Recent ART Initiation and Mortality Risk in HIV-Associated Cryptococcal Meningitis

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BACKGROUND

- Over half of patients diagnosed with HIV-associated cryptococcal meningitis are ART-experienced. The impact of recent ART initiation on outcomes in people living with HIV (PLHIV) who present with cryptococcal meningitis, and how to optimally manage ART in this patient population, are unknown.
- We hypothesised that patients presenting with cryptococcal meningitis following very recent ART initiation (within 14 days) were at higher risk of mortality than ART-naïve individuals or those on ART for longer periods, and that ART interruption reduces this excess mortality.

METHODS

- **Primary outcome of 2- and 10-week mortality was determined from AMBITION-cm trial data.**
- Participants were grouped according to:
- **1. ART status**
  - Not taking ART – ART naïve and ART defaulters
  - On ART
- **2. Duration of ART (Fig 1), capturing the following**
  - i. Individuals with symptomatic cryptococcal meningitis at ART initiation
  - ii. Those with subclinical cryptococcal meningitis at ART initiation or who develop unmasking IRIS
  - iii. Individuals established on ART with lagging CD4 count restitution
  - iv. Those failing ART due to adherence issues or drug resistance
- A generalised linear model assessed differences in mortality rates between groups.

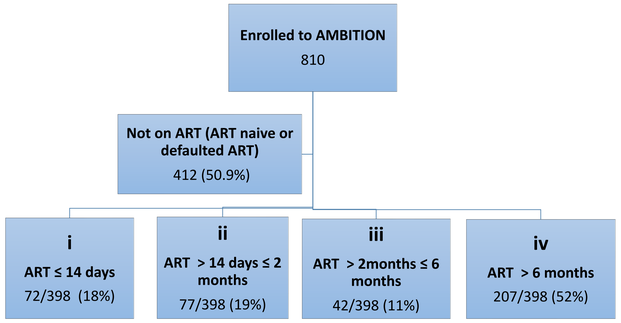


Figure 1: Categorisation of participants according to ART status and duration

Recent ART initiation is associated with excess mortality from cryptococcal meningitis which may be offset by ART interruption at diagnosis

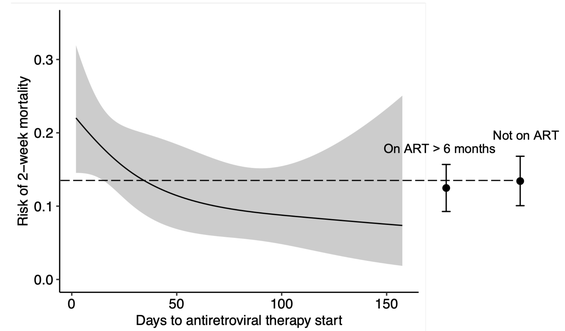
Table 1: Mortality outcomes among AMBITION participants with HIV-associated cryptococcal meningitis stratified by ART status at the time of presentation

ART status		2-week mortality		10-week mortality	
		Mortality risk (95% CI)	N	Mortality risk (95% CI)	N
A.	Impact of ART status and duration on risk of mortality				
Not on ART		12.4% (9.1-16.2)	51/412	26.0% (21.7-30.2)	107/412
On ART	Overall	13.3% (10.0-16.7)	53/398	27.8% (23.4-32.2)	111/398
	≤14 days	20.8% (11.5-30.2)	15/72	37.2% (26.1-48.3)	27/72
	>14 days ≤2 months	10.4% (3.6-17.2)	8/77	22.0% (12.8-31.2)	17/77
	>2 months ≤6 months	7.1% (0.0-14.9)	3/42	23.9% (11.0-37.8)	10/42
	>6 months	13.0% (8.5-17.6)	27/207	27.5% (21.5-33.6)	57/207
B.	Mortality effect of ART interruption				
On ART ≤14 days, ART continued		34.8% (8/23) (0.15-0.54)		52.2% (12/23) (0.32-0.73)	
On ART ≤14 days, ART stopped		14.3% (7/49) (0.05-0.24)		30.6% (15/49) (0.18-0.44)	

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RESULTS

- The median age was 37 years (IQR 32-43); 491/810 (60.6%) were male; median CD4 count was 27 cells/µl (IQR 10-58)
- Among those presenting on ART, CD4 counts, and baseline fungal burdens declined with increasing ART duration
- Participants who had initiated ART within 14 days had higher mortality risk at 2- and 10- weeks post randomization than those on ART for longer **(Table 1)**
- Mortality risk differed significantly according to time on ART but did not decline progressively with increasing ART duration (**Fig 2).**
- There was a significant interaction between the clinical decision to interrupt ART at enrolment and ART timing on mortality risk at 2- and 10-weeks (p 0.01 and 0.05 respectively)



- **Figure 2:** Regression model of mortality risk according to duration of ART

CONCLUSIONS

- Our findings confirm an increased risk of early mortality in cryptococcal meningitis patients who started ART in the past 2 weeks
- ART interruption at CM diagnosis in recent ART initiators does not lead to increased mortality and may be associated with improved outcomes.
- Intervention studies are needed to definitively determine whether ART interruption in patients presenting with cryptococcal meningitis having recently started ART is beneficial.

References

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