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Longitudinal changes in neuronal markers and associations with ART initiation and cognitive function.

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BACKGROUND

Improvements in cognitive function have been described in persons with HIV commencing ART[1].

Simplified dual ART-regimens have demonstrated non-inferiority in maintaining plasma viral suppression, when compared to standard triple ART-regimens[2,3]. Other dual-ART regimens may be used in certain circumstances that are not otherwise recommended as first-line ART, such as NRTI-sparing regimens including a boosted PI and an INSTI.

While initial studies demonstrated viral suppression in the cerebrospinal fluid of persons with HIV on modern, robust dual-ART, further work on the central nervous system safety of such regimens is warranted[4,5].

We assessed longitudinal changes in plasma biomarkers of immune activation, neuronal inflammation and injury, and their associations with cognitive function, in individuals commencing either dual- or triple-ART.

METHODS

Biomarker concentrations were assessed at baseline and after 96 weeks in treatment naive individuals enrolled to a previously reported cognitive sub-study of NEAT-001/ANRS143, who were randomised to commence:

A. darunavir/ritonavir and tenofovir-DF/emtricitabine (triple-ART, n=119)
B. darunavir/ritonavir and raltegravir (dual-ART, n=119)

238 individual had stored plasma samples at week 0 and week 96 and were included for biomarker analysis, of which 172 had corresponding longitudinal cognitive assessments. Plasma biomarkers assessed included **neurofilament light protein (NfL), glial fibrillary acidic protein (GFAP), sCD14, CXCL10, neopterin and IL-6.**

Participants underwent a **neuropsychological test battery at weeks 0 and 96**, assessing **7 cognitive domains affected by HIV**. Cognitive tests included the **trial making test part A and B** (attention and mental flexibility), **digital substitution test** (psychomotor speed), **backward digit span test** (working memory), **free and cued selective reminding test** (retrieval ability and selective memory), **semantic and formal fluency tests** (verbal fluency) and the **frontal assessment battery** (frontal executive function). Raw cognitive test scores were converted to individual domain-specific z-scores, using a norming process which subtracted the mean and divided by the standard deviation (SD) of the total study sample at baseline. **A composite cognitive score (NPZ) was then calculated as an average of the seven z-scores at weeks 0 and 96.**

Multivariable linear regression models, adjusted for age and sex, examined the association between week 0 and week 96 changes in biomarker concentration with:

- Baseline characteristics (CD4 count, composite cognitive test score (NPZ) across 7 domains, duration of known HIV, and smoking status).
- Randomised treatment arm (longitudinal analysis only).

RESULTS

Baseline

- Baseline participant characteristics and biomarker concentrations are displayed in tables 1 and 2, respectively.
- Median age was 38 (IQR 31, 46) years, 87% male and 83% of Caucasian ethnicity.
- Median $\log_{10}$ HIV RNA was 4.73 (IQR 4.23, 5.11) copies/mL and CD4 count 350 (IQR 285, 412) cells/μL.
- Higher W0 biomarker concentrations were associated with lower CD4+ count (NfL, GFAP and CXCL10; p<0.03), higher $\log_{10}$ HIV RNA (sCD14, neopterin and CXCL10; p<0.02) and longer duration of HIV (sCD14; p=0.044).

Week 96

- 94% participants had plasma HIV <50 copies/mL (96% triple-ART, 91% dual-ART, p=0.06).
- NPZ score had increased by a mean of 0.21 points; 0.21 triple-ART vs. 0.27 dual-ART (p=0.46).
- A decline in biomarker concentrations was observed over the study period (table 1).
- NPZ improved by a mean 0.17 points. GFAP, CXCL10, sCD14, neopterin and NfL concentration change scores were negatively associated with change in CD4 (all <0.01) but not with change in NPZ score.
- A greater decline in neopterin concentration was observed with dual-ART (-50%) vs triple-ART (-44%, relative change difference: 13% (95% CI: 1.8%, 26%), p=0.022).
- Change in other biomarkers was not significantly different across arms.

CONCLUSIONS

In treatment naïve persons with HIV commencing ART with dual- or triple-ART, plasma biomarkers of immune activation, neuronal inflammation and injury declined over 96 weeks on ART.

Improvements in neuronal biomarkers were associated with predominantly with improvements in CD4 count, but not with change in cognitive function

Table 1. Baseline participant characteristics.

Baseline characteristic	Overall N = 238[1]	Dual-ART (DRV/r + RGV) N = 119[1]	Triple-ART (DRV/r + TDF/FTC) N = 119[1]
Male gender	208 (87%)	105 (88%)	103 (87%)
Age (years)	38 (31, 46)	35 (31, 44)	40 (31, 48)
White ethnicity	198 (83%)	96 (81%)	102 (86%)
Education (years)	13.0 (10.0, 16.0)	13.0 (10.0, 16.5)	13.0 (9.5, 15.0)
Unknown	46	31	15
Log10 plasma HIV-1 RNA concentration (copies/mL)	4.73 (4.23, 5.11)	4.72 (4.20, 5.19)	4.73 (4.26, 5.00)
CD4 count (cells/mm^3)	350 (285, 412)	350 (280, 411)	350 (288, 415)
<50	8 (3.4%)	2 (1.7%)	6 (5.0%)
50-199	18 (7.6%)	9 (7.6%)	9 (7.6%)
200-349	92 (39%)	48 (40%)	44 (37%)
350-499	107 (45%)	51 (43%)	56 (47%)
≥500	13 (5.5%)	9 (7.6%)	4 (3.4%)
Nadir CD4 cell count nadir (cells/mm^3)	336 (261, 388)	331 (243, 383)	342 (267, 398)
CD4:CD8 ratio	0.37 (0.26, 0.53)	0.38 (0.25, 0.56)	0.36 (0.26, 0.53)
Unknown	12	6	6
NPZ score (Week 0)	0.07 (-0.36, 0.51)	0.03 (-0.34, 0.57)	0.09 (-0.36, 0.46)
Unknown	52	35	17

[1]n (%); Median (Q1, Q3). Abbreviations: DRV/r (Darunavir/ritonavir), FTC (Emtricitabine), NPZ-7 (composite cognitive z-score of 7 neuropsychological tests), RGV (Raltegravir), TDF (Tenofovir disoproxil).

Table 2. Relative change in biomarker concentrations after 96 weeks on antiretroviral therapy

	Week 0		Week 96				
Biomarker	Median (IQR)[1]	N	Median (IQR)[1]	N	**Relative change (%)[2]**	**95% CI[2,3]**	***p*[2]**
NfL (pg/mL)	6.4 (4.6, 8.8)	238	6.1 (4.7, 8.2)	238	-4.4	-9.1, +0.5	0.075
GFAP (pg/mL)	67.9 (54.0, 95.9)	238	62.1 (49.7, 77.8)	238	-14.4	-18.3, -10.3	<0.001
sCD14 (ng/mL)	1,405.9 (1,182.7, 1,655.6)	238	1,291.9 (1,081.6, 1,555.3)	238	-6.8	-9.6, -4.0	<0.001
Neopterin (nmol/L)	14.0 (10.4, 18.5)	238	7.5 (5.7, 9.5)	238	-47.4	-50.1, -44.5	<0.001
CXCL10 (pg/mL)	2,074.0 (1,350.5, 2,954.4)	238	804.6 (615.0, 1,080.5)	238	-58.8	-61.6, -55.7	<0.001
IL6 (pg/mL)	2.2 (1.4, 3.1)	237	1.4 (0.9, 2.3)	238	-29.5	-36.1, -22.4	<0.001

[1]Median (Quartile 1, Quartile 3), [2]Paired t-test, [3]CI = Confidence Interval. Abbreviations: CXCL10 (C-X-C motif chemokine 10), GFAP (Glial fibrillary acidic protein), IL6 (Interleukin 6), NfL (Neurofilament light), sCD14 (Soluble CD14).

Table 3. Multivariate linear regression analysis of factors associated with log10 biomarker concentrations at baseline and change over 96 weeks.

	NFL ($\log^{10}$pg/mL)			GFAP ($\log^{10}$pg/mL)			IL6 ($\log^{10}$ pg/mL)			CXCL10 ($\log^{10}$ pg/mL)			sCD14 ($\log^{10}$ ng/mL)			Neopterin ($\log^{10}$ nmol/L)		
Characteristic	**10^{β}**	**95% CI[1]**	***p***	**10^{β}**	**95% CI[1]**	***p***	**10^{β}**	**95% CI[1]**	***p***	**10^{β}**	**95% CI[1]**	***p***	**10^{β}**	**95% CI[1]**	***p***	**10^{β}**	**95% CI[1]**	***p***
Baseline																		
CD4 (cells/mm^3)																		
<50 (Reference)	—	—		—	—		—	—		—	—		—	—		—	—	
50-199	0.51	0.35, 0.74	**<0.001**	0.97	0.69, 1.37	0.858	1.10	0.60, 2.01	0.765	0.65	0.42, 1.02	0.060	1.06	0.83, 1.34	0.657	1.13	0.80, 1.60	0.474
200-349	0.48	0.35, 0.67	**<0.001**	0.63	0.47, 0.85	**0.003**	0.90	0.53, 1.53	0.697	0.64	0.43, 0.94	**0.022**	0.93	0.75, 1.15	0.491	0.87	0.64, 1.17	0.358
350-499	0.44	0.32, 0.61	**<0.001**	0.62	0.46, 0.84	**0.002**	0.91	0.54, 1.54	0.720	0.64	0.44, 0.95	**0.026**	0.96	0.78, 1.18	0.685	0.89	0.66, 1.20	0.429
≥500	0.46	0.31, 0.69	**<0.001**	0.61	0.42, 0.89	**0.010**	0.76	0.39, 1.47	0.415	0.57	0.35, 0.93	**0.023**	1.07	0.82, 1.39	0.610	0.81	0.56, 1.18	0.270
$\log^{10}$ HIV-1 RNA (copies/mL)	1.08	0.97, 1.20	0.176	1.04	0.94, 1.15	0.413	1.24	1.04, 1.48	**0.016**	1.50	1.32, 1.70	**<0.001**	1.09	1.02, 1.17	**0.016**	1.35	1.22, 1.49	**<0.001**
Duration known HIV (years)[3]	1.02	0.94, 1.11	0.579	0.98	0.91, 1.06	0.697	1.09	0.95, 1.25	0.203	1.06	0.96, 1.17	0.258	1.06	1.00, 1.12	**0.044**	1.03	0.96, 1.12	0.403
Change																		
CD4 (cells/mm^3)	0.53	0.42, 0.67	**<0.001**	0.65	0.50, 0.85	**0.002**	0.82	0.47, 1.41	0.464	0.43	0.29, 0.64	**<0.001**	0.70	0.60, 0.83	**<0.001**	0.56	0.42, 0.75	**<0.001**
NPZ score	1.05	0.89, 1.23	0.579	1.04	0.86, 1.25	0.700	1.02	0.69, 1.51	0.906	0.91	0.69, 1.21	0.515	1.02	0.90, 1.14	0.792	1.01	0.82, 1.24	0.922

[1]CI = Confidence Interval of 10^{β} (relative change ratio (<1 indicating a decrease, and >1 an increase). P-values highlighted in bold indicate factors significantly associated with baseline $\log^{10}$ biomarker concentrations.

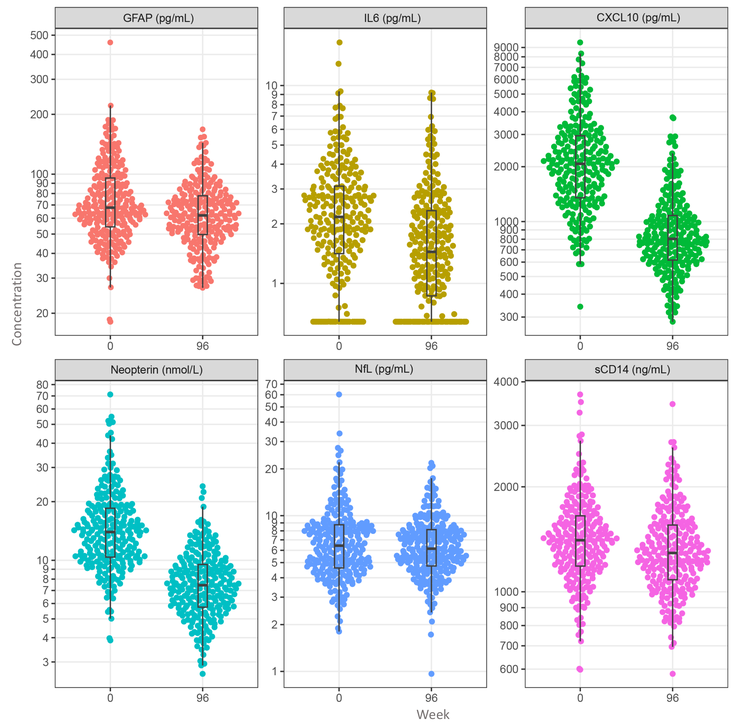


Figure 1. Plasma biomarker concentrations at weeks 0 and 96.
From the top right of the figure, concentrations of plasma GFAP (Glial fibrillary acidic protein), IL6 (interleukin 6), CXCL10 (C-X-C motif chemokine 10), Neopterin, NfL (Neurofilament light) and sCD14 (soluble CD14) at weeks 0 and 96. Median and interquartile range shown as box and whisker plots.

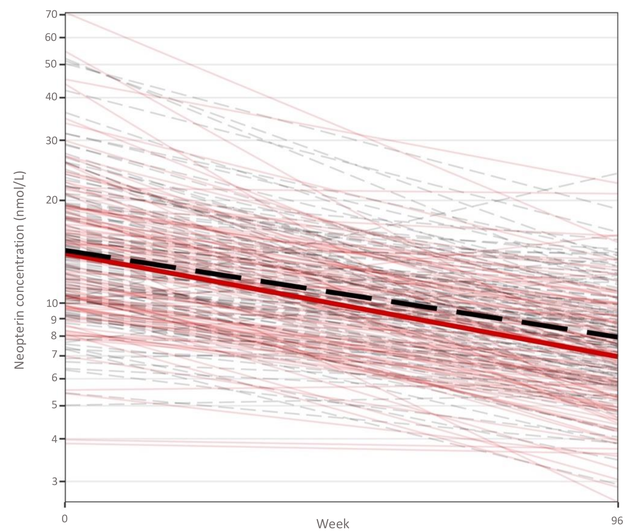


Figure 2. Change in neopterin concentrations over 96 weeks by drug arm.
Median change in Neopterin concentration between weeks 0 and week 96 displayed with red line (dual-ART; darunavir/ritonavir and raltegravir) and dashed black line (triple-ART; darunavir/ritonavir, tenofovir disoproxil/emtricitabine).

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References: 1. JAIDS. 2017;74:185-2. 2. CID. 2022;75(6):975-86, 3. JAIDS. 2020;83(3):310-8., 4. JID. 2021;223(11):1928-33., 5. JAC. 2020;75(3):648-55.