No evidence of increased brain neuronal injury following a *"shock and kill"* HIV cure strategy, in the RIVER trial

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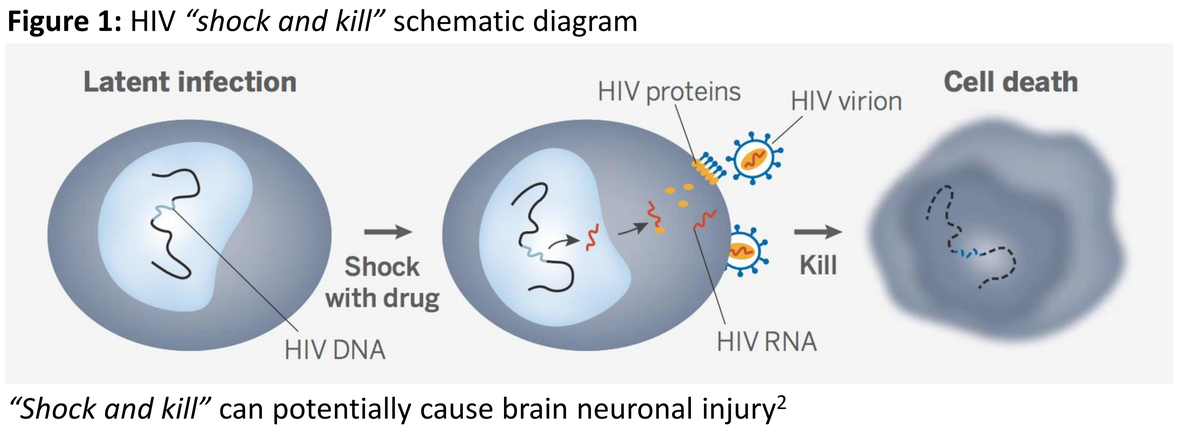
Introduction

"Shock and kill" is a HIV cure strategy being investigated[1]

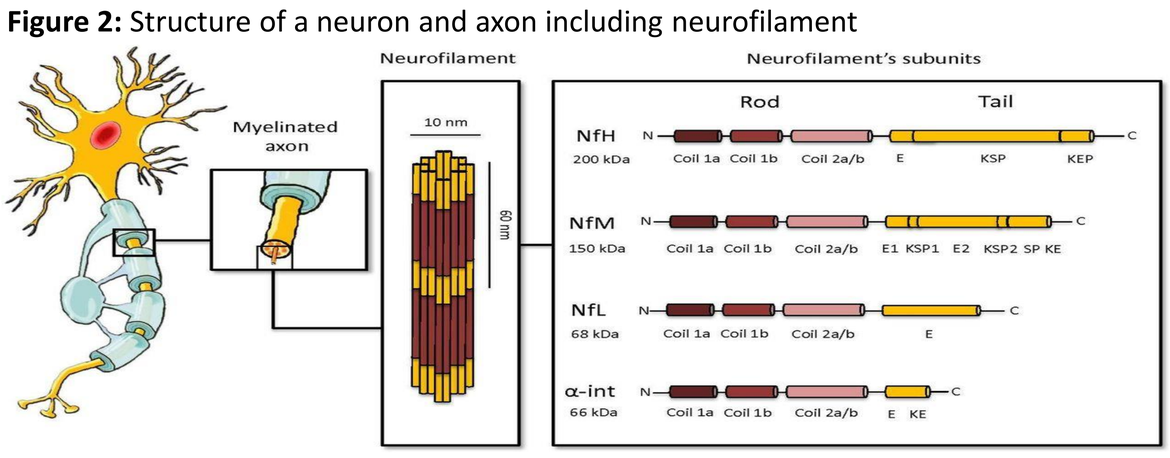
Figure 1: HIV *"shock and kill"* schematic diagram



"Shock and kill" can potentially cause brain neuronal injury[2]
- Directly via neurotoxic viral proteins and latency reversing agents
- Indirectly via inflammation & immuno-activation, caused by virus and/or vaccination

Plasma neurofilament light chain (NFL) has been shown to strongly correlate with cerebrospinal fluid NFL, an established biomarker of brain neuro-axonal injury[3]

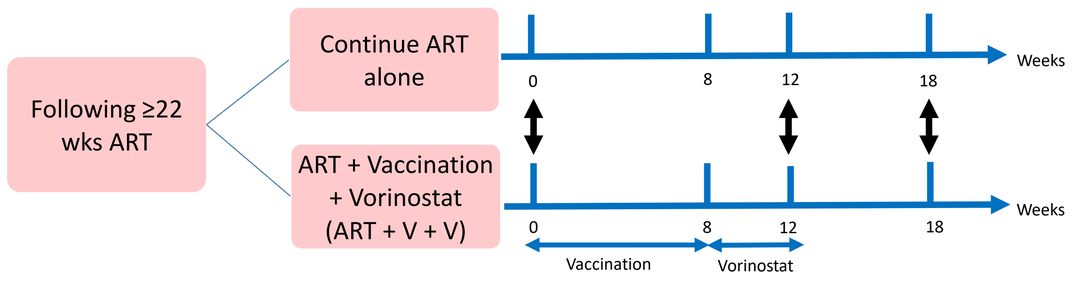
Figure 2: Structure of a neuron and axon including neurofilament



Aim: To determine if there is evidence of neuro-axonal injury following a *"shock and kill"* HIV cure approach in participants who commenced ART during primary HIV infection, using plasma NFL as a surrogate marker

Methods

RIVER[4] is an open-label 1:1 randomised controlled trial in HIV-positive adults initiating ART within 4 weeks of confirmed HIV primary infection, comparing:
- ART alone, versus
- ART with vorinostat (a latency reversing agent) and ChAdV63.HIVconsv prime and MVA.HIVconsv boost T-cell vaccination (ART+V+V)



At randomisation, week 12 and week 18 (see **arrows** above), we measured:
- plasma NFL using an ultra-sensitive Simoa digital immunoassay
- plasma HIV-1 RNA using a single-copy assay

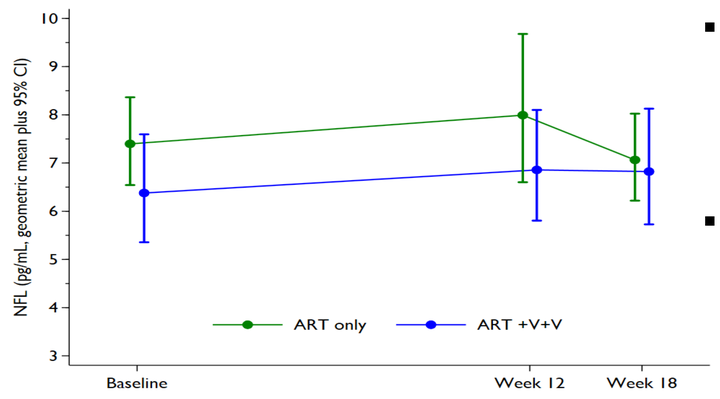
At randomisation and week 12, we measured:
- HIVconsv-specific CD8+ and CD4+ T-cell frequencies by intracellular cytokine staining

Statistical analysis:
- differences in plasma NFL by study arms at each time point: Student's t-test
- changes in plasma NFL over time: mixed models
- associations with baseline clinical parameters: linear regression
- correlations with plasma NFL: rank statistics

Results

- 58 of 60 participants had complete data available
- All participants were male, 69% White, median age 32 years, CD4+ count 696 cells/µL

Figure 3: Longitudinal trends in plasma NFL concentration



- No significant differences in plasma NFL were observed between the three time points **(p = 0.15)**
- No significant differences in plasma NFL were observed by study arm for each time point (Table 1)

TABLE 1: Longitudinal trends in plasma NFL, plasma HIV RNA and HIV-specific T-cell responses

		Baseline: ≥ 22 weeks continuous ART	Week 12: On final day of intervention in the ART+V+V arm	Week 18
Plasma NFL, pg/mL[1]	ART only arm	7.4 (6.5 – 8.4)	8.0 (6.6 – 9.7)	7.1 (6.2 – 8.0)
	ART+V+V arm	6.4 (5.4 – 7.6)	6.9 (5.8 – 8.1)	6.8 (5.7 – 8.1)
	***P* value**	**0.16**	**0.22**	**0.74**
Plasma HIV-1 RNA, copies/mL[2]	ART only arm	16.5 (3 – 30)	9 (1 – 14)	5.5 (1 – 20)
	ART+V+V arm	13 (5 – 23)	5 (1 – 9)	6 (1 – 14)
	***P* value**	**0.56**	**0.21**	**0.81**
% CD154$^+$ IFN-g$^+$ CD4+ cells	ART only arm	0.010 (0.000, 0.024)	0.006 (0.000, 0.014)	
	ART+V+V arm	0.009 (0.000, 0.020)	0.112 (0.048, 0.216)	
	***P* value**	**0.65**	**<0.001**	
% CD107a$^+$ IFN-g$^+$ CD8+ cells	ART only arm	0.076 (0.000, 0.262)	0.063 (0.008, 0.110)	
	ART+V+V arm	0.069 (0.009, 0.362)	0.274 (0.125, 0.668)	
	***P* value**	**0.90**	**<0.001**	

[1] Geometric mean (95% CI)
[2] Median (IQR)

- No significant differences in plasma HIV-1 RNA were observed by study arm at each time point (Table 1) and there was no significant correlation with plasma NFL
- There were significantly higher proportions of HIVconsv-specific T-cell responses at week 12 in ART+V+V (Table 1), but there was no significant correlation with plasma NFL
- In multivariable analysis, baseline plasma NFL was associated with older age only (0.01 increase per year of age, p = 0.004)

Conclusion and Discussion

- Using plasma NFL as a surrogate biomarker, we saw no evidence of increased neuronal injury up to 6 weeks following *"shock and kill"* in RIVER.
- The unchanged plasma NFL concentrations seen may be explained by:
  - the lack of effect of the intervention on plasma viral transcription
  - plasma NFL may not be sensitive enough in this setting
- A limitation is that there was no concurrent CSF sample measurement

Acknowledgements

All the RIVER study participants
RIVER Chief Investigator: Sarah Fidler
RIVER co-investigator and laboratory lead: John Frater
RIVER statisticians: Abdel Babiker, Wolfgang Stöhr
RIVER laboratory investigators: Lucy Dorrell, Tom Hanke, Andrew Lever, Myra McClure, Steve Kaye, Matt Pace, Axel Fun, Mikaila Bandara, Maryam Khan, Andrew Lovell, HongBing Yang, Jakub Kopycinski, Natalia Olejniczak, Helen Brown, Nicola Robinson, Otto Erlwein, Alison Crook
RIVER trial management team: Sarah Pett, Rachel Bennett, Michelle Gabriel, Fleur Hudson, Aminata Sy, Adam Gregory, Hanna Box, Cherry Kingsley, Katie Topping, Mary Rauchenberger, Yinka Sowunmi, Shaadi Shidfar, Dominic Hague, Gemma Wood, Charlotte Russell
RIVER clinical investigators: Sarah Fidler, Sabine Kinloch, Sarah Pett, Julie Fox, Amanda Clarke, Mark Nelson, Margaret Johnson
RIVER Trial Steering Committee (TSC): Independent Members: Eric Sandström , Janet Darbyshire, Frank Post, Chris Conlon, Jane Anderson, Mala Maini
RIVER Independent Data and Monitoring Committee (IDMC): Tim Peto, Peter Sasieni, Veronica Miller, Ian Weller
Community of people living with HIV: Simon Collins, Damian Kelly
CHERUB collaboration
Funders: BHIVA, MRC (MRL00528X1), NIHR Imperial BRC, NIHR Oxford BRC, NIHR Cambridge BRC
Industry partners: MSD, GlaxoSmithKline Biologicals SA
UK Dementia Research Institute, University College London: Henrik Zetterberg, Amanda Heslegrave, Jamie Toombs

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