CSF HIV viral escape is associated with improved survival in adults with HIV-associated meningitis

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Jayne Ellis[1,2], Biyue Dai[3], Laura Nsangi[1], Gila Hale [1,2], Emmanuel Mande[1], Jane Gakuru[1] Enock Kagimu[1], Timothy Mugabi[1], Derrick Kasozi[1], Suzan Namombwe[1], Sara Kimuda[1], Asmus Tukundane[1], David Meya[1], David Boulware[3], Fiona Cresswell[1,2,4]

1.Infectious Diseases Institute, Makerere University, Kampala, Uganda. 2. Clinical Research Department, London School of Hygiene and Tropical Medicine, UK. 3. University of Minnesota, Minneapolis, USA 4. Brighton and Sussex Medical School, UK

BACKGROUND

- Cryptococcal meningitis and tuberculous meningitis (TBM) remain the most common causes of HIV-associated meningitis, accounting for >20% of AIDS-related deaths.
- Acute mortality associated with these infectious meningitides remains devastatingly high (25-50%).
- CSF HIV viral escape – which indicates selectively reduced control of viral replication in the central nervous system compartment - may result in neuroinflammation.

We hypothesised that amongst adults with HIV-associated meningitis, cerebrospinal fluid HIV viral escape may contribute to CNS damage and be associated with increased mortality.

METHODS

- **Study design and setting:** a prospective cohort study of HIV-positive adults (≥18 years) diagnosed with suspected meningitis presenting to Mulago National Referral Hospital, or Kiruddu National Referral Hospital in Kampala, Uganda.
- **HIV viral load testing**: venous blood and CSF were collected on study day 1 for paired point of care Xpert HIV-1 viral load testing (Xpert; Cepheid, Sunnyvale, CA, USA). HIV-1 viral load testing was conducted on both fresh and thawed stored plasma and CSF samples. Testing of CSF with the Xpert HIV VL test was an off-label usage.
- **Cerebrospinal fluid (CSF) HIV viral escape** was defined as the presence of quantifiable HIV ribonucleic acid (RNA) in the CSF at a concentration above that in plasma (as per the Winston et al 2019 consensus case definition).
- **Meningitis diagnoses:**
  - Participants with cryptococcal meningitis had either a first, or recurrent episode of CSF Cryptococcal antigen (CrAg) positive meningitis.
  - Participants with TBM had definite or probable TBM with CSF inflammation.
  - Participants with “other” meningitis did not meet either of these clinical case definitions but presented with a meningitis clinical syndrome.

Amongst adults with HIV-associated meningitis, CSF HIV viral escape was **common** and was associated with CSF pleocytosis and **improved survival.**

CSF HIV viral escape is likely a **by-stander phenomenon** and an indicator of effective host immune response with trafficking of CD4 lymphocytes and monocytes and containing HIV RNA into the central nervous system.

RESULTS

- We recruited 152 adults: 47% were male, median CD4 was 59 (IQR 14-142) cells/μL, and 42% were receiving antiretroviral therapy (ART) at time of presentation.
- The majority (48%, 73/152) had cryptococcal meningitis, 32% (49/152) had definite or probable TBM, 20% (30/152) suspected “other” meningitis.
- **70% of participants had detectable plasma HIV RNA**, with a median HIV-1 viral load of 4,000 copies/mL, and 72% of participants had detectable HIV RNA in the CSF, with a median HIV viral load of 1,760 copies/mL.
- No association with 18-week mortality for either plasma viremia (Hazard Ratio = 1.30; 95%CI 0.65-2.58; p=0.5) or CSF viremia (Hazard Ratio= 0.97; 95%CI 0.49–1.89; p=0.9).
- **CSF HIV viral escape was present in 30%** (46/152) overall.
  - Among those on ART <100 days, CSF HIV viral escape prevalence was 60%.
- CSF HIV viral escape was statistically associated (p<0.001) with **higher CSF white cell count** (103 vs. <5 cells/μL) and shorter duration of ART (2 vs. 20 weeks).
- **CSF HIV viral escape was associated with improved 18-week survival** (Hazard Ratio = 0.46; 95%CI 0.21–0.99; p=0.046). Following adjustment for meningitis diagnosis, and ART status, adjusted Hazard Ratio = 0.51; 95%CI 0.23 – 1.13; p = 0.10)
- The positive association between CSF HIV viral escape and 18-week survival was also observed when the analysis was restricted to participants with:
  - **Cryptococcal meningitis** (adjusted Hazard Ratio = 0.48; 95%CI 0.13-1.71) or
  - **TB meningitis** (adjusted Hazard Ratio = 0.34; 95%CI 0.10-1.19).

TABLE 1: Baseline characteristics and survival outcomes of 152 adults with meningitis, stratified by CSF HIV viral escape status

	N	CSF HIV viral escape n=46	No CSF HIV viral escape n=106	P value
Diagnosis N (%)	152			0.2
Cryptococcal meningitis		24 (52)	49 (46)	
TB meningitis		17 (37)	32 (30)	
Other meningitis		5 (11)	25 (24)	
ART status N (%)	148			0.14
ART naïve		21 (47)	42 (41)	
Currently on ART		21 (47)	40 (39)	
ART defaulter		3 (6.7)	21 (20)	
ART Days N (%)	60			<0.001
<100 (days)		16 (71)	137 (26)	
CD4 cells/μL, median (IQR)	129	55 (16 – 103)	62 (14 - 169)	0.4
CSF white cells/μL, median (IQR)	148	103 (4 – 230)	<5 (<5 – 69)	< 0.001
18-week mortality, N (%)	152	8 (17%)	34 (32%)	0.063

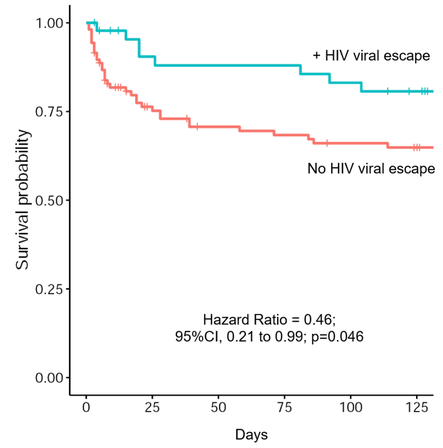

FIGURE 1: Cumulative mortality amongst 152 adults with suspected meningitis stratified by CSF HIV viral escape status over 18-weeks.

CONCLUSIONS: In our cohort of adults with advanced HIV disease and meningitis, CSF HIV viral escape was common, especially amongst participants recently initiated on ART, and amongst those with CSF pleocytosis.

The finding that CSF HIV viral escape was associated with improved 18-week survival is novel, and most likely indicates that CSF HIV viral escape in this context should be considered a by-stander phenomenon.