independently of aging. In the United States, the prevalence of HIV-associated dementia has declined from 15–20% in the pre-ART era to approximately 1–2% in the ART era,[34,35] yet our finding of 22.1% suggests that effective ART suppression alone is insufficient to fully abrogate the risk of PHD, particularly in resource-limited settings where late ART initiation, immunological non-recovery, and ongoing neuroinflammation may persist despite virological suppression. These findings carry important clinical implications: approximately one in five PLWH attending HIV clinics in Central Uganda may be living with undiagnosed PHD, highlighting the urgent need for routine neurocognitive screening integrated into standard HIV care.

The observed prevalence of 22.1% is lower than the 64.4% reported by Nakku et al. among HIV clinic attendees in Uganda[11] and the 68.6% reported by Nakasujja et al. in an ART-naïve Ugandan cohort.[36] These higher estimates likely reflect differences in population characteristics particularly, both prior Ugandan studies enrolled participants with more advanced disease and lower ART coverage. Similarly, our prevalence falls below the 0–80% range reported across Sub-Saharan Africa[37-39] and the broader HAND prevalence of 19–64% documented in a meta-analysis of SSA studies.[40] Globally, a meta-analysis estimated HIV-associated dementia prevalence at 5.0% (95% CI: 3.5–6.8) using the Frascati criteria,[40] which is considerably lower than our estimate; this discrepancy is attributable to the gold-standard Frascati criteria capturing only the most severe, confirmed cases, whereas PHD screening tools used in resource-limited settings capture a broader spectrum of neurocognitive impairment. In East Africa, a Tanzanian study reported a 3.6% prevalence of HAD but a total HAND prevalence of 47%,[41] consistent with the spectrum nature of HAND and reinforcing that the severity captured depends heavily on the diagnostic tool employed. Collectively, our prevalence estimate is contextually consistent with the literature once methodological and population differences are accounted for.

Our study demonstrated a statistically significant and clinically meaningful dose-response relationship between the serum AST-to-ALT ratio and PHD among PLWH on DTG-based ART. The prevalence of PHD increased progressively across tertiles of the AST-to-ALT ratio, from 13% in the lowest tertile to 23% in the second tertile and 31% in the highest tertile (p=0.023), indicating a graded association that strongly supports a biological gradient consistent with a causal relationship. Corroborating this trend, the median AST-to-ALT ratio was significantly higher among participants with PHD

than those without (1.42 vs. 1.25, p=0.007), confirming that participants with PHD exhibit a distinctly elevated hepatic enzyme profile. Crucially, these associations persisted after adjusting for potential confounders, with participants in the second tertile having 2.85-fold and those in the highest tertile having over 4.28-fold higher odds of PHD compared to the lowest tertile. The relatively wide confidence intervals observed for AST-to-ALT ratio tertiles likely reflect limited outcome events relative to the number of estimated parameters in the final potentially resulting in reduced precision and potentially unstable estimates. Additionally, a 0.5 unit increase in AST-to-ALT ratio was associated with 1.40 times increase in the odds of PHD. This dose-dependent gradient in adjusted odds ratios reinforces the independent and robust nature of this association. Regarding its diagnostic utility, at the optimal cut-off of 1.26, the AST-to-ALT ratio demonstrated a statistically significant but poor discriminatory ability for probable HIV dementia (AUC = 0.622), consistent with our predefined AUC interpretation criteria.[32] Although the relatively high sensitivity (73%) and negative predictive value (86%) suggest that the ratio may be useful for identifying individuals unlikely to have PHD, its low specificity (51%) and positive predictive value (29%) indicate a substantial false-positive rate, limiting its utility as a stand-alone screening or diagnostic test. Therefore, these findings present the AST-to-ALT ratio as a potential adjunctive risk stratification biomarker that may help identify individuals warranting further neurocognitive assessment, rather than a definitive diagnostic marker. Prospective validation studies are warranted.

The biological plausibility underlying the observed association resides within the liver-brain axis. AST and ALT play central roles in glutamate production, the primary excitatory neurotransmitter of the central nervous system with critical roles in memory and brain function; a disproportionate elevation of AST relative to ALT, as indexed by a high De Ritis ratio, reflects mitochondrial hepatocellular injury since approximately 80% of AST resides in hepatocyte mitochondria.[18] Reduced ALT activity leads to decreased pyruvate production, impairing liver-related gluconeogenesis, which significantly impacts peripheral and cerebral energy metabolism, and both enzymes have been linked to glutamate synthesis, whose reduction impairs synaptic transmission in hippocampal and cortical areas.[17] Additionally, in PLWH on DTG-based regimens, metabolic syndrome and non-alcoholic fatty liver disease are prevalent, contributing to hepatic inflammation, oxidative stress, and neuroinflammatory signaling via the liver-brain axis, thereby directly amplifying neurocognitive vulnerability.

Our findings are consistent with and corroborated by a growing body of literature. Li et al. using three independent clinical cohorts including two longitudinal follow-up studies, found that an elevated AST/ALT ratio was a significant risk factor for future cognitive impairment in community-dwelling older adults, with the ratio negatively correlated with right hippocampal volume (r = -0.148, p=0.043), proposing hippocampal atrophy as a potential mechanism.[18] Similarly, a 2024 systematic review and meta-analysis of 13 studies demonstrated that a higher AST:ALT ratio was significantly associated with an increased risk of cognitive impairment, even when individual AST and ALT levels showed no independent significant association,[17] a finding that underscores the unique informational value of the ratio over individual enzyme levels consistent with our results. Among community-dwelling older adults investigated for cognitive decline, patients with dementia demonstrated significantly higher AST/ALT ratios compared to controls (p=0.003),[20] directly paralleling our finding of a significantly elevated ratio in PHD participants. In the HIV-specific context, a closely related Ugandan study by Bagenda et al. (2025) found that an elevated AST/HDL-C ratio was significantly associated with probable dementia among PLWH on DTG-based ART in Southwestern Uganda, with participants in the highest tertile having 4.48-fold higher odds compared to the lowest tertile,[21] a finding directionally consistent with ours, though differing in the specific ratio examined. A Chinese cohort study further confirmed that the AST-to-ALT ratio was significantly higher in the cognitive impairment group than in the normal cognitive function group, and the ratio was positively associated with an Alzheimer's disease diagnosis, corroborating the cross-population generalizability of this hepatic biomarker.[42] Regarding diagnostic performance, our AUC of 0.622 indicates a modest but statistically significant discriminatory ability. This is comparable to AUC values reported for other liver-based biomarker ratios in dementia screening contexts, which typically range between 0.60 and 0.70 in population-based studies, reflecting the inherent limitations of single-biomarker models in complex neurocognitive conditions.[17] Collectively, these findings support the AST-to-ALT ratio as a clinically accessible, inexpensive, and routinely available screening biomarker for PHD in PLWH on ART in resource-constrained settings.

Conclusion

Our findings indicate that an elevated AST-to-ALT ratio is significantly associated with probable HIV dementia among people living with HIV on DTG-based ART in Central Uganda. These findings provide preliminary evidence supporting the AST-to-ALT ratio as a potential biomarker for identifying individuals who may be at increased risk of HIV-associated neurocognitive impairment. However, prospective longitudinal studies incorporating comprehensive immunological markers, including CD4 cell count and longitudinal viral load measurements, are needed to validate these findings and establish the clinical utility of the AST-to-ALT ratio for risk stratification and early identification of HIV-associated neurocognitive impairment.

Limitations and Recommendations

The International HIV Dementia Scale used to measure PHD in this study is a screening tool for HIV dementia not a diagnostic assessment tool. For this reason, in this study we report on 'probable HIV dementia' (PHD) and not on a diagnosis of 'HIV dementia'. However this tool has previously been validated to screen for HIV dementia in the Ugandan situation with good psychometric properties observed during the validation study.[23] Furthermore, although we adjusted for several important demographic, clinical, and virological factors, CD4 cell count was not collected in the primary study and therefore not available in the dataset. Consequently, we were unable to adjust for this important HIV-specific factor, and residual confounding cannot be excluded. In addition, the cross-sectional design precludes establishing temporal or causal relationships between an elevated AST-to-ALT ratio and probable HIV dementia. The limited variability in ART and DTG treatment duration, with most participants having prolonged exposure (90.6%), reduced the statistical power to detect potential associations with probable HIV dementia. Consequently, the observed non-significant findings for these variables should be interpreted with caution and not as evidence of the absence of an association.

Future prospective longitudinal studies incorporating comprehensive immunological markers, including CD4 cell count and longitudinal viral load measurements, together with standardized diagnostic assessments for HIV-associated neurocognitive disorders, are warranted to validate these findings and determine the clinical utility of the AST-to-ALT ratio as a biomarker for risk stratification and early identification of HIV-associated neurocognitive impairment.

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Ethical Considerations

Ethical approval for the primary study was granted by Mbarara University of Science and Technology Faculty Research Committee (FRC) under approval number MUST/MLS/25-08U. Prior to performing the study, administrative clearance was also acquired from the Office of the Directorate Clinical Services St. Francis Hospital Nsambya.

Consent to Participate

Prior to participation in this study, each participant provided written informed consent. Participants were also explicitly asked for consent to allow their data to be used for secondary analysis, which they approved. The 1975 Declaration of Helsinki's ethical criteria (1964) were followed in this study protocol. Each study participant was assigned a code that could not be linked to them in order to maintain participant confidentiality. Additionally, participants were made aware that their involvement in the study was completely voluntary and free, and they could leave at any moment. Permission to conduct the secondary analysis was obtained from the principal investigator of the primary study.

Author Contributions

CNB, and CN participated in the conceptualization of the study. CNB and MJM performed data analysis and results interpretation. CNB, CN, MJM, VO, FN, CM, BB, GS, FS, JT, DT participated in methodology and writing of the first draft of the manuscript and with JT, FS, DT providing critical revisions. All authors read and approved the final manuscript.

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Declaration of Conflicting Interests

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Data Availability Statement

The datasets used in this study are available from the corresponding author upon reasonable request.

Supplemental Material

Supplemental material for this article is available online.

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