BMC Infectious Diseases

RESEARCH

Open Access

Risk factors for cryptococcal infection among people with HIV receiving care at a referral hospital in Uganda: a nested case–control study

Sarah Namuyanja[1], Saidi Appeli[2] and Jonathan Izudi[3,4*]

Abstract

Background Cryptococcal infection is a major cause of morbidity and mortality among people with HIV (PWH), particularly those with advanced immunosuppression. Cryptococcal infection, detected by a laboratory-confirmed positive serum cryptococcal antigen (CrAg) test (cryptococcal antigenemia), typically precedes cryptococcal meningitis and provides a critical window for prevention. However, recent data on its risk factors in Uganda are limited. We assessed the risk factors for cryptococcal infection among PWH with non-suppressed viral load and severe immunosuppression receiving care at a referral hospital in midwestern Uganda.

Methods We conducted a facility-based nested case-control study among PWH with non-suppressed viral load (viral load ≥ 1,000 copies/mL) and severe immunosuppression (CD4 < 200 cells/μL) at the Fort Portal Regional Referral Hospital in midwestern Uganda. Cases were PWH with a positive serum CrAg test, and controls were those with a negative serum CrAg test in a 1:2 case-to-control ratio, respectively. Socio-demographic and clinical data were retrospectively extracted from routine records. Multivariable binary logistic regression analysis was used to identify factors independently associated with cryptococcal infection. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were reported.

Results We included 89 cases and 178 controls, with comparable mean age between the groups: 40.3 ± 12.4 years vs. 40.4 ± 11.7 years, respectively; $p = 0.952$. In the multivariable analysis, PWH with advanced World Health Organization (WHO) clinical stages III/IV compared to WHO clinical stages I/II (aOR 3.45, 95% CI 1.28–9.97), and those with missed clinic visits within three months before the serum CrAg testing compared to those without any missed clinic visits (aOR 2.39, 95% CI 1.14–5.02) had higher odds of cryptococcal infection.

Conclusion This study showed that among PWH with non-suppressed viral load and severe immunosuppression, cryptococcal infection is strongly associated with markers of advanced HIV disease and gaps in care engagement. Strengthening retention in care, improving clinic appointment tracking, and ensuring timely serum CrAg screening

*Correspondence:
Jonathan Izudi
jonahzd@gmail.com

Full list of author information is available at the end of the article

© The Author(s) 2026. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

among PWH with non-suppressed viral load may reduce cryptococcal disease burden through early diagnosis and treatment.

Clinical trial number Not applicable.

Keywords Cryptococcal antigenemia, Cryptococcal infection, People with HIV, Uganda

Background

Cryptococcal disease is a severe opportunistic fungal infection and a leading cause of AIDS-related mortality globally, accounting for approximately 19% of deaths among people with advanced HIV disease [1]. Each year, over 180,000 cryptococcal-related deaths occur worldwide, with nearly three-quarters concentrated in sub-Saharan Africa [2]. Infection typically begins with inhalation of Cryptococcus spores and may progress to disseminated disease, most commonly cryptococcal meningitis, which carries high mortality even in the era of antiretroviral therapy (ART) [3]. Accordingly, the early identification of cryptococcal antigenemia, an indicator of cryptococcal infection, represents a critical opportunity to prevent severe disease and death among people with HIV (PWH).

The burden of cryptococcal infection is highest among PWH with advanced immunosuppression, particularly those with CD4 cell counts below 100–200 cells/μL, advanced World Health Organization (WHO) clinical stage, and poor engagement in HIV care [4]. In sub-Saharan Africa, the prevalence of cryptococcal antigenemia ranges from 3% to over 10%, with mortality exceeding 40% among untreated individuals [3, 5]. Studies have consistently identified advanced HIV disease, male sex, tuberculosis (TB), ART interruption, and poor adherence as key risk factors for cryptococcal infection [6, 7]. However, most existing evidence has focused on broadly defined advanced HIV disease, with limited attention to PWH who have non-suppressed viral load despite ART and concurrent severe immunosuppression—a growing and programmatically important subgroup. This population may have distinct risk profiles driven by treatment failure, adherence challenges, and prolonged immune compromise.

In Uganda, cryptococcal antigenemia prevalence rates among ART-naïve or immunosuppressed PWH have been reported at approximately 8–9%, and this underscores the continued public health relevance of this opportunistic infection despite widespread ART availability [8]. However, there is limited evidence on the risk factors for cryptococcal infection among PWH with non-suppressed viral load and severe immunosuppression, a growing and programmatically important group.

At the Fort Portal Regional Referral Hospital in mid-western Uganda, published data examining patient-level predictors of cryptococcal infection among PWH with non-suppressed viral load and severe immunosuppression are scarce, despite data suggesting its increasing magnitude among the subpopulation. This gap limits the ability of HIV programs to refine targeted screening and prevention strategies. This study investigated the risk factors for cryptococcal infection among PWH with non-suppressed viral load and severe immunosuppression at the Fort Portal Regional Referral Hospital. We hypothesized that severe immunosuppression (for example, CD4 cell counts below 200 cells/μL or advanced baseline WHO clinical stages III and IV) is associated with a higher likelihood of cryptococcal infection.

Methods and materials

Study design

We designed and conducted a facility-based nested case–control study (Fig. 1). A nested case-control design is an extension of a cohort study, with both cases and controls drawn from the parent cohort, with the latter category as a random sample of individuals without an event of interest. The design is appropriate for rare events and ensures that both cases and controls are from the same source as recommended in the literature [9–11] and utilized in prior studies [12–14].

Study setting

The study was implemented at the at Fort Portal Regional Referral Hospital, a public hospital located in Fort Portal city in Kabarole district, mid-western Uganda. The hospital serves both urban and rural populations from several districts, including Kabarole, Ntoroko, Bundibugyo, Bunyangabu, Kyenjojo, Kyegegwa, Kasese, and Kamwenge. The hospital provides comprehensive HIV services through a dedicated ART clinic that offers psychosocial counseling and support, laboratory monitoring, and ART based on the universal test and treat HIV policy. At the time of the study, the ART clinic had 7,691 PWH enrolled in care (4,828 females vs. 2,863 males). The clinic routinely conducts viral load monitoring and serum cryptococcal antigen (CrAg) testing as part of advanced HIV disease management.

In clinical practice, the national HIV treatment guidelines recommend that eligible individuals for serum CrAg testing include ART-experienced PWH returning to care after ≥ 90 days of treatment (ART) interruption with CD4 < 200 cells/μL; PWH with non-suppressed viral load (viral load ≥ 1,000 copies/mL) and CD4 < 200 cells/

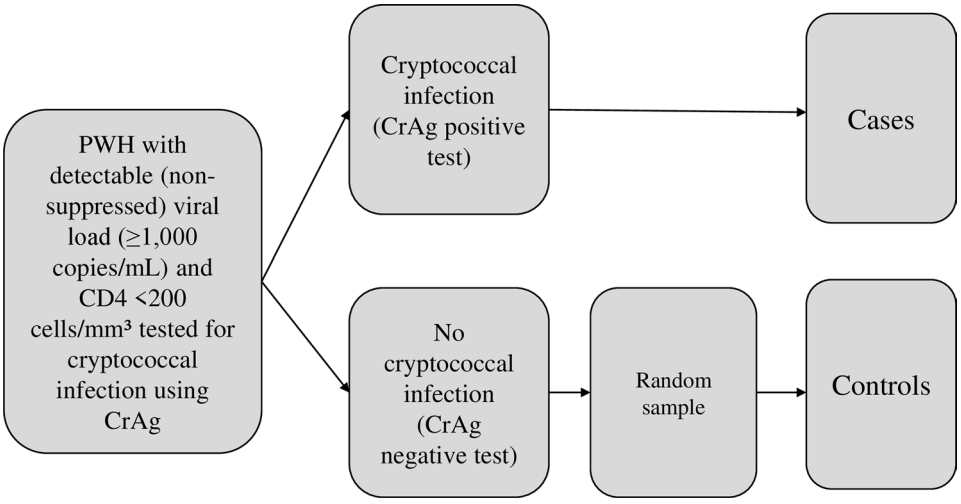


Fig. 1 Nested case-control study design. Conceptual illustration of the nested case–control study design. Cases were individuals with a positive serum cryptococcal antigen (serum CrAg) test, while controls were individuals with a negative serum CrAg test

μL; PWH with WHO stage III or IV clinical events; and PWH with a positive symptom screen on the advanced HIV disease pathway.

Between August 15, 2025, and November 30, 2025, data were retrospectively extracted from the Health Management Information System (HMIS), ART clinic registers, and laboratory databases using a standardized data abstraction checklist that was developed and pre-tested at a nearby ART clinic to ensure clarity and completeness. Extracted variables included socio-demographic characteristics, clinical history, ART-related factors, laboratory measurements, and serum CrAg test results. Data abstraction was conducted without direct participant contact. Extracted data were entered into Epi-Data version 3.1 using an electronic database designed for the study. Data cleaning included consistency checks, correction of entry errors, and verification against source documents.

Study population

The study population comprised PWH on ART aged ≥ 5 years, and the eligible individuals were those with viral load ≥ 1,000 copies/mL and CD4 < 200 cells/μL. We excluded individuals without documented serum CrAg testing and those with missing or undocumented serum CrAg test results. Serum CrAg testing followed the national advanced HIV disease screening recommendations implemented at the study site [15]. The individuals were initiated on ART between January 2018 and December 2023 and had received viral load testing between July 2018 and June 2024, corresponding with ≥ 6 months of ART. The data retrieval period (August 15, 2025, and November 30, 2025) was selected to allow sufficient assessment of trends and accumulation of cases. Participants were identified retrospectively using routinely collected clinical and laboratory records.

Case and control definitions and eligibility criteria

Cases were defined as individuals who had a positive serum CrAg test during the study period and no documented symptoms of cryptococcal meningitis at the time.

Controls were a random sample of individuals with a negative serum CrAg test during the same period. Both the cases and controls were drawn from the same parent cohort of PWH eligible for serum CrAg testing.

Study variables

The primary outcome was cryptococcal infection, measured as a binary variable (yes/no) based on laboratory-confirmed serum CrAg positivity. The independent variables included: (1) Socio-demographic factors: age, sex, residence (urban/rural), body mass index (BMI), mid-upper arm circumference (MUAC), and history of exposure to bird droppings in the past 6 months using clinical records; (2) Clinical factors: duration on ART, baseline WHO clinical stage, baseline CD4 count, most recent viral load preceding serum CrAg testing, TB status, and history of other opportunistic infections such as pneumonia, candidiasis, and toxoplasmosis, among others; and (3) Care-related factors: ART adherence over the preceding 5 months, missed clinic visits within the 3 months before serum CrAg testing. ART adherence, calculated as the number of pills taken divided by the number of pills expected to have been taken, was assessed using routine clinic documentation of self-reported 3-day recall and pill counts. ART adherence was graded as good (≥ 95%), fair (80–94%), or poor (< 80%). TB disease status and opportunistic infections were extracted from clinical records. Cryptococcal infection was assessed

using the serum CrAg test, a rapid diagnostic assay that detects cryptococcal capsular antigen in blood samples. Serum CrAg testing was performed according to national guidelines by experienced and certified laboratory personnel and documented in laboratory registers and HMIS records. Viral load suppression was defined as a viral load < 1,000 copies/mL, while non-suppression was defined as a viral load ≥ 1,000 copies/mL.

Statistical methods

This study used secondary data from all available records between January 2018 and December 2023, which were retrieved. The sample size was determined a priori to ensure adequate statistical power to detect an association between WHO clinical stage and cryptococcal infection in accordance with the study hypothesis. A previous study conducted at a referral hospital in eastern Uganda reported a prevalence of cryptococcal infection of 7.9% among individuals with a CD4 cell count of < 200 cells/μL [16].

Based on prior evidence demonstrating a substantially higher burden of cryptococcal infection among individuals with CD4 counts < 200 cells/μL, and consistent with biological plausibility, we conservatively estimated that individuals with CD4 ≥ 200 cells/μL would have approximately 50% lower prevalence of cryptococcal infection compared with those with CD4 < 200 cells/μL, corresponding to an expected prevalence of 2.9% in the higher CD4 group. This effect size corresponds to an odds ratio of approximately 2.17. With a two-sided level of significance (α) of 0.05, a case-control ratio of 1:2, and a total of 89 cases and 178 controls (overall, $N = 267$), the study achieved 85.2% statistical power to detect the specified association.

Descriptive analysis included summarizing categorical variables using frequencies and percentages, and continuous variables using means and standard deviations if normally distributed or medians and interquartile ranges if skewed. Bivariate analysis included cross-tabulation of the factors with the outcome (cases vs. controls) and the assessment of statistically significant differences with categorical data using the Chi-square test or Fisher's exact test if the cell count was ≥ 5 or < 5, respectively. For continuous variables, mean differences were assessed using the Student's t-test if the data were normally distributed, or else the Wilcoxon rank-sum test was used if skewed. To determine the factors associated with the outcome, a univariable and multivariable binary logistic regression analyses were performed. Variables with a p-value < 0.15 in the univariable analysis and those identified a priori from the literature based on biological plausibility and clinical relevance were included in the multivariable model. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). The statistical significance was set at $p < 0.05$. Multicollinearity was assessed using the variance inflation factor (VIF). Variables with evidence of collinearity (VIF ≥ 5) were not included simultaneously in the multivariable model.

Stratified analysis

To assess whether missed clinic visits modified the association between baseline WHO clinical stage and cryptococcal infection, a stratified analysis was performed. Here, crude stratum-specific odds ratios and a Mantel–Haenszel pooled odds ratio were calculated. Effect modification was evaluated using the test of homogeneity, with $p < 0.05$ indicating statistically significant interaction. All analyses were performed in R version 4.2.1 (2022-06-23 ucrt).

Model diagnostics

Model performance and assumptions were evaluated using standard logistic regression diagnostics. Model specification was assessed with the link test, with a non-significant squared predicted term indicating no misspecification. Discrimination was evaluated using the area under the receiver operating characteristic curve (AUC), where < 0.5 indicates worse than random, 0.5–0.59 very poor, 0.6–0.69 modest, and ≥ 0.7 acceptable performance. Calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test, and overall fit was compared across models using the Akaike and Bayesian Information Criteria (AIC and BIC).

Ethical considerations

Ethical approval was obtained from the Clarke International University Research Ethics Committee (reference number: CLARKE-2024-1191). As this was a retrospective records review, the need for consent to participate was waived by the Clarke International University Research Ethics Committee that approved the study. Administrative clearance was granted by the Fort Portal Regional Referral Hospital. All data were anonymized before the analysis. The study adhered to the ethical principles outlined in the Declaration of Helsinki, namely autonomy, beneficence, nonmaleficence, and justice.

Results

Study profile

A total of 667 clinical records were reviewed, and 89 individuals with a positive serum CrAg test were identified as cases. Of the 578 individuals with a negative serum CrAg test, 178 were randomly selected as controls, yielding a total of 267 participants (89 cases, 178 controls) for the nested case-control analysis (Fig. 2).

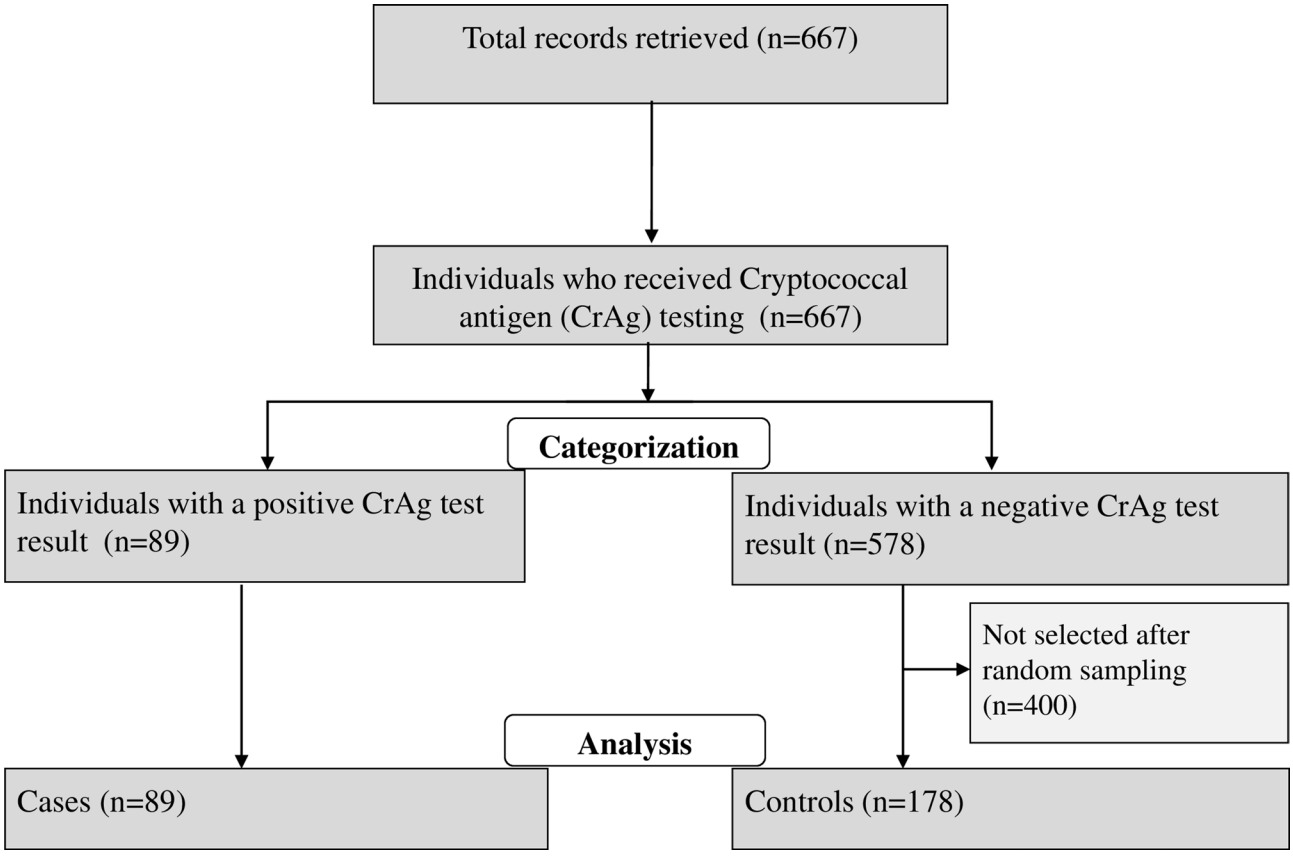


Fig. 2 Study profile. Study profile showing participant selection based on eligibility criteria. Cases included all individuals with a positive serum CrAg test, while controls were randomly selected from individuals with a negative serum CrAg test

Participant characteristics

Table 1 shows the characteristics of the study participants. We did not find any differences in the mean age between cases and controls: 40.3 ± 12.4 vs. 40.4 ± 11.7 years, respectively ($p = 0.952$). Females comprised 52.8% of cases and 53.4% of controls (p = > 0.990). Most participants were aged ≥ 35 years (62.9% cases vs. 66.9% controls). Most controls resided in rural settings compared to cases (83.7% vs. 74.2%, respectively), though the difference was not statistically significant ($p = 0.090$).

Other characteristics, including baseline CD4 count < 200 cells/μl (cases: 89.2%; controls: 88.5%; $p > 0.990$), viral load suppression (94.4% in both groups), sex, age, and ART duration, were comparable between the groups.

We observed statistically significant differences between cases and controls concerning the baseline WHO clinical stages (III/IV: cases 15.7% vs. controls 3.9%; $p = 0.002$), hospitalization before serum CrAg testing (cases 95.5% vs. controls 2.2%; $p < 0.001$, baseline moderate/severe malnutrition based on MUAC assessment (cases 29.2% vs. controls 17.4%; $p = 0.039$), missed clinic visits in the prior three months to serum CrAg testing (cases 21.3% vs. controls 9.6%; $p = 0.013$), and TB status ($p < 0.001$).

Factors associated with cryptococcal infection

In the unadjusted analyses (Table 2), advanced WHO clinical stages III/IV (unadjusted odds ratio [uOR] 4.56, 95% CI 1.82–12.46), missing a clinic visit in the prior 3 months to serum CrAg testing (uOR 2.57, 95% CI 1.26–5.29), moderate/severe malnutrition (uOR 1.96, 95% CI 1.07–3.56), recent opportunistic infections (uOR 2.69, 95% CI 1.02–7.30), and presumptive TB (uOR 5.40, 95% CI 1.39–24.21) were associated with cryptococcal infection. Nevertheless, age, sex, and baseline CD4 count ≥ 200 cells/μl were not significantly associated with cryptococcal infection. In the adjusted analyses, only two factors remained independently associated with cryptococcal infection: advanced WHO clinical stages III/IV (adjusted odds ratio [aOR] 3.45, 95% CI 1.28–9.97) and missed clinic visits in the prior three months to serum CrAg testing (aOR 2.39, 95% CI 1.14–5.02). Associations with malnutrition, age, sex, baseline CD4 count, opportunistic infection history, and TB status were not statistically significant after adjustment. Model diagnostics indicated adequate fit, no evidence of misspecification (link test

Table 1 Distribution of participant characteristics by case-control status

Variables	Levels	Cases ($n=89$)	Controls ($n=178$)	*p*-value
Age group (years)	≤ 24	8 (9.0)	7 (3.9)	0.239
	25–34	25 (28.1)	52 (29.2)	
	≥ 35	56 (62.9)	119 (66.9)	
	mean (SD)	40.3 (12.4)	40.4 (11.7)	0.952
Sex	Female	47 (52.8)	95 (53.4)	> 0.990
	Male	42 (47.2)	83 (46.6)	
Residence	Rural	66 (74.2)	149 (83.7)	0.090
	Urban	23 (25.8)	29 (16.3)	
Substance/drug use	No	77 (86.5)	161 (90.4)	0.444
	Yes	12 (13.5)	17 (9.6)	
Exposure to bird droppings in the past 6 months	No	22 (24.7)	0 (0.0)	< 0.001
	Yes	67 (75.3)	178 (100.0)	
Baseline CD4 (cells/μL)	< 200	74 (89.2)	154 (88.5)	> 0.990
	≥ 200	9 (10.8)	20 (11.5)	
Baseline WHO clinical stage	I/II	75 (84.3)	171 (96.1)	0.002
	III/IV	14 (15.7)	7 (3.9)	
Hospitalized before the serum CrAg test	No	4 (4.5)	174 (97.8)	< 0.001
	Yes	85 (95.5)	4 (2.2)	
Baseline nutritional status based on MUAC	Well nourished	63 (70.8)	147 (82.6)	0.039
	Moderate/ severe malnutrition	26 (29.2)	31 (17.4)	
BMI (kg/m^2)	Mean (SD)	194.2 (96.3)	189.0 (102.3)	0.696
ART duration (years)	< 5	54 (66.7)	114 (64.8)	0.877
	≥ 5	27 (33.3)	62 (35.2)	
Missed clinic visit/s in the past 3 months before the serum CrAg test	No	70 (78.7)	161 (90.4)	0.013
	Yes	19 (21.3)	17 (9.6)	
Suppressed viral load (viral load < 1,000 copies/mL)	No	5 (5.6)	10 (5.6)	> 0.990
	Yes	84 (94.4)	168 (94.4)	
TB disease status	On treatment	10 (11.2)	8 (4.5)	< 0.001
	No TB disease	49 (55.1)	158 (88.8)	
	Presumptive TB	27 (30.3)	4 (2.2)	
	Completed TB treatment	3 (3.4)	8 (4.5)	
Opportunistic infection in the 3 months before the serum CrAg test	No	79 (88.8)	170 (95.5)	0.07
	Yes	10 (11.2)	8 (4.5)	
ART adherence in the past 5 months before serum CrAg testing	Fair/poor	0 (0.0)	3 (1.7)	0.538
	Good	89 (100.0)	175 (98.3)	

$p=0.80$), good calibration (Hosmer-Lemeshow $p=0.87$), and modest discrimination (AUC = 0.63).

Stratified analysis

In Table 3, stratified analysis by missed clinic visits showed that baseline WHO clinical stage remained associated with cryptococcal infection among those who did not miss visits (OR 4.27, 95% CI 1.34-15.0). Among participants who missed visits, the association was similar but not statistically significant (OR 4.11, 95% CI 0.35–222.7). The imprecise findings are likely due to sparse data. The Mantel–Haenszel pooled estimate confirmed a strong overall association (OR 4.30, 95% CI 1.64–11.3), with no evidence of effect modification ($p=0.969$).

Discussion

This study on the risk factors for cryptococcal infection among PWH with non-suppressed viral load and severe immunosuppression showed that baseline WHO clinical stages III/IV and missed clinic visits in the 3 months preceding serum CrAg testing are independently associated with cryptococcal infection. These findings highlight the continued vulnerability of individuals with advanced HIV disease and suboptimal engagement in care to opportunistic infections.

The study finding that advanced WHO clinical stages III and IV are associated with cryptococcal infection is consistent with evidence from Uganda and other high HIV burden settings [17, 18]. Advanced WHO clinical stages III and IV reflect severe immunosuppression and are commonly associated with low CD4 cell counts and high or non-suppressed viral load, which is a

Table 2 Unadjusted and adjusted analyses of factors associated with cryptococcal infection

Variables	Level	Logistic regression analysis	
		Univariable	Multivariable
		uOR (95% CI)	aOR (95% CI)
Age group (years)	≤ 24	1	1
	25–34	0.42 (0.13–1.30)	0.50 (0.15–1.62)
	≥ 35	0.41 (0.14–1.20)	0.47 (0.15–1.47)
Sex	Female	1	1
	Male	1.02 (0.61–1.70)	0.97 (0.57–1.67)
Residence	Rural	1	
	Urban	1.79 (0.96–3.32)	
Baseline WHO clinical stage	I/II	1	1
	III/IV	4.56** (1.82–12.46)	3.45** (1.28–9.97)
Baseline nutritional status based on MUAC	Well nourished	1	1
	Moderate/severe malnutrition	1.96* (1.07–3.56)	1.40 (0.72–2.69)
Missed clinic visit/s in the past 3 months before the serum CrAg test	No	1	1
	Yes	2.57** (1.26–5.29)	2.39* (1.14–5.02)
Opportunistic infection in the 3 months before the serum CrAg test	No	1	
	Yes	2.69* (1.02–7.30)	
TB disease status	On treatment	1	
	No TB disease	0.25 (0.09–0.66)	
	Presumptive TB	5.40* (1.39–24.21)	
	Completed TB treatment	0.30 (0.05–1.42)	
Baseline CD4 (cells/μl)	< 200	1	
	≥ 200	0.94 (0.39–2.10)	

Note: MUAC: Mid-upper arm circumference; WHO: World Health Organization; uOR denotes crude/unadjusted odds ratio; aOR denotes adjusted odds ratio; Statistical significance codes at 5% level: *$p<0.05$, **$p<0.01$, ***$p<0.001$. Baseline CD4, TB disease status, and history of opportunistic infection are collinear with baseline WHO clinical stage

Table 3 Stratified analysis of the association between WHO clinical staging and cryptococcal infection by missed clinic status

Missed TB clinic visit/s	Mantel–Haenszel OR	95% CI	*P*-value
No	4.27	1.34-15.0	0.008
Yes	4.11	0.35–222.7	0.342
Mantel–Haenszel pooled estimate	4.3	1.64–11.3	0.0016
Homogeneity test			0.969

well-established risk factor for cryptococcal disease. The finding underscores the importance of early identification and management of advanced HIV disease, as profound impairment of cell-mediated immunity facilitates susceptibility to Cryptococcus neoformans.

The study showed that individuals with missed clinic visits are more likely to have cryptococcal infection. This suggests that interruptions in HIV care potentially contribute to ongoing viral replication, poor immune recovery, and increased risk of opportunistic infections due to interruptions in ART. Similar findings have been reported elsewhere, where missed appointments and disengagement from care were linked to cryptococcal disease [19]. These results reinforce the importance of sustained retention in care and adherence to ART as critical components of cryptococcal disease prevention.

The finding that missed clinic visits do not modify the association between baseline WHO clinical stage and cryptococcal infection suggests that advanced HIV disease remains a dominant risk factor for cryptococcal infection regardless of recent clinic attendance. This finding aligns with previous studies in sub-Saharan Africa that show individuals with WHO clinical stages III/IV or low CD4 counts have a higher risk of cryptococcal infection [16].

The implications of these findings are several. First, our study is unique in evaluating all serum CrAg-positive infections among PWH in routine care settings, rather than focusing solely on cryptococcal meningitis or hospitalized patients. Second, by linking serum CrAg positivity to advanced HIV disease and recent care interruptions, we provide actionable insights into high-risk groups in real-world clinical practice. These results support the prioritization of targeted serum cryptococcal screening and enhanced clinical monitoring among such individuals. Lastly, strengthening retention in care, improving appointment tracking, and timely serum CrAg screening and testing among PWH with non-suppressed viral load may enhance early diagnosis and treatment, hence contribute to reducing the cryptococcal disease burden.

Study strengths and limitations

This study analyzed routinely collected HIV program data, and this enhances its relevance to real-world HIV care settings. However, the findings should be interpreted in light of several limitations. The study was conducted at a single site, although serving as a referral point for the surrounding seven districts, which may limit generalizability to other settings. Residual confounding from unmeasured factors such as alcohol use or other comorbidities is possible. Data inaccuracies resulting from recording and transcription errors are a possibility.

We studied individuals with non-suppressed viral load and severe immunosuppression; therefore, the findings may not fully generalize to other subgroups eligible for serum CrAg testing, including ART-experienced PWH returning to care after ≥90 days of ART interruption with CD4 < 200 cells/μL, PWH with WHO stage III or IV clinical events, and PWH with a positive symptom screen along the advanced HIV disease pathway.

Conclusions and recommendations

This study showed that people with advanced HIV disease and recent interruptions in HIV care have a higher risk of cryptococcal infection. In particular, baseline WHO clinical stages III/IV and missed clinic visits were the key risk factors. This finding underscores the importance of early identification of advanced HIV disease and sustained engagement in HIV care to prevent opportunistic infections. HIV programs should prioritize targeted cryptococcal screening among individuals with advanced HIV disease and non-suppressed viral load after ≥6 months on ART. Therefore, strengthening retention in care, improving clinic appointment tracking, and ensuring timely serum CrAg screening among PWH with non-suppressed viral load may reduce cryptococcal disease burden through early diagnosis and treatment.

Abbreviations

AIC	Akaike Information Criterion
ART	Antiretroviral therapy
AUC	Area under the receiver operating characteristic curve
BIC	Bayesian Information Criterion
BMI	Body Mass Index
CD4	Cluster of Cell Differentiation 4
CrAg	Cryptococcal antigen
HIV	Human Immunodeficiency Virus
HMIS	Health Management Information System
MUAC	Mid-upper arm circumference
PWH	People with HIV
VIF	Variance Inflation Factor
WHO	World Health Organization

Acknowledgements

We are grateful to the School of Public Health, Clarke International University, and the Fort Portal Regional Referral Hospital for all their support. This manuscript arose from the MPH dissertation of SN.

Author contributions

SN and JI conceptualized and designed the study. SN acquired the data. SA analyzed and interpreted the data. SN, SA, and JI drafted the manuscript. All authors (SN, SA, and JI) critically revised the manuscript and approved it for submission.

Funding

None.

Data availability

The dataset used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Clarke International University Research Ethics Committee (reference number: CLARKE-2024-1191). As this was a retrospective records review, the need for consent to participate was waived by the Clarke International University Research Ethics Committee that approved the study. Administrative clearance was granted by the Fort Portal Regional Referral Hospital. All data were anonymized before the analysis. The study adhered to the ethical principles outlined in the Declaration of Helsinki, namely autonomy, beneficence, nonmaleficence, and justice.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]School of Public Health, Clarke International University, Kampala, Uganda
[2]Department of Secondary Education, Ministry of Education and Sports, Kampala, Uganda
[3]Directorate of Graduate Training, Research and Innovation, Muni University, Box 725, Arua, Uganda
[4]Department of Community Health, Mbarara University of Science and Technology, Mbarara, Uganda

Received: 7 February 2026 / Accepted: 21 April 2026
Published online: 27 April 2026

References

1. Rajasingham R, Govender NP, Jordan A, Loyse A, Shroufi A, Denning DW, et al. The global burden of HIV-associated cryptococcal infection in adults in 2020: a modelling analysis. Lancet Infect Dis. 2022;22(12):1748–55.
2. Akaihe CL, Nweze EI. Epidemiology of cryptococcus and cryptococcosis in Western Africa. Mycoses. 2021;64(1):4–17.
3. Tenforde MW, Gertz AM, Lawrence DS, Wills NK, Guthrie BL, Farquhar C, et al. Mortality from HIV-associated meningitis in sub-Saharan Africa: a systematic review and meta-analysis. J Int AIDS Soc. 2020;23(1):e25416.
4. Zhao Y, Ye L, Zhao F, Zhang L, Lu Z, Chu T, et al. Cryptococcus neoformans, a global threat to human health. Infect Dis poverty. 2023;12(1):20.
5. Muzazu SGY, Assefa DG, Phiri C, Getinet T, Solomon S, Yismaw G, et al. Prevalence of cryptococcal meningitis among people living with human immunodeficiency virus and predictors of mortality in adults on induction therapy in Africa: a systematic review and meta-analysis. Front Med. 2022;9:989265.
6. Jemal M, Deress T, Belachew T, Adem Y. Prevalence of cryptococcal antigenemia and associated factors among HIV/AIDS patients at Felege-Hiwot Referral Hospital, Bahir Dar, Northwest Ethiopia. Int J Microbiol. 2021;2021:8839238.
7. Bongomin F, Kwizera R, Namusobya M, van Rhijn N, Andia-Biraro I, Kirenga BJ, et al. Re-estimation of the burden of serious fungal diseases in Uganda. Therapeutic Adv Infect disease. 2024;11:20499361241228345.
8. Namuju OC, Namuwenge PM, Kwizera R, Obuya E, Kirumira P, Naluyima R, et al. Adherence of health workers to guidelines for screening and management of cryptococcal meningitis in Uganda. PLoS ONE. 2023;18(4):e0284165.
9. Bonita R, Beaglehole R, Kjellström T. Basic epidemiology: World Health Organization; 2006.
10. Webb P, Bain C, Page A. Essential epidemiology: an introduction for students and health professionals. Cambridge University Press; 2017.
11. Gordis L. Epidemiology e-book. Elsevier Health Sciences; 2013.

12. Opolot G, Olupot-Olupot P, Okware S, Izudi J. Retreatment TB is a risk factor for multidrug-resistant TB among people with HIV in rural eastern Uganda: a nested case-control study. J Clin Tuberc Other Mycobact Dis. 2025;41:100562.
13. Izudi J, Castelnuovo B, King R, Cattamanchi A. Risk factors for unsuppressed viral load after intensive adherence counseling among HIV infected persons in Kampala, Uganda: a nested case-control study. AIDS Res therapy. 2023;20(1):90.
14. Lodiong LJD, Izudi J, Amos T, Twinomugisha B, Kulaba N, Lumori BAE. HIV and body mass index are associated with prolonged corrected QT interval among people with drug-resistant tuberculosis on bedaquiline-containing regimen in Uganda. IJID Reg. 2024;13:100438.
15. Republic of Uganda. Consolidated guidelines for the prevention and treatment of HIV and AIDS in Uganda. Kampala, Uganda: Ministry of Health; 2022.
16. Eric E, Olupot-Olupot P, Bwayo D, Meya D, Katuramu R. Prevalence and factors associated with cryptoccocal antigenemia among patients with advanced human immunodeficiency virus in Eastern Uganda: a facility-based cross-sectional study. Open forum Infect Dis. 2023;10(7):ofad351.
17. Oyella J, Meya D, Bajunirwe F, Kamya MR. Prevalence and factors associated with cryptococcal antigenemia among severely immunosuppressed HIV-infected adults in Uganda: a cross-sectional study. J Int AIDS Soc. 2012;15(1):15.
18. Woldegeorgis BZ, Zekarias Z, Adem BG, Obsa MS, Kerbo AA. Prevalence and determinants of opportunistic infections among HIV-infected adults receiving antiretroviral therapy in Ethiopia: a systematic review and meta-analysis. Front Med. 2023;10:1087086.
19. Lowane MP, Lebese RT. Why adult patients on antiretroviral therapy miss clinical appointments in rural villages of Limpopo Province, South Africa: an exploratory study. Health SA = SA Gesondheid. 2022;27:1989.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.