Epstein–Barr virus and Cytomegalovirus co-infections and mortality risk in patients with HIV-associated cryptococcal meningitis: a prospective nested cohort

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BACKGROUND

- *Cryptococcus* is the most common cause of HIV-associated meningitis globally, accounting for 19% of all AIDS-related deaths.
- Case fatality is 24-45%, even in the context of clinical trials. Co-prevalent infections including Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) - may contribute to poor outcomes.

METHODS

- We measured CMV and EBV viral load by qPCR in baseline plasma and CSF samples collected prospectively as part of AMBITION-CM.
- AMBITION-CM was a multi-site, randomized trial which investigated the use of single high dose liposomal amphotericin B for the treatment of HIV-associated cryptococcal meningitis conducted in Uganda, Botswana, South Africa, Malawi and Zimbabwe.
- We described the prevalence of CMV- and EBV-viraemia (in plasma), and CNS co-infections (CSF qPCR positivity), and associations of any detectable CMV- or EBV-viremia or viremia >1000 IU/ml with 2- and 10-week mortality using logistic regression modelling.

RESULTS

- 811 participants were enrolled: 60% male, median age 37 (IQR 32-43) years, median baseline CD4 count 27 (IQR 10-58) cells/mcL.
- CMV viraemia was present in 49% (395/804)
- EBV plasma viraemia in 73% (585/804)
- 5% (39/707) had detectable CMV in CSF
- 27% (191/708) had detectable EBV in CSF

Amongst 811 adults with cryptococcal meningitis, half had CMV viraemia.

High-level CMV viraemia (≥1000 copies/ml) was significantly associated with greater than double the odds of 2-, and 10-week mortality.

CMV viremia represents a potentially modifiable risk factor to improve survival amongst adults with advanced HIV disease. Pre-emptive CMV treatment trials are now planned.

RESULTS

- CMV viraemia was associated with a pauci-inflammatory response: lower CD4 counts, less CSF inflammation, and higher CSF fungal burdens.
- EBV co-infections were associated with a pro-inflammatory cryptococcal phenotype: higher CD4 counts and more CSF inflammation.

TABLE 1: Baseline characteristics of 804 adults with cryptococcal meningitis stratified by (i) CMV and EBV viraemia co-infection status

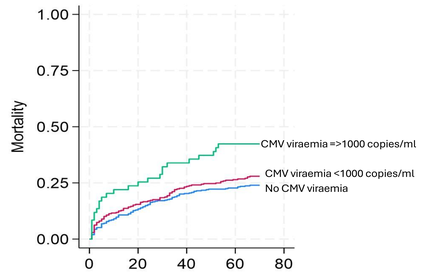
Variable	No CMV viraemia N (%) or median (IQR)	CMV viraemia N (%) or median (IQR)	P value	No EBV viraemia N (%) or median (IQR)	EBV viraemia N (%) or median (IQR)	P value
Total	409 (50.9)	395 (49.1)		219 (27.2)	585 (72.8)	
Age (years)	37 (32-43)	37 (31-43)	0.74	35 (30-41)	38 (32-44)	<0.001
ART experienced	266 (65.0)	250 (63.3)	0.61	141 (64.4)	375 (64.1)	0.94
Baseline CD4 (cells/μL)	33 (12-68)	23 (9-51)	<0.001	20 (8-49)	30 (11-64)	0.002
HIV viral load (copies/ml)	39,729 (739-222,701)	46,296 (603-287,555)	0.62	75,657 (1,440-249,200)	37,811 (532-260,382)	0.48
CSF white cell count (cells/μL)	10 (4-77)	4 (2-45)	<0.001	4 (2-39)	6 (4-70)	0.01
CSF fungal burden (CFU/ml)	30,000 (250-350,000)	70,000 (1,100-465,000)	0.001	46,500 (365-495,000)	45,500 (415-370,000)	0.48

TABLE 2: Multivariate analysis of the association between CMV and EBV co-infections and 2-week mortality

Cryptococcal meningitis cohort group	2-week mortality N/N (%)	cOR 2-week mortality (95% CI)	aOR for 2-week mortality[1] (95% CI)	P-value
No CMV viraemia	44/409 (10.8)	1	1	
CMV viraemia	59/395 (14.9)	1.32 (0.97-1.79)	1.42 (0.92-2.21)	0.11
CMV viraemia <1000 copies/ml	46/336 (13.7)	1.32 (0.85-2.04)	1.29 (0.81-2.04)	0.28
CMV viraemia ≥1,000 copies/ml	13/59 (22.0)	2.34 (1.17-4.68)	2.31 (1.12-4.75)	0.02
No CNS CMV infection	86/668 (12.9)	1	1	
CNS CMV infection	8/39 (20.5)	1.75 (0.78-3.92)	2.03 (0.87-4.70)	0.10
No EBV viraemia	30/219 (13.7)	1	1	
EBV viraemia	75/585 (12.5)	0.90 (0.57-1.42)	0.89 (0.54-1.45)	0.63
No CNS EBV infection	72/517 (13.9)	1	1	
CNS EBV infection	22/191 (11.5)	0.80 (0.48-1.34)	0.88 (0.51-1.51)	0.64

1= Adjusted for age (continuous variable), baseline CD4 count (continuous variable), sex and study site, using logistic regression models.

FIGURE 1: Cumulative 10-week mortality amongst 804 adults with Cryptococcal meningitis, stratified by CMV viral load burden



CONCLUSION

- Amongst 811 adults with advanced HIV disease and cryptococcal meningitis, half had CMV viraemia, and three-quarters have EBV viraemia.
- The two co-infections were associated with contrasting phenotypes.
- EBV was associated with a pro-inflammatory cryptococcal phenotype and was not associated with poor outcomes indicating a probable bystander infection.
- Conversely, CMV co-infections were associated with a pauci-inflammatory response and increased mortality.