0455

A Cross-Sectional Analysis of Antiretroviral Regimen Activity in Cerebrospinal Fluid

Fletcher CV, McCarthy C, Bosch RJ, Spudich S, Podany AT, Avedissian S, Winchester LC, Mykris T, Weinhold J, Macatangay BJ, Cyktor JC, Eron J, Mellors J, Gandhi RT and McMahon D.

University of Nebraska Medical Center, Omaha; Harvard T.H. Chan School of Public Health, Boston; Yale University, New Haven; University of North Carolina, Chapel Hill; University of Pittsburgh, Pittsburgh; and Massachusetts General Hospital, Boston.

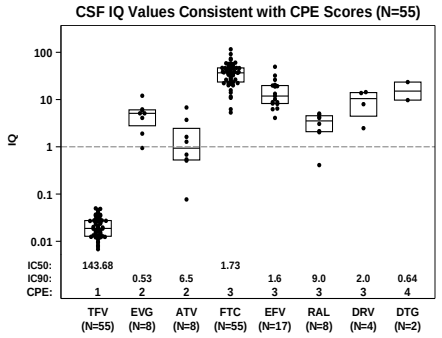
METHODS

- Participants started ART in ACTG treatment-naïve trials and were on ART for ≥2 years with well-documented sustained plasma viral suppression.
- CSF ARV concentrations, cell-associated HIV DNA and inflammatory biomarkers were measured at LP. ARV levels were quantified by LC/MS/MS.
- inhibitory quotients (IQ) were calculated for each drug in ART regimen as ratio of measured CSF concentration to literature values for in vitro inhibitory concentration. Participants were ranked (low to high) by IQs for TFV, FTC, and third ARV, then drug ranks were averaged to give an overall rank for the ART regimen; a participant with highest IQ for all individual components would have the highest regimen IQ score.
- Rank-based analyses were used to evaluate associations among regimen IQ ranks and biomarkers.

RESULTS

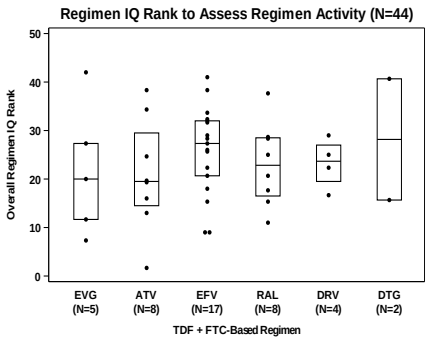
- CSF ARV concentrations were available on 55 participants on TDF/FTC-based regimens: 52 males (95%); 40 (73%) white non-Hispanic, 10 (18%) black non-Hispanic; median age, 48 yrs; median yrs on ART, 8.1 yrs; median CD4 count, 651 cells/μL; and 54 (98%) with plasma HIV-RNA <40 copies/mL and one with 63 copies/mL.
- Third drugs in ART regimens included: EFV (n=17), ATV/r (8), EVG/c (8), RAL (8), DRV/r (4) and DTG (2). RPV and NVP (n=8) were not analyzed as CSF levels were unavailable. Figure 1 shows CSF IQ values for ARV drugs, which were consistent with CNS Penetration Effectiveness (CPE) scores.
- Associations among ART CSF IQ and HIV-1 persistence measures were restricted to participants treated during chronic infection (n=44). Average regimen IQ rank was slightly higher in those with undetectable CSF HIV DNA vs detectable (Figure 3; median [Q1, Q3]: 25 [19.7, 34.3] for TND vs. 21.2 [15.7, 28.7] for detected); p=0.25. CSF neopterin was positively associated with average IQ rank (Table 4; Spearman r = 0.28, p = 0.07 adjusting for age and pre-ART CD4:8 ratio).

Fig 1. CSF IQ SCORES OF EACH ARV



IC_{50} used where IC_{90} unavailable.

Fig 2. ART REGIMEN AVG CSF IQ RANKS



Higher rank: higher regimen IQ in CSF.

CONCLUSIONS and FUTURE DIRECTIONS

- **CSF IQ values (Figure 1) are consistent with the hierarchy of CPE scores (higher IQ <–> higher CPE), but allow interpatient variability the CPE does not.**
- **The ART regimen IQ rank (Figure 2) in these subjects ranged from 1.7 to 42, which may provide improved discrimination of the CSF activity of a subject's ART regimen.**
- **The ART regimen IQ rank is a new approach to assess regimen vs individual drug activity. This tool provides a basis for continued work to expand regimen IQ data and investigate longitudinal relationships with biomarkers of HIV CSF persistence and inflammation.**

Table 1. Participant characteristics at time of LP for participants on TDF + FTC

		Total (N=55)
A5321 group	1	49 (89%)
	2	4 (7%)
	3	2 (4%)
Sex	Male	52 (95%)
	Female	3 (5%)
Race/ethnicity	White Non-Hispanic	40 (73%)
	Black Non-Hispanic	10 (18%)
	Hispanic (Regardless of Race)	4 (7%)
	American Indian, Alaskan Native	1 (2%)
Age (years) at LP	Median	48
	Q1, Q3	40, 55
	Min, Max	26, 72
	N	55
Years on ART at LP	Median	8.1
	Q1, Q3	6.2, 9.3
	Min, Max	2.3, 16.4
	N	55
Other ARVs in regimen	EFV	17 (31%)
	EVG COBI	8 (15%)
	RAL	8 (15%)
	RTV ATV	8 (15%)
	RPV	7 (13%)
	RTV DRV	4 (7%)
	DTG	2 (4%)
	NVP	1 (2%)
CD4+ T-cell count (cells/mm³) most recent prior to LP	Median	651
	Q1, Q3	502, 831
	Min, Max	240, 1,429
	N	55
Plasma HIV-1 RNA (cps/mL) most recent prior to LP	<40	54 (98%)
	≥40	1 (2%)
If ≥40 copies/mL	Median	63
	Q1, Q3	63, 63
	Min, Max	63, 63

In ACTG 5321, sex at birth was collected, but gender was not collected.

RESULTS

Table 2: ARV Concentrations (ng/mL) in CSF and Plasma for Participants on TDF + FTC (N=55)

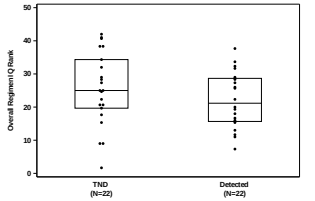
		CSF	Plasma
TFV	Median	3.2	88.5
	Q1, Q3	2.1, 4.7	61.5, 167.1
	Min, Max	0.5, 9.5	5.0, 290.1
	N	55	55
FTC	Median	93.5	303.5
	Q1, Q3	50, 113	127.0, 652.8
	Min, Max	10.6, 250.0	5, 2,047
	N	55	55
EFV	Median	19.0	2,766
	Q1, Q3	13.2, 31.7	1,873, 3,768
	Min, Max	6.5, 79.1	895, 10,600
	N	17	17
DTG	Median	10.6	2,178.5
	Q1, Q3	6.2, 15.0	1,789, 2,568
	Min, Max	6.2, 15.0	1,789, 2,568
	N	2	2
RAL	Median	32.1	468.5
	Q1, Q3	18.8, 41.0	235, 785
	Min, Max	3.7, 45.4	80.4, 2,240.0
	N	8	8
ATV	Median	6.4	847.5
	Q1, Q3	3.4, 17.4	334.1, 1,618.6
	Min, Max	0.5, 44.2	10, 3,965
	N	8	8
RTV	Median	0.5	145.8
	Q1, Q3	0.5, 0.5	48.6, 218.4
	Min, Max	0.5, 1.7	10.0, 912.9
	N	12	12
DRV	Median	21.7	2,307
	Q1, Q3	10.5, 28.1	1,345.0, 4,467.5
	Min, Max	5.0, 28.7	1,219, 5,792
	N	4	4

Table 3: CSF-to-Plasma ARV Concentration Ratio by Tertile of Average Time Since Last Dose of ARV (hrs) to LP (N=55)

		0-10 hrs post-dose	>10-16 hrs post-dose	>16-30 hrs post-dose
TFV	Median	3.1%	3.6%	3.8%
	Q1, Q3	1.7%, 4.0%	2.7%, 4.9%	2.9%, 5.5%
	Min, Max	0.2%, 5.3%	2.2%, 6.1%	2.0%, 10.0%
	N	19	18	18
FTC	Median	11.4%	32.3%	45.8%
	Q1, Q3	9.1%, 26.8%	28.6%, 38.6%	34.3%, 58.2%
	Min, Max	1.4%, 52.6%	14.3%, 71.4%	19.0%, 212.0%
	N	19	18	18
EFV	Median	0.7%	0.8%	0.9%
	Q1, Q3	0.3%, 0.8%	0.7%, 0.8%	0.7%, 1.1%
	Min, Max	0.3%, 0.8%	0.5%, 1.0%	0.7%, 1.1%
	N	3	11	3
DTG	Median	0.5%	-	-
	Q1, Q3	0.3%, 0.6%	-	-
	Min, Max	0.3%, 0.6%	-	-
	N	2	0	0
RAL	Median	7.2%	5.2%	4.6%
	Q1, Q3	4.0%, 9.5%	5.2%, 5.2%	4.6%, 4.6%
	Min, Max	1.6%, 11.5%	5.2%, 5.2%	4.6%, 4.6%
	N	6	1	1
ATV	Median	0.8%	1.1%	1.2%
	Q1, Q3	0.5%, 1.1%	1.1%, 1.1%	1.1%, 3.2%
	Min, Max	0.5%, 1.1%	1.1%, 1.1%	1.1%, 5.0%
	N	3	1	4
DRV	Median	0.3%	1.4%	0.4%
	Q1, Q3	0.3%, 0.3%	0.9%, 1.9%	0.4%, 0.4%
	Min, Max	0.3%, 0.3%	0.9%, 1.9%	0.4%, 0.4%
	N	1	2	1

RESULTS

Figure 3. CSF HIV RNA Detection by ART Regimen IQ Rank



Target not detected (TND): results with reported qualifier "<"

Average regimen rank and CSF HIV DNA detection. Average regimen IQ rank was slightly higher in those with undetectable CSF HIV DNA vs detectable (median [Q1, Q3]: 25 [19.7, 34.3] for TND vs. 21.2 [15.7, 28.7] for detected.

Table 4. Spearman rank-based correlation between average rank of TFV_{24hr}, IQ_{3rd}, FTC_{24-hr}, IQ_{FTC}, and IQ_{3rd} of third drug and each CSF inflammatory biomarker (N=44)

	Spearman	P-value	Partial Spearman	P-value
CSF IL-6 (pg/mL)	0.16	0.31	-0.12	0.45
CSF IP-10 (pg/mL)	0.05	0.72	-0.02	0.89
CSF MCP-1 (pg/mL)	0.15	0.33	0.12	0.43
CSF neopterin (nMol/L)	0.36	**0.018**	0.28	0.07
CSF sCD14 (ng/mL)	0.23	0.14	0.14	0.39
CSF sCD163 (ng/mL)	0.07	0.66	-0.07	0.67

Note: Partial correlations were calculated adjusting for age at LP and pre-ART CD4:CD8 ratio.

Among CSF inflammatory biomarkers, CSF neopterin was positively associated with average IQ rank (Spearman = 0.36, p=0.018; Partial Spearman r = 0.28, p = 0.07 adjusting for age and pre-ART CD4:8 ratio).