CYTOMEGALOVIRUS VIREMIA AS A RISK FACTOR FOR MORTALITY IN HIV-ASSOCIATED MENINGITIS

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Introduction

- Cryptococcal and tuberculous (TB) meningitis, along with cytomegalovirus (CMV) disease, are prevalent opportunistic infections in significantly immunocompromised patients with CD4+ T cell counts < 100 cells/μL.
- We previously demonstrated CMV viremia being associated with a 2.2-fold increased risk of 10-week mortality in ART-naïve persons with 1st episode cryptococcal meningitis.
- We hypothesize that CMV may be exerting a detrimental effect by impairing Type 1 helper T cell (Th1) responses, which is thought critical for controlling both *Cryptococcus* and TB.
- We examined whether CMV viremia persisted as a risk factor for mortality across a broader HIV-associated meningitis cohort. Given that CMV is treatable, such an association has potential management implications.

Methods

- CMV DNA concentrations were measured from baseline cryopreserved plasma or serum samples via RT-PCR using UL83 primers and a lower limit-of-detection of ~100 IU/mL of plasma.
- Persons with detectable CMV DNA were compared against those without any detectable CMV DNA.
- Primary outcome of this study was 18-week all-cause mortality.
- Survival was analyzed categorically by viral load groupings, in a time-to-event model, and using a multivariate proportional hazards model. Analysis used SAS v9.4 (SAS Institute; Cary, NC).

Study Population

- Study used stored samples* from two completed parent trials:

ASTRO-CM Trial (NCT01075152)

- Enrolled persons with cryptococcal meningitis from March 2015 to May 2017.
- All participants received standard-of-care amphotericin-based induction therapy.
- Participants were additionally randomized to receive sertraline 400mg daily for 2 weeks, followed by 200mg daily for 12 weeks; or placebo.
- No difference in survival at 18 weeks was found between the experimental and control arms.

RifT Trial (ISRCTN42218549)

- Enrolled persons with suspected or confirmed TB meningitis from January to December 2019.
- All participants received 4-drug therapy (plus dexamethasone).
- The rifampicin component was randomized to oral rifampicin 10mg/kg/day, oral rifampicin 35mg/kg/day, or IV rifampicin 20mg/kg/day.
- No difference in survival at 24 weeks (study was not powered to detect a survival difference).

* Samples were selected randomly and by convenience. Samples represent baseline blood draw (maximum 14 days from diagnosis, with >90% within 3 days).

Baseline Characteristics

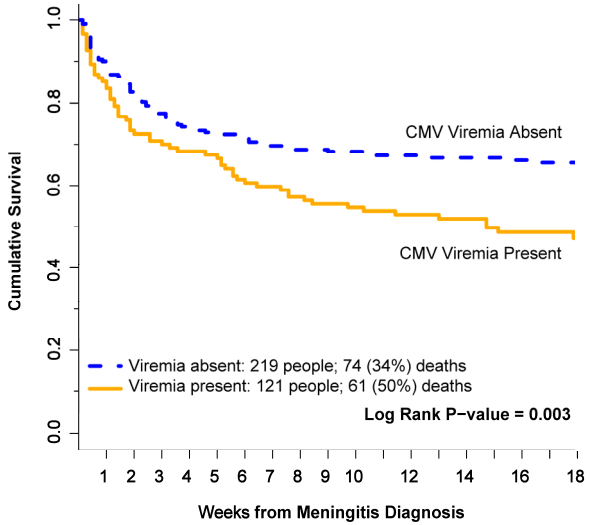
Table 1: Baseline Characteristics Based on CMV Viremia Status

Baseline Data	CMV Viremia Present	CMV Viremia Absent	P-Value
N per group	121	219	
N with cryptococcal meningitis	111 (92%)	197 (90%)	
N with TB meningitis	10 (8%)	22 (10%)	
Women	52 (43%)	81 (37%)	.28
Age, years	35 [29, 40]	35 [30, 40]	.63
CD4 count per μL	14 [6, 53]	24 [8, 61]	.07
Receiving ART	57 (47%)	98 (45%)	.68
CMV plasma DNA, IU/mL	452 [142, 2450]	0 [0, 0]	
Glasgow Coma Scale score <15	49 (41%)	88 (40%)	.95
Hemoglobin, g/dL	11.0 [9.5, 12.6]	11.6 [10.3, 13.0]	.01
CSF white cells ≤5 cells/μL	85 (73%)	126 (60%)	.03

Data are N (%) or median [IQR].
P-values from Chi-square or Wilcoxon rank sum testing.
Abbreviations: CMV, cytomegalovirus; ART, antiretroviral therapy; IU, international units; CSF WBC, cerebrospinal fluid white blood cell count; IQR, interquartile range.

Outcomes

Figure 1: Death through 18 Weeks by CMV Viremia Status



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Figure 2: Death through 18 Weeks by CMV Viral Load Groups

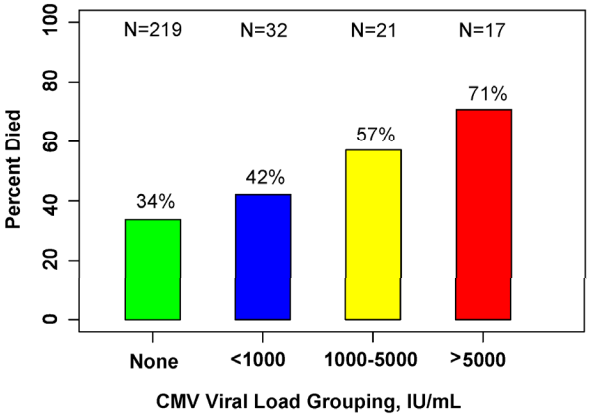


Table 2: Proportional Hazards Regression Model for 18-week Mortality

	Overall		Cryptococcal Meningitis		TB Meningitis	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Univariate Analyses						
CMV viremia present	1.66 (1.18, 2.33)	.003	1.48 (1.04, 2.09)	.03	17.1 (2.04, 143)	.009
Per log_{10}CMV DNA IU/mL increase	1.24 (1.11, 1.38)	<.001	1.19 (1.07, 1.33)	.002	2.59 (1.45, 4.62)	.001
CD4 <25 cells/μL	1.24 (0.84, 1.83)	0.28	1.16 (0.77, 1.75)	.49	0.44 (0.05, 3.80)	.46
Glasgow Coma Scale <15	1.58 (1.12, 2.21)	.008	1.88 (1.33, 2.67)	<.001	∞	
Multivariable Model #1						
CMV viremia present	1.59 (1.13, 2.23)	.008	1.43 (1.00, 2.03)	.05	19.7 (2.22, 174)	.007
Multivariable Model #2						
Per log_{10}CMV DNA IU/mL increase	1.21 (1.09, 1.35)	<.001	1.18 (1.05, 1.31)	.004	2.53 (1.29, 4.96)	.007

Multivariable Models #1 and #2 adjust for CD4+ T cell count <25 cells/μL and Glasgow coma scale score <15.

Conclusions

- Persons with CMV viremia had 66% greater risk of death than those without CMV viremia in the setting of HIV-associated meningitis.
- Greater CMV viral load further increased the risk of mortality through 18 weeks, reaching 71% in those with >5000 IU/mL.
- It remains unknown whether CMV is contributing to the observed mortality, or whether it is a sensitive marker of immune dysfunction.
- A randomized trial using anti-CMV therapy is warranted to elucidate whether CMV viremia is a modifiable risk factor in persons with HIV-associated meningitis in advanced disease.