Abstract 791

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High Mortality Associated with Unmasking Cryptococcal Meningitis

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Abstract

Introduction: Increased antiretroviral therapy (ART) availability in Africa has led to more patients developing cryptococcosis after ART initiation. Despite this changing epidemiology, data regarding cryptococcal meningitis (CM) in those already receiving ART are lacking. Preliminary analyses (2015; n=172) suggested poor outcomes of unmasking CM with recent ART initiation. We sought to confirm and further characterize this observation by comparing clinical presentation and outcomes in a large cohort of ART-naïve and ART-experienced adults.

Methods: We prospectively enrolled 627 HIV-infected persons with CM in Uganda from August 2013 to May 2017. Participants were classified by ART status and the timing of ART initiation. Statistical comparisons were made with Kruskal-Wallis or Fisher's Exact tests, with a primary endpoint of 2-week survival.

Results: Overall, 48% (301/627) of participants were receiving ART at presentation, having initiated ART a median of 126 (IQR, 29-760) days prior to CM diagnosis. Compared with those not receiving ART, participants receiving ART had higher CD4 counts (median 30 (IQR, 10-79) vs 12 (IQR, 6-46) cells/μL; p=.02) and lower CSF fungal burdens (median 4.1 (IQR, 2.1-5.2) vs 5.0 (IQR, 4.0-5.6) log10 CFU/mL CSF; p<.001). Of those receiving ART, 50% (150/301) had initiated ART ≤ 4 months, and 16% (48/301) had initiated ART ≤ 14 days. Persons starting ART ≤ 4 months prior were more likely to present with CSF pleocytosis (47% vs 30%; p=.003) compared to those initiating ART > 4 months prior to diagnosis. Among persons receiving ART for > 4 months, 80% had HIV viral loads > 1000 copies/mL. Two-week mortality did not differ by overall ART status (27% vs 26%; p=.86). However, 50% (24/48) of those receiving ART for ≤ 14 days died within 2-weeks compared with 19% (19/102) of those receiving ART for 15-122 days and 23% (35/151) of those receiving ART for > 4 months (p<.001). Hazard ratio for mortality decreased as the duration from ART initiation to development of CM increased from 7 to 28 days.

Conclusions: Cryptococcosis after ART initiation is common in Africa. Patients initiating ART who unmask cryptococcal meningitis are at a high risk of death. Immune recovery in the setting of CNS infection is detrimental, and management of this population requires further study. Implementing pre-ART cryptococcal antigen screening is urgently needed to prevent CM after ART initiation.

Introduction

- Expanded access to ART and improved HIV screening have led to increasing numbers of patients presenting with opportunistic infections after initiating ART.
- While the development of cryptococcal meningitis (CM) in persons initiating ART can be largely prevented through cryptococcal antigen screening, this practice has yet to be widely implemented.
- Most CM trials to date have involved individuals that are ART naïve and outcome data for persons developing CM while receiving ART is lacking.
- We compared clinical presentation and outcomes in ART-naïve and ART-experienced Ugandans with cryptococcal meningitis.

Methods

- 627 HIV-infected patients diagnosed with first-episode CM in Uganda were prospectively enrolled as part of a trial investigating the use of adjunctive sertraline for CM treatment (**Figure 1**).
- At CM diagnosis, patients were classified by ART status and timing:
  1. **ART status** – whether or not patient had received any ART within previous 30 days, and
  2. **Timing of ART initiation** – time from either ART initiation (N=240), ART reintroduction (ART defaulters; N=18), or ART switch after failure (N=33).
- ART timing groups were defined as:
  - **≤ 14 Days** – ART initiated within 14 days of CM diagnosis,
  - **15-122 Days** – ART initiated within 4 months of diagnosis,
  - **> 4 Months** – ART initiated more than 4 months prior to diagnosis.
- All participants received amphotericin-based therapy according to locally accepted guidelines.
- Baseline characteristics were collected and outcomes compared.

Study Population

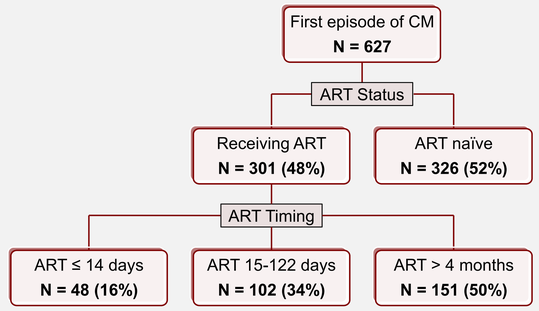

Figure 1: Analysis Cohort: Roughly half of all participants with first-episode cryptococcal meningitis were receiving ART at time of diagnosis, and of those receiving ART, half had initiated ART within 4 months of diagnosis.

Comparisons by ART Status

Table 1. Clinical presentation and outcomes by ART Exposure Status

	No ART	Receiving ART	P-value*
N per group	326	301	
ART duration, days		126 [29, 760]	
Demographics			
Age, years	35 (30, 41)	35 (30, 40)	0.76
Male sex	203 (62%)	183 (61%)	0.74
On TB treatment	16 (5%)	40 (13%)	**<0.001**
Baseline Clinical Parameters			
GCS < 15	140 (43%)	138 (46%)	0.52
Weight, kg	52 (48, 58)	50 (44, 56)	0.09
Hemoglobin, g/dL	11.9 (10.3, 13.2)	11.2 (9.7, 12.7)	**<.01**
Creatinine, mg/dL	0.7 (0.6, 0.9)	0.7 (0.6, 0.9)	0.09
CD4 count, cells/μL	12 (6, 46)	30 (10, 79)	**0.02**
CD4 < 100, cells/μL	70 (93%)	56 (84%)	0.11
Baseline CSF Parameters			
OP > 250 mmH_2O	163 (57%)	142 (53%)	0.44
QCC, $\log_{10}$ CFU/mL	5.0 (4.0, 5.6)	4.1 (2.1, 5.2)	**<0.001**
Sterile culture	10 (3%)	45 (15%)	**<0.001**
WBC < 5 cells/L	208 (67%)	173 (61%)	0.20
Outcomes			
Hospitalized, days	16 (12, 18)	16 (12, 19)	0.78
Received corticosteroids	33 (10%)	50 (17%)	**0.02**
Number of LPs received	3 (2, 4)	3 (2, 4)	0.20
Attained CSF sterility†	138 (45%)	136 (54%)	**0.03**
EFA‡	0.34 (0.20, 0.48)	0.36 (0.23, 0.58)	0.19
Mortality, N (%)			
Within 2 Weeks	87 (27%)	78 (26%)	0.86
Within 10 Weeks	139 (43%)	132 (44%)	0.81

Data are median (P25, P75) or N (%). Abbreviations: ART, Antiretroviral Therapy; GCS, Glasgow Comal Scale; OP, opening pressure; QCC, quantitative cryptococcal culture; EFA, Early Fungicidal Activity.

*Kruskal-Wallis or Fisher Exact tests.

†Within 18 days of CM diagnosis. Excludes those who started with a sterile culture.

‡Expressed as –($\log_{10}$CFU/mL CSF/day), calculated using patient-specific regression models.

Table 1: Clinical presentation and outcomes by ART exposure status. Individuals that were receiving ART at time of CM diagnosis had higher CD4 counts and lower initial CSF cryptococcal burdens. Those receiving ART were also more likely to receive corticosteroids and to attain CSF sterility given their lower initial fungal burden. Other outcomes, including 2- and 10-week mortality, were similar.

Comparisons by Timing of ART

Table 2. Clinical presentation and outcomes by timing of ART

ART Duration	≤ 14 Days	15-122 Days	> 4 Months	P-value*
N per group	48	102	151	
ART duration, days	7 (5, 10)	55 (27, 87)	760 (335, 1489)	
Demographics				
Age, years	35 (28, 41)	35 (30, 40)	36 (30, 42)	0.65
Male sex	29 (60%)	66 (65%)	88 (58%)	0.60
On TB treatment	3 (6%)	17 (17%)	20 (13%)	0.21
Baseline Clinical Parameters				
GCS < 15	25 (52%)	52 (51%)	61 (40%)	0.17
Weight, kg	46 (41, 54)	48 (40, 51)	52 (47, 63)	0.09
Hemoglobin, g/dL	11.2 (10.3, 12.4)	11.5 (9.8, 12.9)	11.1 (9.3, 12.7)	0.60
Creatinine, mg/dL	0.7 (0.6, 1.1)	0.7 (0.5, 0.9)	0.7 (0.5, 0.8)	0.25
CD4 count, cells/μL	20 (11, 52)	59 (13, 93)	27 (7, 71)	0.49
CD4 < 100 cells/μL	10 (91%)	19 (79%)	27 (84%)	0.75
Baseline CSF Parameters				
OP > 250 mmH_2O	21 (49%)	52 (57%)	69 (52%)	0.61
QCC, $\log_{10}$ CFU/mL	4.4 (2.5, 5.1)	3.9 (1.6, 5.1)	4.1 (2.3, 5.3)	0.49
Sterile culture	5 (10%)	19 (19%)	21 (14%)	0.40
WBC < 5 cells/L	25 (53%)	50 (53%)	98 (70%)	**0.01**
Outcomes				
Hospitalized, days	15 (7, 19)	18 (15, 22)	15 (14, 19)	0.12
Received steroids	15 (31%)	21 (21%)	14 (9%)	**<0.001**
LPs received	3 (2, 4)	3 (2, 4)	3 (2, 4)	0.78
Attained sterility†	18 (44%)	51 (62%)	67 (52%)	0.14
EFA‡	0.35 (0.22, 0.66)	0.40 (0.25, 0.66)	0.32 (0.23, 0.47)	0.15
Mortality, N (%)				
Within 2 Weeks	24 (50%)	19 (19%)	35 (23%)	**<0.001**
Within 10 Weeks	30 (63%)	43 (42%)	59 (39%)	**0.02**

Data are median (P25, P75) or N (%). Abbreviations: ART, Antiretroviral Therapy; GCS, Glasgow Comal Scale; OP, opening pressure; QCC, quantitative cryptococcal culture; EFA, Early Fungicidal Activity.

*Kruskal-Wallis or Fisher Exact tests.

†CSF sterility within 18 days of CM diagnosis. Excludes those who started with a sterile culture.

‡Expressed as –($\log_{10}$CFU/mL CSF/day), calculated using patient-specific regression models.

Mortality in ART-Associated CM

Figure 2: Kaplan-Meier Survival Plot by ART Status and Timing

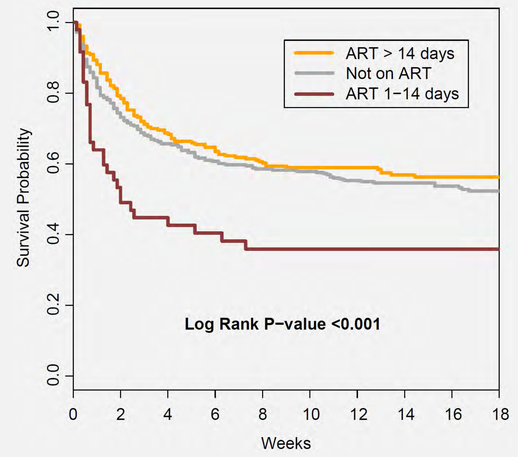

Figure 2: Mortality was highest among participants receiving ART for ≤14 days or compared with those who were ART-naïve. The differences in mortality occurred over the initial ~3weeks.

High Mortality in Unmasking CM

- Among participants receiving ART, those developing cryptococcal meningitis within 28 of initiating ART had increased mortality.
- This risk was less pronounced as the duration between ART initiation and development of cryptococcal meningitis increased.

Figure 3: Hazard ratio for mortality within 30 days by duration from ART initiation to development of cryptococcal meningitis.

Days ART Cut−off*	No. in Group 1	No. in Group 2	P−value
7	25	276	<0.001
14	48	253	<0.001
21	66	235	0.01
28	75	226	0.01

*Comparing Group 1 (ART duration at or less than cut-off) to Group 2 (ART duration greater than cut-off) for 30−day mortality.

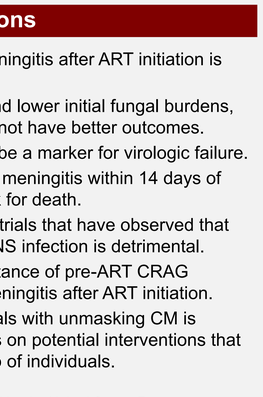

Figure 3: The figure, which plots the hazard ratio for mortality within 30 days as a function of ART duration, demonstrates a decrease in the hazard ratio when ART was initiated anytime in the last 28 days prior to the development of cryptococcal meningitis.

Virologic Failure in Late ART-Associated CM

- Late ART-associated CM was an indication of HIV virologic failure.
  - HIV viral loads were obtained in 36% (54/151) of participants with late ART-associated CM.
- Of those obtaining viral loads:
  - 83% (45/54) had detectable HIV virus of ≥40 copies/mL,
  - 80% (43/54) with >1000 copies/mL, and
  - 46% (25/54) with >100,000 copies/mL.

Conclusions

- The development of cryptococcal meningitis after ART initiation is common in Africa.
- Despite having higher CD4 counts and lower initial fungal burdens, patients with ART-associated CM do not have better outcomes.
- Late ART-associated CM appears to be a marker for virologic failure.
- Individuals that develop cryptococcal meningitis within 14 days of initiating ART are at an increased risk for death.
- Our study supports other ART timing trials that have observed that immune recovery in the context of CNS infection is detrimental.
- These findings underscore the importance of pre-ART CRAG screening to prevent cryptococcal meningitis after ART initiation.
- The optimal management of individuals with unmasking CM is unclear, and future trials should focus on potential interventions that could improve outcomes in this group of individuals.

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