

No evidence of neuro-axonal injury following a HIV cure strategy: the RIVER trial

Alagaratnam J^{1,2}, Stöhr W³, Toombs J⁴, Heslegrave A⁴, Zetterberg H^{4,5}, Pett S³, Nelson M⁶, Kinloch S⁷, Clarke A⁸, Nwokolo N⁶, Johnson M⁷, Hanke T⁹, Fox J¹⁰, Babiker A³, Frater J⁹, Winston A^{1,2}, Fidler S^{1,2} on behalf of the RIVER trial investigators

¹Imperial College London, UK, ²Imperial College Healthcare NHS Trust, UK, ³MRC Clinical Trials Unit at University College London, UK, ⁴University College London, UK, ⁵University of Gothenburg, Sweden, ⁶Chelsea & Westminster NHS Foundation Trust, UK, ⁷Royal Free Hospital NHS Foundation Trust, UK, ⁸Brighton & Sussex University Hospitals NHS Trust, UK, ⁹University of Oxford, UK, ¹⁰Guy's & St Thomas' NHS Foundation Trust, UK

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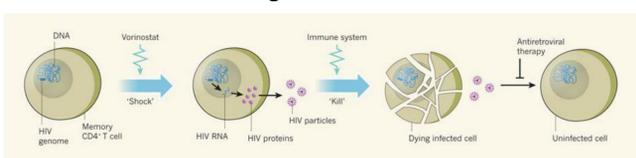
Imperial Biomedical Research Centre

Correspondence: j.alagaratnam@imperial.ac.uk

Introduction

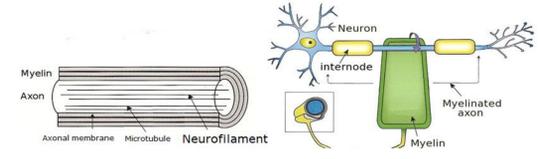
- Research into HIV cure has intensified following reports of patients in long-term HIV remission^{1,2,3} but data on the safety aspects of HIV cure strategies are limited⁴
- The HIV cure 'shock and kill' approach involves stimulation and expression of HIV antigens from latent reservoirs ('shock'), followed by removal of the HIV-expressing cells e.g. by cytotoxic T-lymphocyte clearance ('kill')⁵

Figure 1: HIV 'shock and kill' schematic diagram⁵



- Concerns about the potential life-threatening impact of 'shock and kill' on the central nervous system (CNS), include⁴:
 - 'Shock' (e.g. latency reversal) may cause direct neuronal injury via:
 - upregulation of viral proteins
 - immuno-activation following viral rebound
 - 'Kill' (e.g. immunotherapeutic agents which modify neuroinflammatory responses) may cause indirect neuronal injury via cytokine storms and IRIS
- Cerebrospinal fluid (CSF) neurofilament light (NFL) is a sensitive biomarker of CNS neuro-axonal injury, and is elevated in neurodegenerative diseases including HIV⁶

Figure 2: Structure of a simplified neuron and axon including neurofilament



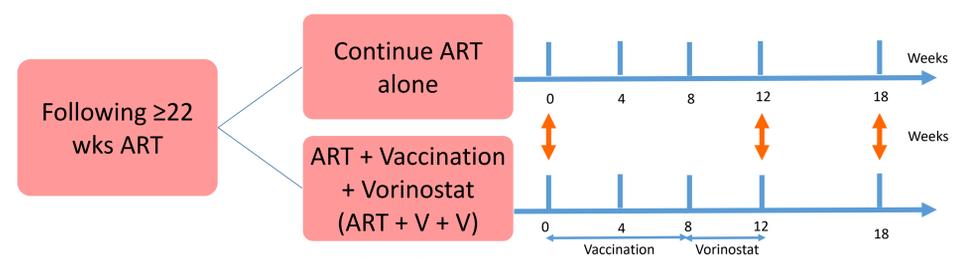
- A novel assay has been developed to measure plasma NFL, which strongly correlates with CSF NFL⁷

Research question:

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 biomarker.

Methods

- RIVER is an open-label 1:1 randomised controlled trial assessing ART alone versus ART with vorinostat (a latency reversing agent) and ChAdV63.HIVconsV prime and MVA.HIVconsV boost T-cell vaccination (ART+V+V) in HIV-positive adults initiating ART within 4 weeks of confirmed primary infection
 - Primary outcome results: no difference in measures of HIV reservoir in circulating CD4+ T cells by study arm⁸



- At randomisation, week 12 and week 18 (see arrows above):
 - plasma NFL was measured using an ultra-sensitive Simoa digital immunoassay
 - plasma HIV-1 RNA was measured using a single-copy assay (SCA)
- Statistical analysis:
 - differences in log₁₀ plasma NFL between study arms and each time point: t-test
 - changes in log₁₀ plasma NFL over time: linear regression
 - associations with baseline clinical parameters (age, ethnicity, duration from seroconversion, mode of HIV acquisition, CD4+ count): mixed models

Acknowledgements

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Results

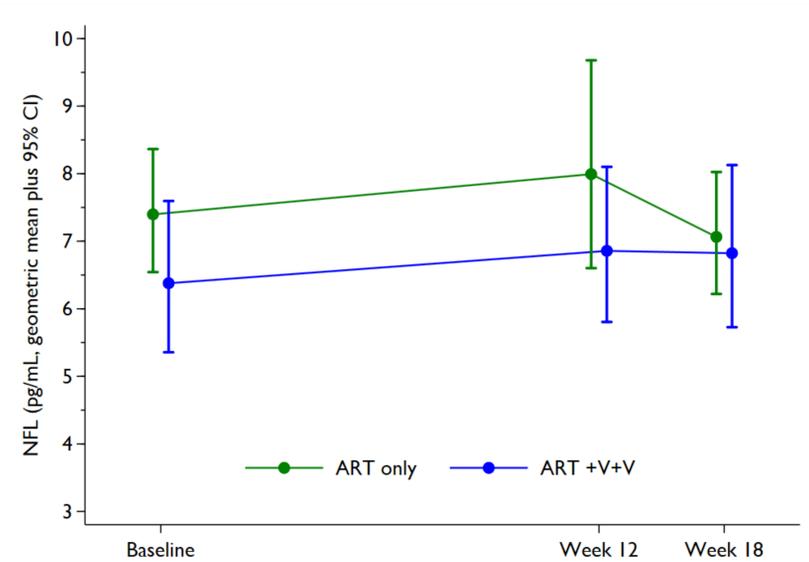
- 58 of 60 participants had complete data available.
- All study participants were male, median (IQR) age was 32 years (28-40), 40 (69%) were Caucasian, 53 (91%) acquired HIV via sex between men and median time since primary HIV infection diagnosis (IQR) was 28 weeks (27-37).

TABLE 1: Longitudinal trends in plasma NFL concentration and ultra-sensitive HIV-1 RNA

		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
Ultra-sensitive HIV 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

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

Figure 3: Longitudinal trends in plasma NFL concentration



- No significant differences in plasma NFL were observed between the three time points ($p = 0.154$), and by study arm for each time point (Table 2)
- No significant differences in plasma ultra-sensitive HIV-1 RNA were observed by study arm for each time point (Table 2)
- No significant correlation was observed between plasma HIV-1 RNA and plasma NFL
- In multivariable analysis, baseline log₁₀ plasma NFL was associated only with older age (0.01 increase per year of age, $p = 0.004$)

Conclusions

Using plasma NFL as a surrogate biomarker, we saw no evidence of neuro-axonal injury up to 18 weeks following ART+V+V in the RIVER trial.

This is reassuring given that plasma NFL is a sensitive biomarker of neuronal injury.

The unchanged plasma NFL concentrations seen by study arm and over time might be explained by the lack of effect of the intervention on viral transcription in the plasma, and on measures of HIV reservoir in circulating CD4+ cells.

References

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