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12th International Symposium on Neuropsychiatry and HIV
14th June 2019

Investigating neuronal injury in a HIV cure strategy

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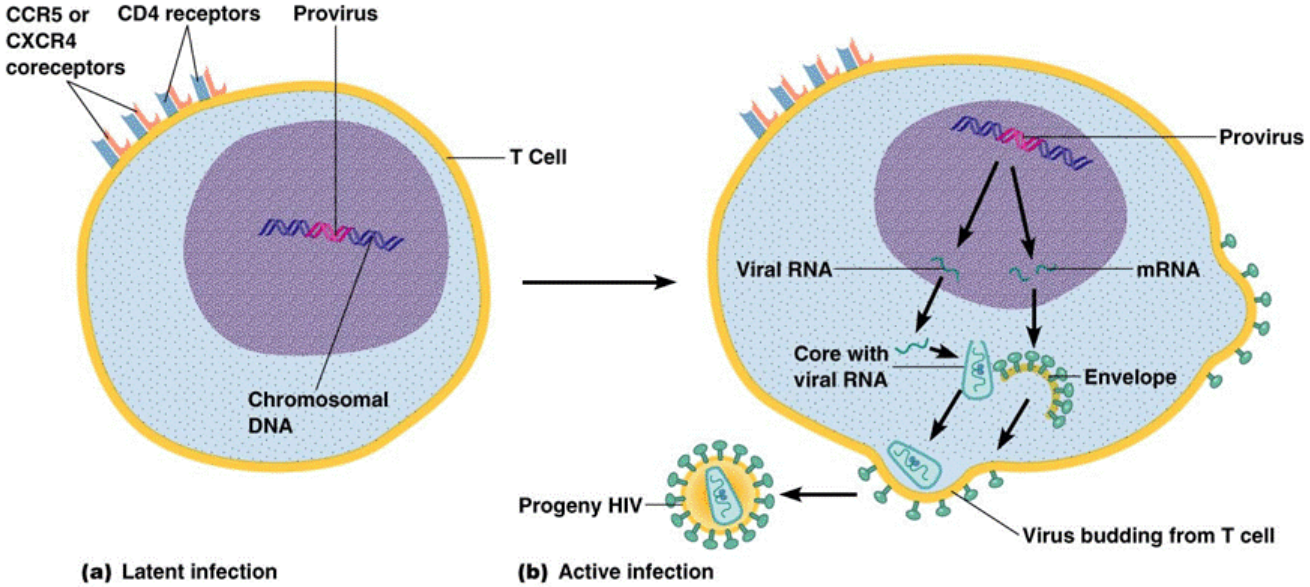
Why can't ART cure HIV? The viral reservoir



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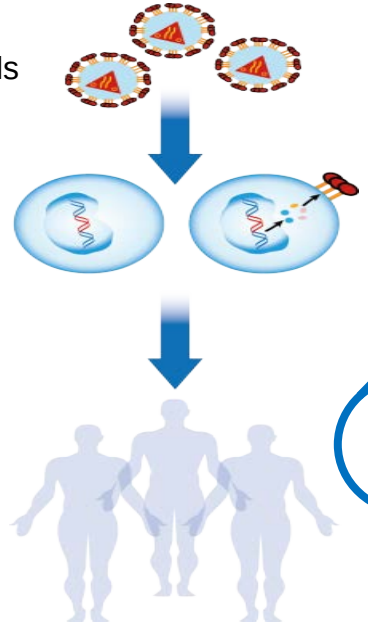
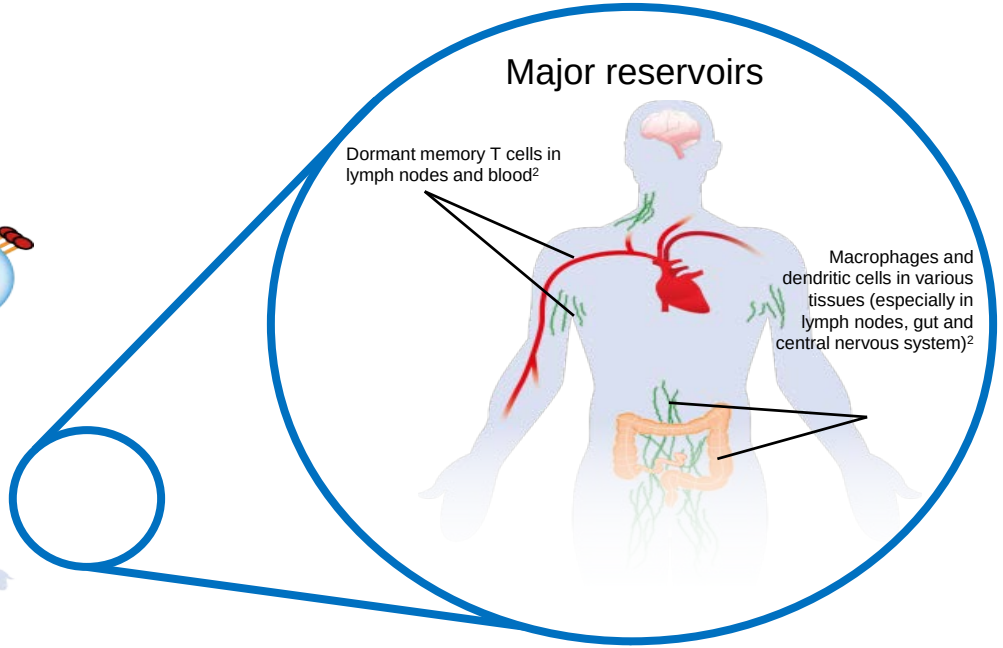
HIV reservoir sites

HIV infects CD4+ cells

Some become resting memory cells; ‘reservoir’





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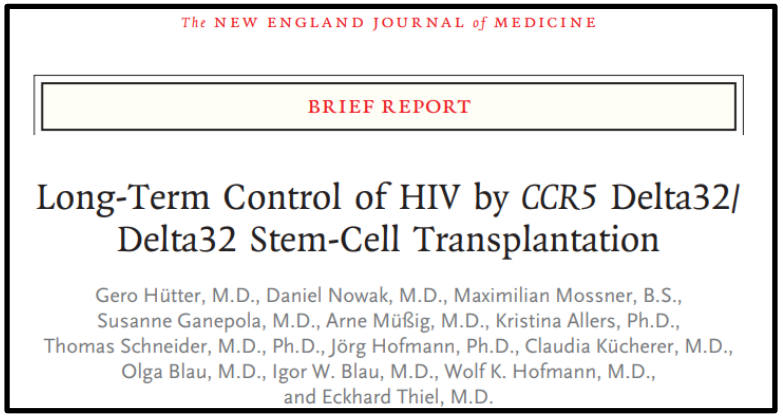
Research into HIV cure has intensified

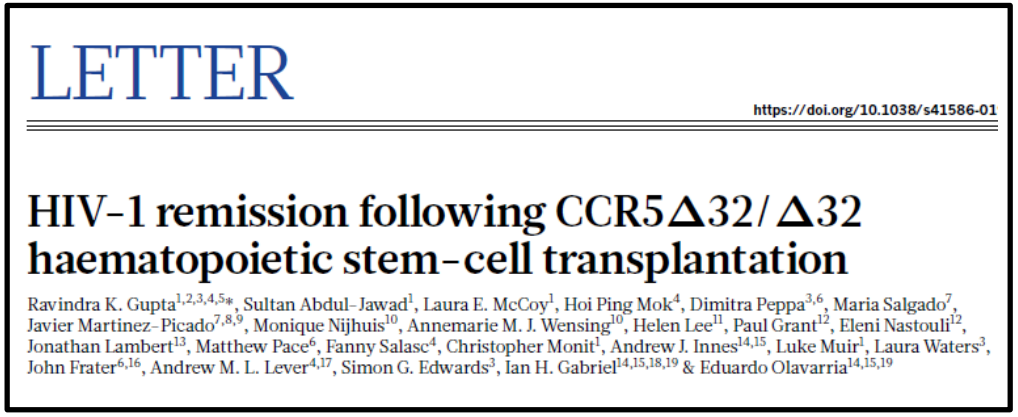


The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Long-Term Control of HIV by *CCR5* Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.



LETTER

https://doi.org/10.1038/s41586-01

HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation

Ravindra K. Gupta[1,2,3,4,5*], Sultan Abdul-Jawad[1], Laura E. McCoy[1], Hoi Ping Mok[4], Dimitra Peppa[3,6], Maria Salgado[7], Javier Martinez-Picado[7,8,9], Monique Nijhuis[10], Annemarie M. J. Wensing[10], Helen Lee[11], Paul Grant[12], Eleni Nastouli[12], Jonathan Lambert[13], Matthew Pace[6], Fanny Salasc[4], Christopher Monit[1], Andrew J. Innes[14,15], Luke Muir[1], Laura Waters[3], John Frater[6,16], Andrew M. L. Lever[4,17], Simon G. Edwards[3], Ian H. Gabriel[14,15,18,19] & Eduardo Olavarria[14,15,19]

Data on the safety aspects of HIV cure strategies are limited[1]

1. Dubé K. Trends Microbiol. 2014 Oct;22(10):547-9

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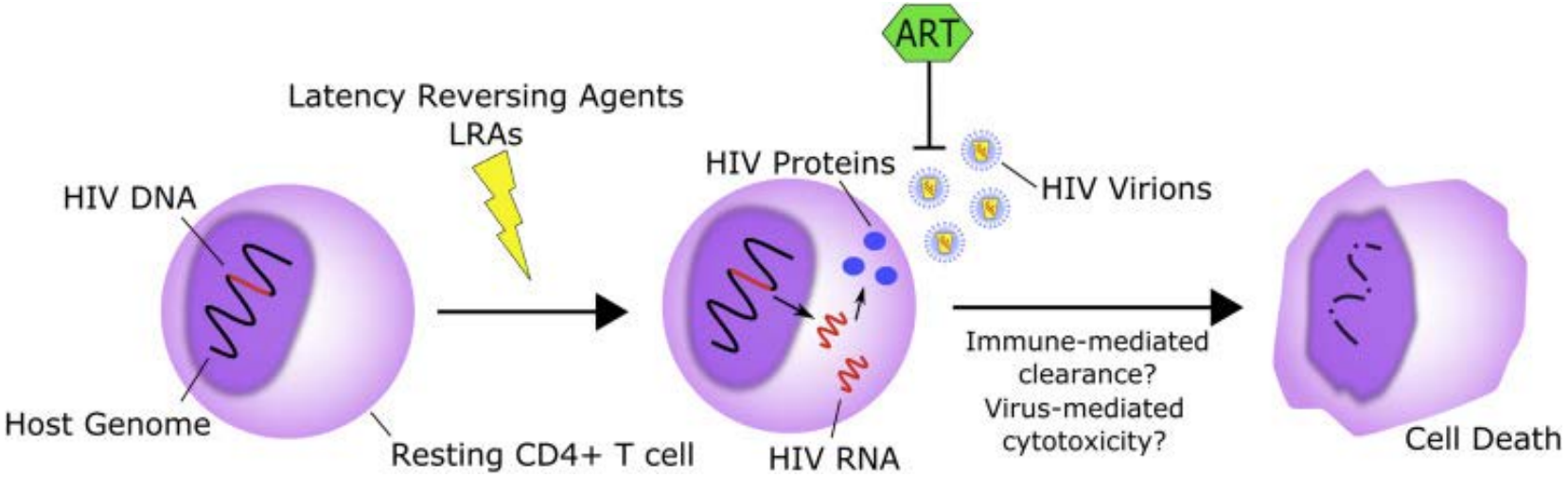
Kick and kill



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Potential CNS risks of ‘kick and kill’

1. **Direct neuronal injury:**
   - Viral rebound releasing viral proteins which are neurotoxic
   - LRA toxicities
2. **Indirect neuronal injury:**
   - CNS IRIS, CD8+ mediated encephalitis
     - Following HIV vaccines which may modify immune responses
   - Inflammation & immune activation
     - Following viral rebound or HIV vaccines
3. **Removal of cells with crucial function**
4. **Reversal of other integrated viruses in a resting phase**

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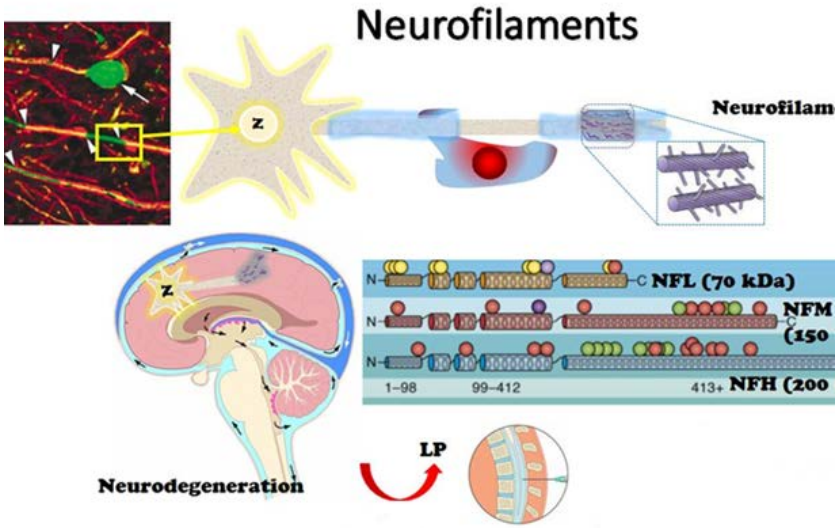
CSF Neurofilament Light Chain protein (NFL)

- NFL maintains structure of axons
- Sensitive and dynamic biomarker of active neuroaxonal damage in the CNS
- Elevated concentrations are reported in a variety of neurodegenerative conditions including HIV



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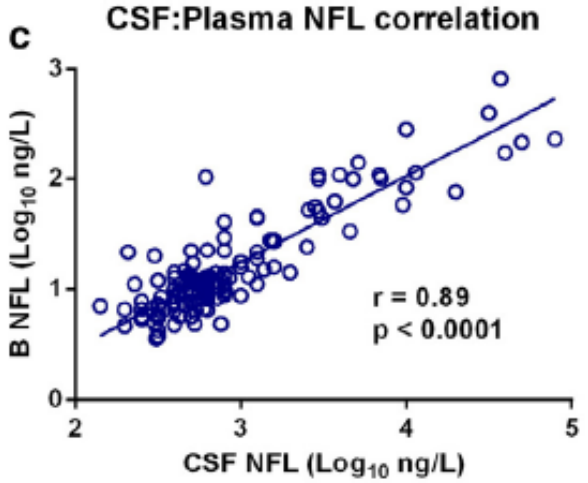
Plasma neurofilament light chain (NFL)

- Highly sensitive assay measuring plasma NFL has recently been developed
- Strongly correlates with CSF NFL
- Removes the barriers of repeated CSF sampling
- Allows more frequent measurements



Gisslen M et al, EBioMedicine 2015 Nov 22;3:135-140.

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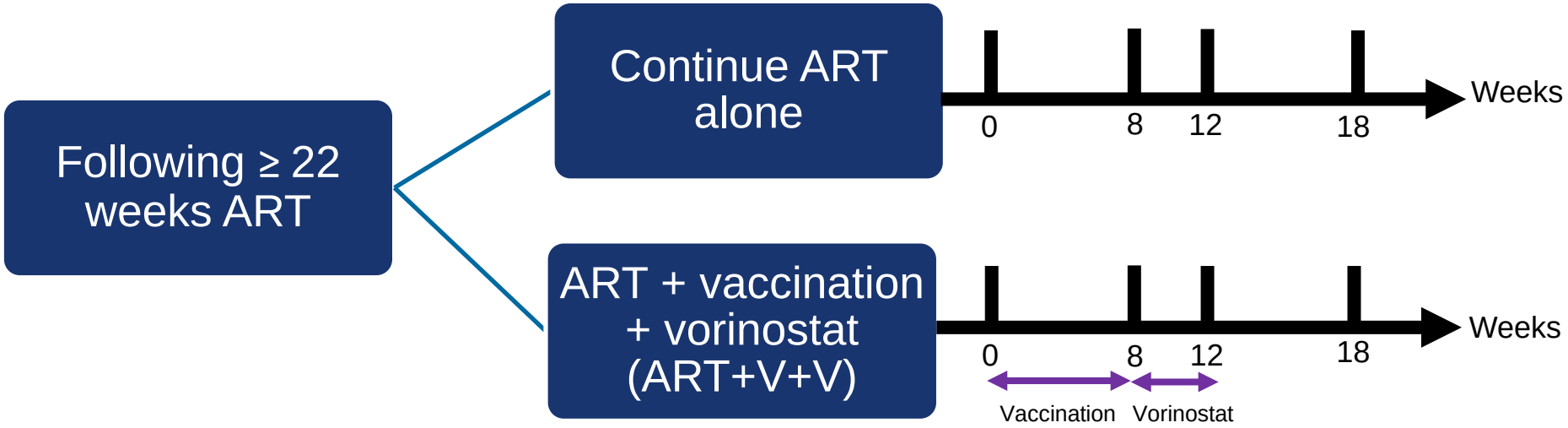
RIVER
Research In Viral Eradication of HIV Reservoirs

Investigating the impact of kick and kill on neuronal injury



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Methods

Marker measured	Method	Timepoints		
		Week 0 (at randomisation, ≥22 weeks cART)	**Week 12** (following completion vaccination and vorinostat)	**Week 18**
Plasma NFL	Simoa digital immunoassay	✓	✓	✓
Ultra-sensitive HIV RNA	Single-copy assay	✓	✓	✓

Statistical analyses:

- Differences between study arms at each time point
- Changes over time
- Correlations
- Associations with baseline clinical parameters

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Research In Viral Eradication of HIV Reservoirs

Results: Baseline demographics

Parameter, median (IQR) or total (%)	n = 58
Age	32 (28 – 40)
Ethnicity - White - Black - Asian or Hispanic - Mixed or Other	 40 (69) 4 (7) 7 (12) 7 (12)
Mode of HIV acquisition - Sex between men - Heterosexual sex - Unknown	 53 (91) 2(3) 3(5)
Weeks since PHI diagnosis	28 (27 – 37)

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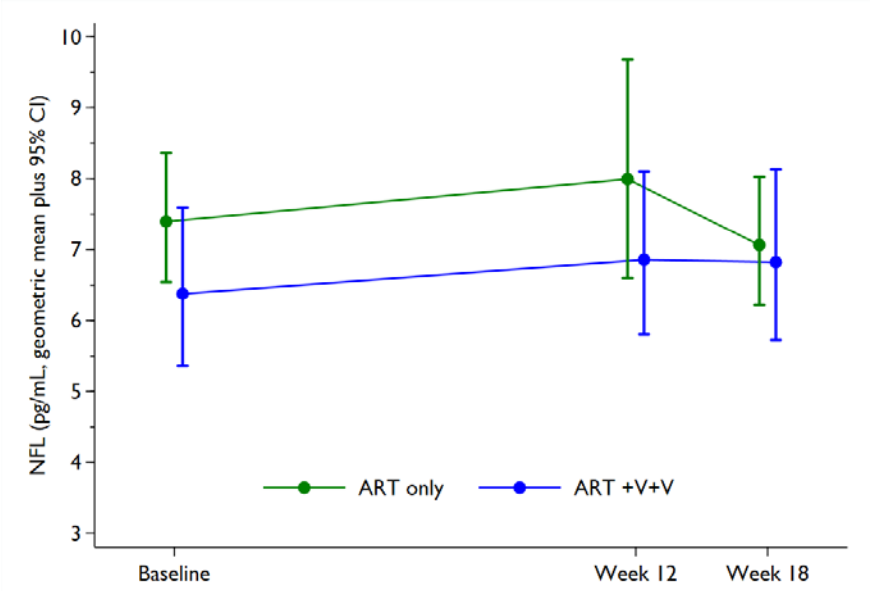
Longitudinal changes in plasma NFL



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No significant difference in plasma NFL by study arm

Study week		Week 0 (At randomisation)	Week 12 (Following completion of V+V)	Week 18
Plasma NFL, pg/mL[1]	ART	7.4 (6.5-8.4)	8.0 (6.6-9.7)	7.1 (6.2-8.0)
	ART+V+V	6.4 (5.4-7.6)	6.9 (5.8-8.1)	6.8 (5.7-8.1)
	P value	**0.160**	**0.218**	**0.742**
Ultra-sensitive HIV RNA, copies/mL[2]	ART	16.5 (3 – 30)	9 (1 – 14)	5.5 (1 – 20)
	ART+V+V	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)

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RIVER Research In Viral Eradication of HIV Reservoirs

Plasma NFL: Correlations and associations

- Ultra-sensitive HIV RNA:
  - No sig. correlation with plasma NFL seen

- Baseline $\log_{10}$ plasma NFL was associated only with older age (0.01 increase per year of age, $p = 0.004$) in multivariate analyses
  - Not associated with ethnicity, duration from seroconversion, mode of HIV acquisition, CD4+ count

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Conclusions

- Using plasma NFL as a surrogate marker, we saw **no evidence of neuro-axonal injury following ART+V+V in the RIVER trial**

- Possible reasons for the unchanged plasma NFL concentrations seen:
  - Lack of effect of the intervention on viral transcription in the plasma and on the HIV reservoir in circulating CD4+ T cells
  - Intervention may not have entered the CNS
  - Plasma NFL not sufficiently sensitive
  - Did not capture the neuronal injury episode (measured too early or too late)

Monitoring for CNS adverse events in HIV cure research remains important

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Further results being presented at IAS, July 2019

- HIV-specific CD4+ and CD8+ T cell responses in RIVER
- Correlations with plasma NFL and HIV RNA

- Monday 22nd July: 12:30pm
- Abstract number: MOPEB274

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RIVER Research In Viral Eradication of HIV Reservoirs

NHS National Institute for Health Research

CHERUB

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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
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CHERUB collaboration
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BHIVA British HIV Association | UCL | University of Oxford | King's College London | Imperial College London | University of Cambridge

Thank you

Questions?

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Extra slides

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Clinically undetectable viraemia in the absence of ART

Sterilising Cure

"INFECTIOUS DISEASE" MODEL

- The 'Berlin' patient
- Aviraemia; no transmission
- No replication competent virus
- No detectable HIV-infected cells

'Functional' Cure

"CANCER" MODEL

- No disease progression
- No CD4 cell loss
- No transmission
- But…no agreed duration

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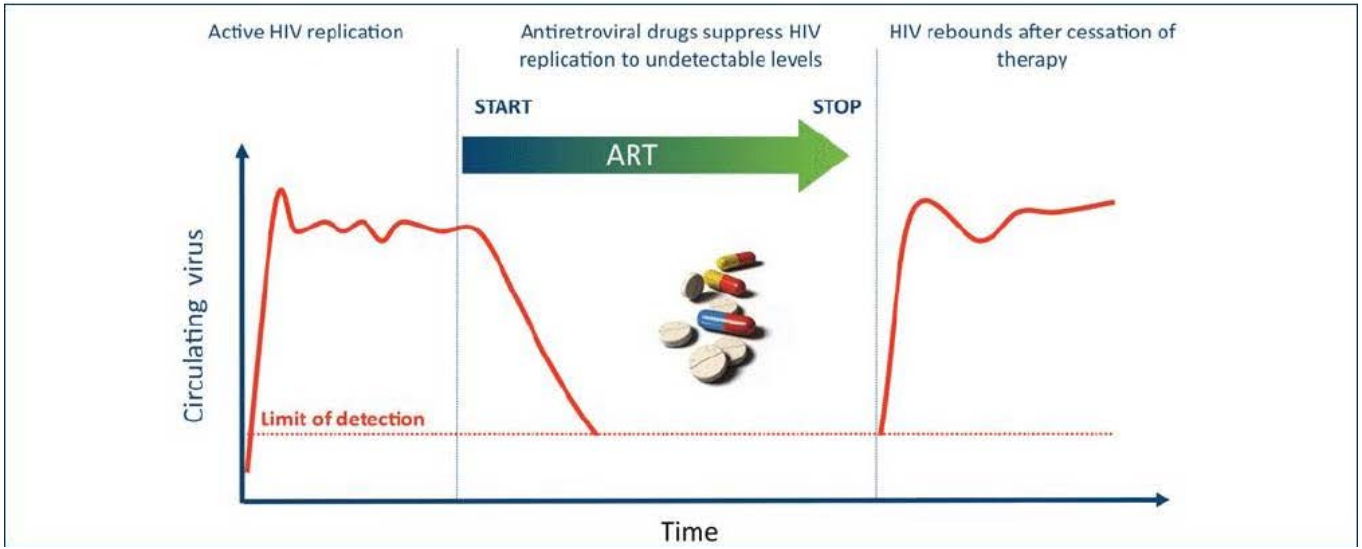
ART alone cannot cure HIV



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HIV cure strategies currently being trialled:

Comparison of different strategies for curing HIV					
Approach	**Summary**	**Cost**	**Scalability**	**Successes**	**Comments**
Genetic	Altering host genome to resist HIV	$$$	×	Berlin patient	Unlikely to be a global cure
Kick and kill	Stimulate HIV expression from reservoir, then clearance of HIV expressing cells	$	✓	HIV expression from reservoir induced using HDACi	2 step approach
Immune based	Alter immune system to clear infected cells	$	??	SIV clearance in Rhesus macaques	May need reservoir stimulation for cure
Early treatment	Start ART in acute infection	$	✓	Post-treatment controllers	Won't help those with chronic infection
ART: antiretroviral treatment; HDACi: histone deacetylase inhibitors					

Adapted from Pace M, et al. Expert Rev Anti Infect Ther. 2014 Jul;12(7):783-91

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CSF NFL

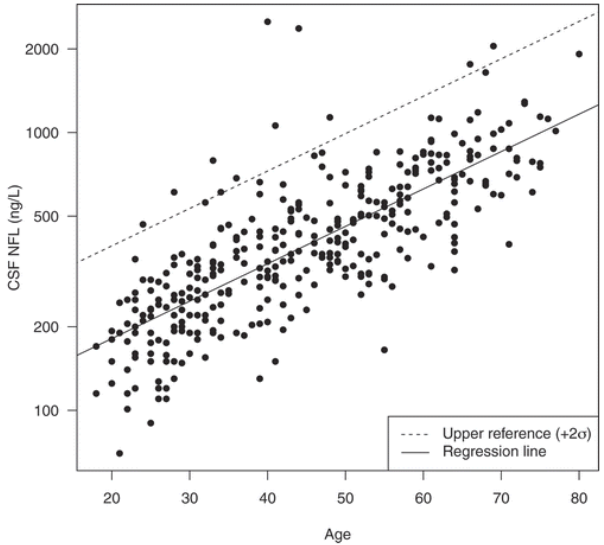

Figure 1: CSF NFL vs age in HIV-negative controls

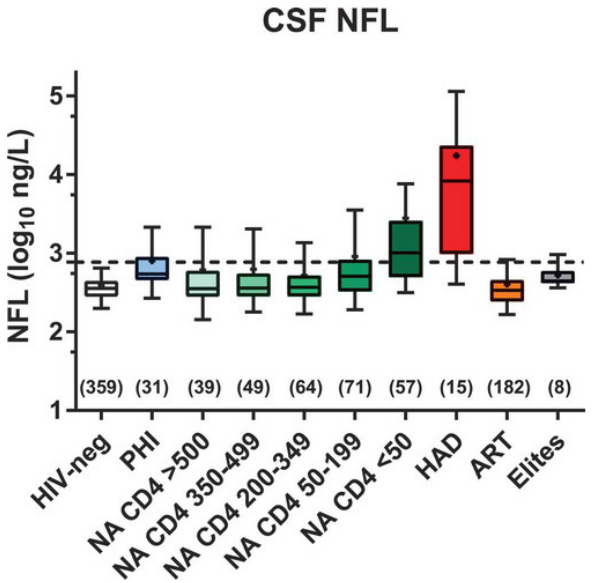

Figure 2: CSF NFL in HIV-positive subjects and HIV-negative controls