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Sero-prevalence of cryptococcal antigen and its immune-virological correlates in HIV-1 positive individuals: a prospective cross-sectional study

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Abstract

Background Cryptococcal infection remains a leading cause of mortality among HIV-1-positive individuals, particularly in regions with limited access to antiretroviral therapy and diagnostics. This study aimed to assess Cryptococcal Antigen (CrAg) seroprevalence and its immune-virological correlates among ART-naïve and ART-experienced HIV-1 positive individuals.

Methods This prospective cross-sectional study was conducted from May 2023 to August 2024 at Edo State University Teaching Hospital, Nigeria. Blood samples were analyzed for CD4 + T-cell counts using a Partec™ CyFlow analyzer, HIV-1 viral load using the COBAS® AmpliPrep/COBAS® TaqMan® Test, and CrAg detection with the Immy Latex-Crypto Antigen Lateral Flow Assay.

Results Among 229 HIV-1 positive individuals, 72.5% were aged 15–20 years, and 69% were female. Most (68.6%) were ART-experienced, while 31.4% were ART-naïve. Severe immunosuppression (CD4 + < 200 cells/mm^3) was present in 64.6%, and 71.2% had viral loads > 1,000 copies/mL. Cryptococcal infection (CI) prevalence was 10.04%. No significant link was found between CI and age or gender, but ART-naïve status, low CD4 + counts, and high viral loads were significantly associated with CI. ART-naïve individuals had higher viral loads (median 4.95 vs. 4.19 log10 copies/mL, $p = 0.00$). A stronger inverse correlation between CD4 + counts and viral load was observed in ART-experienced patients ($r = -0.535$).

Conclusions These findings emphasize the necessity for routine Cryptococcal screening, particularly in ART-naïve and severely immunocompromised individuals, to facilitate timely interventions and improve clinical outcomes.

Keywords Cryptococcal antigen, HIV-1, Sero-Prevalence, ART, CD4 + T-cell counts, Viral load, Immune-Virological correlates

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Background

HIV-1 infection remains a critical public health challenge globally, particularly in regions with high endemicity where opportunistic infections significantly contribute to morbidity and mortality [1]. Among these infections, cryptococcosis—primarily caused by Cryptococcus neoformans—poses a substantial threat to immunocompromised individuals, especially those with advanced HIV disease characterized by low CD4 + T-cell counts < 100 [2]. Cryptococcal infection is most prevalent in ART-naïve individuals with severe immune suppression, where uncontrolled viremia and CD4 + T-cell depletion impairs antifungal immunity, increasing susceptibility to opportunistic infections.

In Sub-Saharan Africa, where HIV prevalence is highest, studies indicate that the seroprevalence of cryptococcal antigenemia (CrAg) among HIV-infected individuals ranges from 5 to 15%, with some areas reporting rates as high as 20% in severely immunocompromised patients [3, 4]. In Nigeria, the situation is particularly concerning, with recent studies revealing CrAg prevalence rates between 10% and 15% among HIV-1 positive individuals [3, 5]. Cryptococcal antigenemia serves as a reliable biomarker for diagnosing cryptococcal infection, enabling early identification and treatment to prevent severe outcomes, including meningitis and death [6]. However, the sero-prevalence of CrAg among HIV-1 positive individuals, particularly among young populations, remains underexplored, creating a knowledge gap in understanding the epidemiological trends of cryptococcal infection.

Recent studies have highlighted the critical relationship between immune function, as indicated by CD4 + T-cell counts, and virological factors, such as HIV-1 viral load, in determining susceptibility to cryptococcal infection [7–9]. A better understanding of these immune-virological correlates can aid in identifying high-risk populations and tailoring interventions accordingly [1, 10–18]. The present prospective cross-sectional study seeks to address these concerns by investigating the sero-prevalence of CrAg in a cohort of HIV-1 positive individuals aged 15 to 26 years and exploring its associations with immune and virological markers.

Table 1 Prevalence and demographic characteristics of the study participants

Characteristics	CrAgI (%) (*N* = 229) (*n* = 23)	NCrAgI (%) (*n* = 206)	*P* value
Age (Years)			
15–20	16(69.6)	150(72.8)	= 0.81
21–26	7(30.4)	56(27.2)	
Gender (n%)			
Male	6(26.1)	64(31.1)	= 0.81
Female	17(73.9)	142(68.9)	
ART Status (n%)			
Naïve	13(56.5)	59(28.6)	= 0.0
Experienced	10(43.5)	147(71.4)	
CD4 + T-cell counts (/mm3			
< 200	19(82.6)	129(62.6)	= 0.1
> 200	4(17.4)	77(37.4)	
Viral load (copies/ml)			
< 1,000	2(8.7)	64(31.1)	= 0.0
> 1,000	21(91.3)	142(68.9)	

CrAgI: Cryptococcal Antigen Infection, NCrAgI: Non- Cryptococcal Antigen Infection

Methods

Study settings and design

This prospective cross-sectional study was conducted among HIV-1 positive individuals receiving care at Edo State University Teaching Hospital Auchi, Nigeria between March 2023 and June 2024. The study aimed to determine the sero-prevalence of Cryptococcal Antigen (CrAg) among HIV-1 positive individuals and to explore its immune-virological correlates, focusing on the differences between antiretroviral therapy (ART)-naïve and ART-experienced populations.

Study participants

The participants included confirmed HIV-positive individuals (aged 15 years) who were ART-naïve and experienced. Sex workers and pregnant women were excluded. Patients with apparent co-morbidities were also excluded. Eligible participants were enrolled. All participants were on a first-line ART regimen in line with WHO strategy [11].

Ethics statement and informed consent

The study protocol was approved by the research ethics committee of the ESUTH, Auchi, Nigeria (ethics approval number: EDSUREC23/0074). All study procedures were conducted per the Declaration of Helsinki. Written informed consent was obtained from participants before participation; voluntariness and strict confidentiality were maintained throughout the study.

Socio-demographic and clinical data

Relevant socio-demographic characteristics and clinical data (Table 1) were collected through a structured questionnaire and a review of the patient's clinical records, as outlined in prior studies [1, 2].

Sample collection and analysis

In this study, 5 mL of blood was collected from each participant by a trained phlebotomist and properly labelled. The blood samples were then divided into aliquots: one portion was transferred into EDTA tubes for serum extraction, which was used for cryptococcal antigen detection and HIV-1 viral Load, while another

portion was poured into another EDTA tubes to determine CD4 + T-cell counts.

Determination of absolute CD4 T-cell count

The clusters of differentiation (CD) 4 cell count in whole blood was analyzed using the Partec™ Cyflow analyzer (Model SL3, Germany). This state-of-the-art flow cytometry technique operates on the principles of laser-induced fluorescence and light scattering, enabling precise identification and quantification of CD4 + T cells. Specimen preparation and assay were all performed according to the manufacturer's instructions, as outlined in the method described by Balogun et al. [11].

Detection of Cryptococcal antigen using lateral flow assay (LFA)

Cryptococcal antigen detection was conducted using the Immy Lateral Flow Assay (LFA) Crypto Antigen kit (Immuno-Mycologics, Inc., Norman, Oklahoma). This immunochromatographic test employs strips coated with gold-conjugated monoclonal antibodies to identify the glucuronoxylomannan antigen of the cryptococcal capsule, covering all four serotypes (A-D) of *C. neoformans*. A patient specimen drop was tested with the CrAg LFA strip, incubated for 10 min, and results were categorized as "positive" (two lines), "negative" (control line only), or "invalid" (test line only), following the manufacturer's protocol.

Quantification of HIV-1 viral load

HIV-1 RNA quantification was determined using the COBAS® Ampliprep/COBAS® Taqman® HIV1 Test, v2.0. (Roche Diagnostics, Indianapolis, USA). The test had a dynamic detection range of 20 to 10,000,000 copies/mL, ensuring that viral loads could be accurately measured even in cases of low or high viremia. Specimen preparation and assay were all performed according to the manufacturer's instructions, as outlined in the method described by Balogun et al. [11].

Definitions

CD4 T-cell decline was categorized based on CD4 T-lymphocyte counts, with values below 200 cells/mm^3 indicating severe immunosuppression and values of 200 cells/mm^3 or higher reflecting a more stable immune status. HIV viral loads were classified as virologically suppressed if the count was less than 1,000 copies/mL, while viral loads exceeding 1,000 copies/mL were categorized as virologically non-suppressed [12].

Statistical analysis

Data obtained were presented in tables as percentages, median (interquartile range, IQR) and mean ± standard deviation. The Shapiro-Wilks test was employed to check the normal distribution of quantitative variables. According to variable distribution, comparison among groups was analysed using t-test (and non-parametric test) or a non-parametric (Mann-Whitney test). Chi Squared tests (χ^2) was used to find an association between all variables. Graphpad prism software (v 6) and SPSS "were used for all data analysis. The significance level was set at $P \leq 0.05$.

Results

Prevalence, demographic and clinical characteristics of the study participants

A total of 229 HIV-1-positive individuals were recruited for the study. The overall prevalence of CrAgI was 10.04% (23/229), and 89.96% (206/229) were non-Cryptococcal antigen infection (NCrAgI). The age of the studied participants ranged from 15 to 26 with a mean age of 20.5 ± 3.2 years. The study found no significant association between age ($p = 0.81$) or gender ($p = 0.81$) and CrAgI. In the CrAgI group, 16 participants were aged 15–20 years and 7 were aged 21–26 years, compared to 150 and 56, respectively, in the Non- Cryptococcal Antigen Infection (NCrAgI). Similarly, 6 males and 17 females had CrAgI, while 64 males and 142 females were in the NCrAgI group, indicating no gender effect on infection prevalence. However, ART status was significantly associated with CrAgI ($p = 0.00$). Among the CrAgI group, 56.5% (13/23) were ART-naïve, compared to 28.6% (59/206) in the NCrAgI group, showing that ART-naïve individuals were more prone to infection ($p = 0.00$). CD4 + T-cell depletion was strongly associated with CrAg positivity, as 82.6% (19/23) of CrAgI participants exhibited severe immunosuppression (CD4 + < 200 cells/mm^3), compared to 62.6% (129/206) in the NCrAgI group. However, this association did not reach statistical significance ($p = 0.1$). Lastly, viral load was a significant factor ($p = 0.00$), with 91.3% (21/23) of those with CrAgI having viral loads > 1,000 copies/ml, compared to 68.9% (142/206) in the NCrAgI group (Table 1).

Comparison of CD4 T-cell count and HIV-1 viral load among Cryptococcal infected study participants

The comparison of CD4 + T-cell counts and HIV-1 viral loads among Cryptococcal- positive individuals based on ART status revealed the following: the median CD4 + T-cell count was 2.11 (IQR: 1.99–2.28) log10 cells/mm^3 for ART-naïve participants and 2.23 (IQR: 2.06–2.30) log10 cells/mm^3 for ART-experienced participants, with no significant difference ($p = 0.32$). However, the HIV-1 viral load was significantly higher in ART-naïve participants, with a median of 4.95 (IQR: 4.46–5.00) log10 copies/ml, compared to 4.19 (IQR: 3.17–4.46) log10 copies/ml in ART-experienced participants ($p = 0.00$). This indicates that ART significantly lowers viral load,

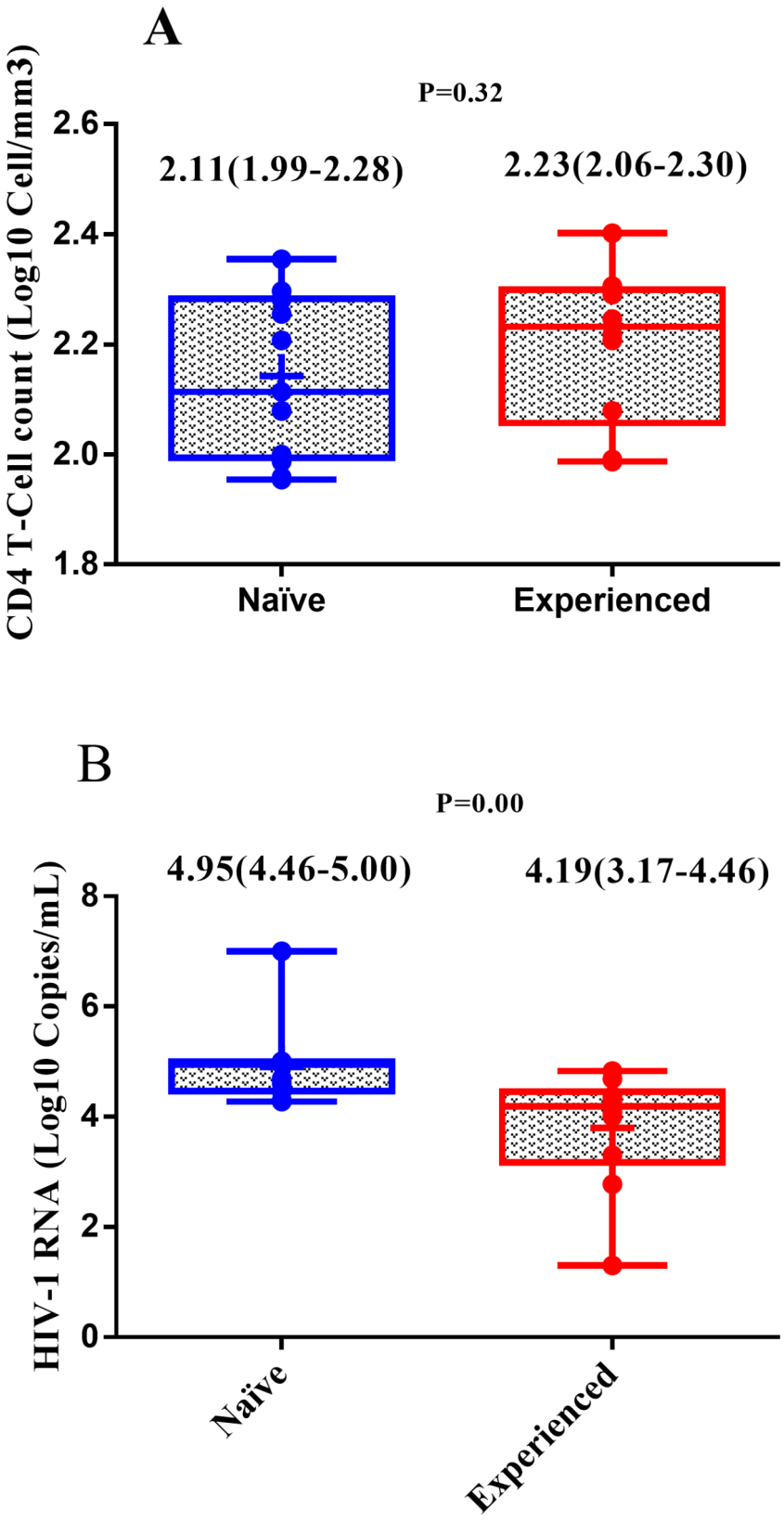

Fig. 1 Comparison of CD4 T-cell count and HIV-1 Viral Load among Cryptococcal positive individuals. Dots represent each participant along the pre-define levels of CD4 T-cell counts and HIV-1 viral Load. **A** represent CD4 T-cell counts levels. **B** represents HIV-1 Viral Load; Mann-whitney test ($P \leq 0.05$)

though CD4 + T-cell counts did not differ meaningfully between the groups (Fig. 1).

Correlation analysis between CD4 + T-cell counts and HIV-1 viral load in ART-naïve and ART-experienced individuals positive for Cryptococcal Antigen.

A correlation analysis was conducted to evaluate the relationship between CD4 + T-cell counts and HIV-1 viral load in ART-naïve and ART-experienced individual positive for Cryptococcal Antigen (crAg). In ART-naïve participants, a weak inverse correlation was found (r = -0.407, $p = 0.14$), while ART-experienced participants showed a stronger inverse correlation (r = -0.535, $p = 0.11$). Although neither was statistically significant, the results suggest a trend where ART-experienced patients exhibit a more pronounced association between lower CD4 + T-cell counts and higher viral loads (Fig. 2).

Discussion

HIV-1 infection remains a major public health concern, particularly in regions with high endemicity, where opportunistic infections such as cryptococcosis present significant risks [13]. This study aims to enhance the growing body of research on cryptococcal infection by examining its prevalence and immune-virological correlates in HIV-1-positive individuals from Edo-North, Nigeria—a region where high HIV prevalence and delayed ART initiation contribute to an increased risk of opportunistic infections [3].

This study reveals a 10.04% prevalence of cryptococcal infection among HIV-1-positive individuals in Edo-North, Nigeria, indicating a substantial burden of cryptococcal disease among individuals positive for HIV-1. This rate aligns with similar findings across rural Nigeria and sub-Saharan Africa, where limited healthcare access and delayed ART contribute significantly to the incidence of opportunistic infections. In Nigeria, reported cryptococcosis rates range from 3% to over 15%, varying with ART availability, healthcare access, and environmental exposure to Cryptococcus species [1–3, 5, 19–27]. This heterogeneity highlights the need for region-specific strategies, particularly for young adults and adolescents disproportionately impacted by HIV/AIDS, to enhance early HIV diagnosis and timely ART initiation. Globally, cryptococcosis prevalence shows marked variability, influenced by healthcare infrastructure and ART access. For instance, rates in countries like Uganda, South Africa, and Thailand range from 6 to 20% in advanced HIV/AIDS cases, contrasting with less than 5% in North America and Europe, where ART and cryptococcal screening are more accessible [1–4, 19]. This global disparity highlights the critical role of early ART, comprehensive HIV care, and routine screening in reducing cryptococcal infection rates among HIV-positive populations, especially in high HIV-endemic regions like sub-Saharan Africa, Southeast Asia, and Latin America [1, 19, 28].

This study provides significant findings on the prevalence of Cryptococcal antigen infection (CrAgI) among participants, categorized by demographic and clinical characteristics. As detailed in Table 1, the study did not find significant associations between age ($p = 0.81$) or gender ($p = 0.81$) and the prevalence of CrAgI. Within the CrAgI group, 16 participants were aged 15–20 years, while 7 were aged 21–26 years. In contrast, the Non Cryptococcal antigen infection (NCrAgI) group comprised 150 individuals aged 15–20 years and 56 aged 21–26 years. Similarly, the gender distribution indicated no significant differences, with 6 males and 17 females in the CrAgI group compared to 64 males and 142 females in the NCrAgI group. This lack of association aligns with findings from previous studies that also reported no significant demographic risk factors influencing CrAgI prevalence, suggesting that CrAgI may affect individuals across various ages and genders without predisposition [29, 30].

In contrast to demographic factors, the analysis revealed significant associations between clinical characteristics and CrAgI, particularly regarding antiretroviral therapy (ART) status, CD4 + T-cell counts, and viral load. ART status was found to be significantly associated with CrAgI ($p = 0.00$). Among the CrAgI group, 56.5% (13/23) were ART-naïve, compared to 28.6% (59/206) in the NCrAgI group. This finding highlights the increased vulnerability of ART-naïve individuals to cryptococcal infection, consistent with existing literature that emphasizes the protective role of ART in reducing opportunistic infections [31, 32]. The initiation of ART not only lowers viral load but also enhances immune function, thereby reducing the risk of infections such as cryptococcosis. CD4 + T-cell counts also demonstrated a strong association with CrAgI, with 82.6% (19/23) of CrAgI participants exhibiting CD4 counts < 200/mm^3, compared to 62.6% (129/206) in the NCrAgI group. This finding reaffirms the critical role of immune suppression in the pathogenesis of cryptococcal infections. Low CD4 + T-cell counts are a well-documented risk factor for opportunistic infections, including cryptococcosis, as they reflect the compromised immune status of HIV-infected individuals [33, 34]. Viral load was another significant factor associated with CrAgI ($p = 0.00$). Notably, 91.3% (21/23) of those with CI had viral loads > 1,000 copies/ml, in comparison to 68.9% (142/206) in the NCrAgI group. This finding suggests that higher viral loads are indicative of increased risk for cryptococcal infection, aligning with studies that have established a correlation between viral load levels and the likelihood of opportunistic infections in HIV-positive individuals [35, 36]. Elevated viral loads can lead to more rapid disease progression and further immune

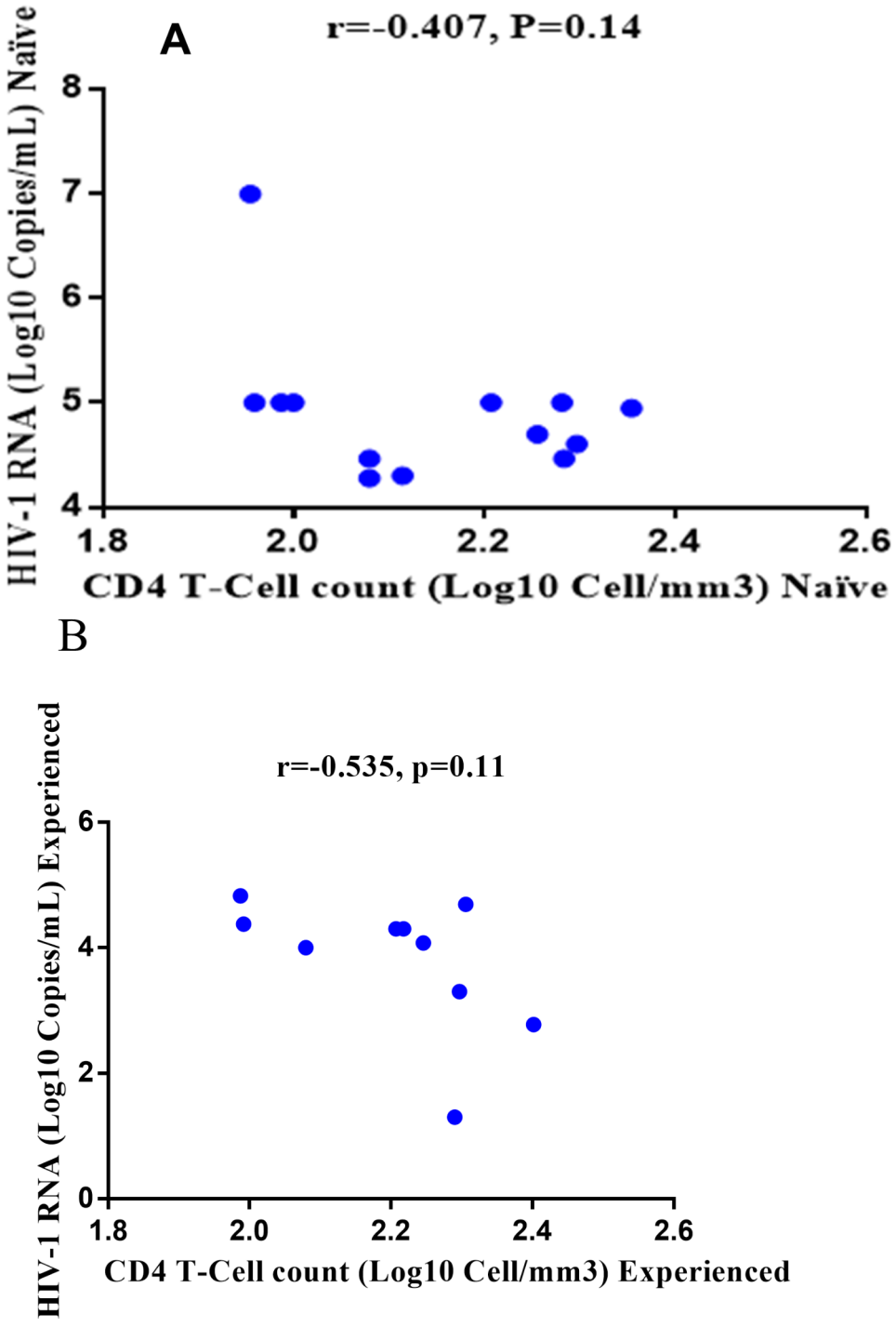

Fig. 2 Correlation analysis between CD4 T-cell counts-HIV-1 viral load of ART Naïve and CD4 T-cell counts- HIV-1 viral load of ART Experienced individual positive with CrAg. **A** represents the CD4 T-cell counts-HIV-1 viral load of ART Naïve and **B** represents the CD4 T-cell counts-HIV-1 viral load of ART Experienced individual positive with crAg. ($P \leq 0.05$)

deterioration, creating an environment conducive to the development of infections like Cryptococcosis [36].

The relationship between CD4 + T-cell counts and HIV-1 viral load is essential for assessing the immune status of individuals positive with HIV-1 and Cryptococcus. In this study, the median CD4 + T-cell count among ART-naïve participants was found to be 2.11 (IQR: 1.99–2.28) log10 cells/mm^3. In contrast, ART-experienced individuals exhibited a median CD4 + T-cell count of 2.23 (IQR: 2.06–2.30) log10 cells/mm^3. Notably, the difference in CD4 + T-cell counts between the two groups was not statistically significant ($p = 0.32$).

This finding suggests that while ART may help in maintaining immune function, it does not dramatically alter CD4 + T-cell counts in the short term among Cryptococcal-positive individuals. Previous studies have indicated that ART is more effective at improving immune reconstitution over an extended period, often requiring several months to show meaningful increases in CD4 + T-cell counts [37, 38]. Additionally, the lack of significant change in CD4 + T-cell counts could suggest that clinicians should not rely solely on CD4 counts as a marker of immune reconstitution in the early stages of ART among Cryptococcal-positive individual [39]. In stark contrast to the CD4 + T-cell count findings, the HIV-1 viral load was significantly higher in ART-naïve participants, with a median of 4.95 (IQR: 4.46–5.00) log10 copies/ml. ART-experienced participants had a lower median viral load of 4.19 (IQR: 3.17–4.46) log10 copies/ml, with this difference being statistically significant ($p = 0.00$). These results highlight the effectiveness of ART in achieving viral suppression among individuals with concurrent Cryptococcal infections. The observed reduction in viral load among those on ART aligns with established knowledge that effective ART can reduce HIV-1 replication to undetectable levels, thereby improving patient outcomes [40, 41].

The correlation between CD4 + T-cell counts and HIV-1 viral load is a crucial aspect related to opportunistic infections such as Cryptococcosis. The inverse correlations identified in both groups provide insights into the immune dynamics of people living with HIV-1 and coexisting cryptococcal infections. In ART-naïve patients, the weak correlation could reflect the initial immune compromise typical of untreated HIV infections, where CD4 + T-cell counts are low and HIV-1 viral loads are high. These findings align with previous research demonstrating that low CD4 + T-cell counts correlate with increased susceptibility to opportunistic infections, including cryptococcosis [42, 43].

In contrast, the stronger inverse correlation found in ART-experienced patients may indicate a more complex relationship. While ART is designed to suppress viral load and improve immune function, the presence of cryptococcal antigen suggests that these patients may still experience immune dysregulation [2]. Prior studies have shown that even in patients on ART, suboptimal immune reconstitution can occur, particularly in those with persistent cryptococcal infections [44]. This persistent immune challenge may lead to continued low CD4 + T-cell counts despite effective viral suppression, which is supported by the findings of our analysis. The trends observed also indicate that monitoring CD4 + T-cell counts in both ART-naïve and ART-experienced patients may be essential for assessing the risk of cryptococcal infections and guiding treatment decisions [3].

Limitations of the study

This study has some limitations. First, its cross-sectional design prevents causal inferences regarding Cryptococcal infection and immune-virological correlates. Second, the study was conducted at a single centre, which may limit the generalizability of the findings. Third, the exclusion of certain high-risk populations, such as pregnant women and sex workers, may have influenced prevalence estimates. Lastly, reliance on self-reported ART adherence may introduce reporting bias. Future multi-center, longitudinal studies are recommended to validate these findings.

Conclusion

This study identified a 10.04% prevalence of cryptococcal infection among HIV-1-positive individuals in Edo-North, with a higher risk observed among ART-naïve individuals, those with low CD4 + T-cell counts, and high viral loads. These findings underscore the potential benefits of routine Cryptococcal screening in high-risk groups to enable timely interventions. However, the cross-sectional design limits causal inferences, and the single-center setting may restrict generalizability. Additionally, excluding certain vulnerable populations and relying on self-reported ART adherence may have introduced bias. Further multi-center, longitudinal studies are recommended to validate these findings and inform broader public health strategies.

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Author contributions

BIS: conception, design of the work, acquisition, analysis, interpretation of data, drafted the work and revised it. AM: design of the work, acquisition, interpretation of data, drafted the work, substantively revised it. FM: acquisition, interpretation of data, drafted the work, revised it. BHA: acquisition, interpretation of data, drafted the work, revised it.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the hospital research ethics committee of Edo State University, Uzarue, Nigeria (ethical approval number: EDSUREC23/0074). Informed consent was obtained from all the participants in accordance with Helsinki Declaration of 1975, as revised in 2000; voluntariness and strict confidentiality were maintained throughout the study.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial
Not applicable.

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