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ABSTRACT

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Keywords: advanced HIV disease (AHD), cryptococcal antigen (CrAg), people living with HIV (PLHIV), human immunodeficiency virus (HIV).

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This study explored the existing relationships between Advanced HIV Disease (AHD), Tuberculosis (TB), and Cryptococcal Antigen (CrAg) among People Living with HIV (PLHIV) in Nasarawa State, Nigeria. This was achieved by investigating the relationship and prevalence of TB and CrAg among individuals diagnosed with AHD in Nasarawa State; and by assessing the distribution and association of demographic characteristics of the study population with TB and Cryptococcal Antigen. This study employed a cross-sectional survey design, sampling respon-dents across different demographics at the same time. The study sample were individuals who are currently receiving antiretroviral treatment from six healthcare facilities in Nasarawa State, Nigeria. Results showed that TB and CrAg has low prevalence among the study population, however, compared to a larger population, this will be a serious concern. The study also suggests that the demographic information of the study population had no significant relationship on the development or presence of TB or CrAg, however, the study was able to establish that PLHIVs who had AHD were mostly women (59.8%) in the State. Recommendations were made based on the study findings and the study concluded that the existing relationships among the study variables were not impacted significantly by either age or gender of the population.

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I. INTRODUCTION

The challenge of HIV disease continues to pose a global threat despite measures and interventions to contain the spread of the infection. Primarily, the HIV virus once contracted can be managed to mitigate potential effects on the immune system of the carrier (Meloni et al., 2020; Oku et al., 2014). This is achievable when the individual carrier (herein referred to as 'patient' or 'study population' in this report) adheres strictly to the drug regimen. For the efforts made in the HIV interventions programs from Organisations such as USAID, WHO, PEPFAR, etc, to be effective to both manage and prevent transmission of the disease, adherence to medications and the use of contraceptives have been encouraged globally, with adequate awareness creation (Abou Ghayda et al., 2020; Drain et al., 2020; Meloni et al., 2020; Oku et al., 2014; Yombi & Mertes, 2018).

However, some persons who either do not adhere to their medication, or did not ascertain their HIV status until their immune system becomes incapable of handling the commobids of the viral disease, may become liable to the advanced stage of the disease, otherwise known as Advanced HIV Disease (AHD).

Common diseases that often occur in AHD patients are Tuberculosis and Cryptococcal meningitis (Dabla et al., 2015; Oladele et al., 2023). Tuberculosis (TB) is an infectious disease which is solely caused by the presence of bacterium 'Mycobacterium tuberculosis' (Boulware et al., 2021; Oladele et al., 2023). TB is transmitted through airborne particles, called droplet nuclei, and primarily affects the lungs but can also impact other body parts (De Cock et al., 1992; Lawn et al., 2011). It is recognised as one of

the leading infectious killer diseases worldwide (Boulware et al., 2021; Dabla et al., 2015; Oladele et al., 2023; WHO, 2023; 2002). The relationship between TB and AHD is that AHD is a level of HIV presence in the human system where the immune system has been highly compromised (CD4 < 200 cells/uL) An individual with a highly compromised immune system stands a higher risk of contracting TB infection (Balachandra et al., 2020; Dabla et al., 2015; De Cock et al., 1992).

Cryptococcal Meningitis is another disease that AHD carriers stand a high chance of being infected with (Balogun et al., 2016). Cryptococcal Antigen, specifically the cryptococcal polysaccharide antigen (CrAg), is a core component associated with the fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii (Balogun et al., 2016; De Cock et al., 1992). The detection of Cryptococcal Antigen serves as a diagnostic measure employed to identify the presence of this antigen within the body, primarily in the blood or cerebrospinal fluid (CSF), thereby facilitating the diagnosis of cryptococcal infections (Binnicker et al., 2012; Ezenabike et al., 2020).

These infections predominantly affect the lungs and central nervous system, posing significant risks to individuals with compromised immune systems, notably those infected by Advanced HIV Disease (AHD) (Balogun et al., 2016). It is however important to note that timely identification of the Cryptococcal Antigen plays a pivotal role in its early detection and management, which ultimately enables the prompt initiation of appropriate treatment strategies to mitigate the associated morbidity and mortality (Binnicker et al., 2012; Ezenabike et al., 2020). As an infection that thrives on a compromised immune system, individuals with AHD are at higher risk of this fungal infection (WHO 2002; De Cock et al., 1992).

The co-occurrence of Advanced HIV Disease (AHD), Tuberculosis (TB), and Cryptococcal Antigen presents a profound and multifaceted health challenge. This is because AHD is a stage of HIV infection where the individual's immune system has been compromised, hence the increased tendencies for other health complications and opportunistic infections (Oladele et al., 2023). Therefore, understanding the intricate interplay and potential relationships between these conditions is imperative for developing comprehensive strategies to mitigate their devastating consequences.

While extensive research has been conducted over the years on each of these conditions individually, the effect of co-infection of TB and CrAg with AHD and the risk it poses to the AHD patient requires further studies. The combination of AHD, TB, and Cryptococcal Antigen creates a complex medical scenario where each condition exacerbates the deleterious effects of the other, thus, creating a synergistic decline in health status and outcomes for affected patients. Although, there has not been a global prevalence report of AHD, as at the last report of WHO (WHO, 2023), however, the concerns about the deleterious opportunistic infections such as TB remains a significant challenge, especially with people living with HIV (WHO, 2023).

The presence of TB and Cryptococcal Antigen infections in PLHIV's intensifies the burden of disease, leading to accelerated disease progression, increased mortality rates, and diminished treatment response (WHO, 2023). The weakened immune system associated with AHD not only heightens susceptibility to TB infection but also hampers the body's ability to control the spread of TB bacteria, resulting in more severe manifestations and heightened transmission risks, as well as high risk of death (WHO, 2023).

This study aims to address the gap in knowledge by examining the interplay of AHD and the other two opportunistic infectious diseases, as well as identifying potential factors that may contribute to their simultaneous occurrence, and the study also examined whether there is any significant relationship between age/sex and TB or CrAg among people who had AHD. By unravelling the intricate connections between these conditions, this research endeavours to provide important insights that can inform the development of tailored interventions, improve diagnostic accuracy, enhance treatment approaches, and

enhance the overall prognosis and quality of life for PLHIV, as well as individuals living with the challenging triad of AHD, TB, and Cryptococcal Antigen.

II. OBJECTIVES

This study aims to examine the interplay between AHD, TB, and Cryptococcal Antigen (CrAg). To achieve this broad objective, the following specific goals were set:

1. Investigate the relationship and prevalence of TB and CrAg among individuals diagnosed with AHD in Nasarawa State;
2. Assess the distribution and association of demographic characteristics of the study population with TB and Cryptococcal Antigen.

III. METHODS

3.1 Study Design

This study was a cross-sectional study, collecting specified data across age groups for the purpose of investigating the study variables within the age groups. The study population are the patients newly diagnosed (over the last 12 months)with HIV who have AHD in six health facilities in Nasarawa State. The primary data collected were subjected to rigorous statistical analysis as highlighted in subsequent sections.

3.2 Data Source and Collection

This study utilised data extracted from the Retention and Audit Determination Tool (RADET), the electronic medical records system managed by our organisation, which contain all the medical information of all the PLHIV who are currently receiving Antiretroviral treatment from our facilities. The study population are the patients newly diagnosed (over the last 12 months) with HIV who have AHD in six health facilities in Nasarawa State. The data extraction process was conducted by our Documentation associates who also serve as research assistants, ensuring compliance with data privacy and security regulations. All data were de-identified, with identifiers withheld to maintain patient confidentiality.

IV. DATA ANALYSIS

The first objective which focused on the relationship and the prevalence rates of TB and CrAg among individuals diagnosed with AHD in Nasarawa State was analysed using both descriptive and inferential statistics. Prevalence rates were presented using frequencies and simple percentages, while the association among the variables were examined using Chi-square. The second objective was aimed at assessing the distribution of demographic characteristics among the study population and examining their association with the presence of TB and Cryptococcal Antigen. The demographic information was analysed using descriptive statistics such as frequencies and simple percentages, while the association between variables were examined using Chi-square.

V. LIMITATIONS

It is important to acknowledge the limitations of this study, including the retrospective nature of the data and the findings may be specific to the population of individuals with AHD captured in the RADET system, particularly for Nasarawa State, and the generalisation based on the current data may not be applicable to other States within the country where there are cultural or social normative peculiarities. Lastly, confounding factors not accounted for in the analysis could influence the observed associations.

VI. RESULTS AND DISCUSSIONS

Objective 1

The first objective was to investigate the relationship between as well as prevalence rates of TB and Cryptococcal Antigen among individuals diagnosed with AHD in Nasarawa State. We therefore examined the association using the chi-square test, and also calculated the prevalence rates of TB and Cryptococcal Antigen within the population using descriptive statistics, such as percentages and frequencies. Results are presented in Table 1 and 2.

Table 1: Descriptive Statistics, Showing the Prevalence of Tuberculosis (TB) and Cryptococcal Antigen (CrAg) Among AHD Patients in Nasarawa State

Age Category	Sex	TB n (%)	CrAg (%)	Total Sample (n)
Adult (20 and above)	Female	6 (3.3)	2 (1.1)	122
	Male	0 (0)	0 (0)	61
Adolescent	Female	1 (7.7)	0 (0)	11
	Male	0 (0)	0 (0)	2
Children	Female	0 (0)	0 (0)	3
	Male	0 (0)	0 (0)	4
Total	Female	7 (3.4)	2 (1)	136
	Male	0 (0)	0 (0)	67

The results in Table1 indicate that the prevalence rate of TB and CrAg is significantly low among the AHD population (TB = 3.4%, CrAg = 1%).

However, when added up on a much larger sample (e.g., 10,000), the prevalence rate of 3.4% for TB and 1% for CrAg is a concern as it implies that there are at least 340 and 100 individuals in a population of 10,000 people with AHD who have developed TB and CrAg respectively. Also, the figures indicate that all the individuals who had TB (7) and CrAg (2) were females. To further understand how much these variables associate with each other, a chi-square test was computed, based on the prevalence of AHD and the results are presented in Table 2.

Table 2: Chi-Square Statistics Showing the Relationship Between the Prevalence of TB and Cryptococcal Antigen (CrAg) Among Individuals With AHD in Nasarawa State

	Chi-square	df	p-value
Association	79.27	4	<.001

Note DV is Advanced HIV Disease (AHD)*

The chi-square test revealed a significant association between TB and Cryptococcal Antigen among individuals with AHD in Nasarawa State ($\chi^2 = 79.27$, df = 4, $p < .001$). This finding provides comprehensive insight into the relationship between these variables within the specific population of individuals diagnosed with AHD in the state. The observed chi-square value of 79.27 indicates a substantial departure from the expected frequencies under the assumption of independence. This association indicates that TB and Cryptococcal Antigen are not independent conditions among individuals with AHD in Nasarawa State. These results therefore ensure the reliability and validity of the study's findings.

Furthermore, the obtained p-value of less than .001 demonstrates a high level of statistical significance. It indicates that the association between TB and Cryptococcal Antigen is unlikely to be attributed to random chance alone.

Although there is paucity of empirical data on the existing relationship between AHD and opportunistic infections like TB and CrAg, however, this study was able to document evidence that AHD patients who test positive on TB are likely to test positive on CrAg and vice versa. This is in tandem with the findings of Balogun et al (2023) and Rajasingham et al (2019) who reported similar figures (1.6% and 1.4% respectively) of CrAg among immunocompromised PLHIVs. Even though they (Balogun et al., 2023; Rajasingham et al., 2019) did not particularly focus on TB, their documented reviews suggest that TB is strongly associated with CrAg. Also, the prevalence studies available on HIV especially from the World Health Reports did not report any prevalence of CrAg, despite the

emphasis on HIV and opportunistic factors such as TB.

Although our current findings did not indicate any prevalence report on AHD, it documents the prevalence of TB and CrAg as mild among the AHD population within the study area (see Table 1). But in a previous study, we reported AHD prevalence in six healthcare facilities in Nasarawa State to be high (51%) among newly enrolled HIV patients (Umeozulu et al., 2023). This was also corroborated in Auld et al. (2017) and Balogun et al. (2021). This implies that AHD remains a concern, not only for existing patients but also for the newly enrolled. Furthermore, it has been corroborated in literature that there are chances that HIV gets more severe among people living in Sub-Saharan African nations including Nigeria (Balanchandra et al., 2019; Balogun et al., 2016; Meya et al., 2021). Other studies also support our findings that a compromised immune system leaves PLHIV susceptible to opportunistic infections, including TB and CrAg (Balogun et al., 2016; Meya et al., 2021; World Health Statistics, 2023).

Objective 2

The second objective of this study aimed to assess the distribution of demographic characteristics among the study population (people with AHD) and also examine their association with the presence of TB and Cryptococcal Antigen.

Specifically, we investigated the demographic characteristics of the population, including age and sex. Furthermore, we explored the relationship between these demographic characteristics and the occurrence of TB and Cryptococcal Antigen in individuals with AHD.

The demographic information was analysed using descriptive statistics such as frequencies and simple percentages, while the association between variables were examined using Chi-square. Results are presented in Tables 3 and 4.

Table 3: Descriptive Statistics Showing the Distribution of the Demographic Characteristics of the Population

Age_Group	Sex	Frequency (n)	Percentage (%)
Adult	Female	122	59.8
	Male	61	29.9
Adolescent	Female	11	5.39
	Male	2	0.98
Children	Female	3	1.47
	Male	4	1.96
Population Total		204	99.5

Missing System = 1 (0.5%)

Results in Table 3 indicate that the majority of the AHD population are adult females [122 (59.8%)], which is exactly twice the adult male population (For breakdown of the prevalence, see Table 1).

This implies that AHD is more prevalent among adult females within the study area compared to adult males. Other information on the population presented mild coverage of adolescents, among whom the female gender was still significant, although there were more male children among this population than females. However, to understand whether or not these demographic characteristics are strongly associated with TB and CrAg, a further analysis was computed, as shown in Table 4.

Table 4: Chi-Square Statistics Showing the Association between Demographic Characteristics, TB and CrAg Among Individuals with AHD in Nasarawa State

Relationships	Chi-square	df	p-value
Sex*CrAg	1.82	2	.403
Sex*TB	4.51	2	.105
Age_Group*CrAg	0.76	2	.944
Age_Group*TB	1.85	2	.763

The results in Table 4 shows that the demographic characteristics of an AHD patient has no significant relationship with the presence or development of TB and or CrAg. The association between sex and Cryptococcal Antigen was assessed using Pearson Chi-square test, yielding a non-significant result ($\chi^2 = 1.82$, df = 4, p = .403).

Similarly, the association between sex and TB was not found to be significant ($\chi^2 = 4.51$, df = 4, p = .105). Also, the relationship between age group and Cryptococcal Antigen ($\chi^2 = 0.76$, df = 4, p = .944) as well as the relationship between age group and TB ($\chi^2 = 1.85$, df = 4, p = .763) were examined, and the results showed no significant associations.

These findings indicate that there is no significant association between the demographic characteristics (sex and age group) and the presence of TB or Cryptococcal Antigen among individuals diagnosed with AHD. These results are supported in literature that although a significant proportion of PLHIVs, especially those who are already immunocompromised, are females, gender difference has no significant effect on the presence of TB or CrAg (Akinbami et al., 2012; Laah & Ayiwulu, 2010). Also, studies have ascertained that socio-demographic characteristics of PLHIV does not necessarily determine the presence of TB or CrAg (Akinbami et al., 2012). Therefore, our study has been well supported in literature.

VII. CONCLUSION

The findings of this study reveal important insights regarding the relationships between tuberculosis (TB), Cryptococcal Antigen (CrAg), and demographic characteristics among individuals diagnosed with advanced HIV disease (AHD) in Nasarawa State, Nigeria. Firstly, the prevalence rates of TB and CrAg were found to be significantly low within the AHD population, but when extrapolated to a larger sample size, the number of affected individuals raises concernsThis highlights the importance of addressing these infections in individuals with AHD to prevent adverse health outcomes.

Secondly, a significant association was identified between TB and CrAg, indicating that these conditions are not independent among individuals with AHD in Nasarawa State. This finding emphasises the need for comprehensive management and treatment strategies that consider both TB and CrAg in this population. Finally, the study established that demographic characteristics (that is, age and sex) had no significant associations with the presence or absence of TB and CrAg among individuals with AHD in Nasarawa State. These results align with previous studies suggesting that socio-demographic factors may not be primary determinants of TB or CrAg occurrence in people living with HIV/AIDS. Further exploration is necessary to identify other contributing factors and understand the complex interplay between these variables.

VIII. RECOMMENDATIONS

Based on the findings of this study, we suggest the following:

1. *Strengthen TB and Cryptococcal Antigen Screening:* Given the significant association

between TB and CrAg among individuals with AHD, it is crucial to enhance screening efforts for both conditions. Healthcare providers should be trained to routinely test individuals with AHD for TB and CrAg, particularly in high- prevalence areas. This will help in early detection, prompt treatment initiation, and prevention of complications.

2. *Integrated Treatment Approaches:* Considering the association between TB and CrAg, it is recommended to adopt an integrated approach to the management of individuals with AHD. Collaboration between tuberculosis control programs and HIV/AIDS clinics should be strengthened to ensure coordinated care. This may involve establishing joint clinics, developing shared treatment protocols, and facilitating seamless referral systems.
3. *Expansion of Prevalence Studies:* The prevalence of AHD, TB, and CrAg should be further explored through larger-scale studies. It is recommended to conduct comprehensive prevalence studies involving a diverse population of individuals with AHD, including both newly diagnosed and existing patients. This will provide a more accurate understanding of the burden of these conditions and inform public health interventions.
4. *Awareness and Education Programs:* Public health campaigns should be developed to raise awareness about AHD, TB, and CrAg among healthcare providers, individuals living with HIV/AIDS, and the general population. These campaigns should focus on promoting early detection, reducing stigma, and educating individuals about the importance of adherence to treatment and regular follow-up care.

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