A New Measure of ART Activity in CSF and Association with Persistence and Cognitive Function

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METHODS

- Participants were on antiviral therapy (ART) for a median of 8.1 years with sustained plasma HIV suppression at time of lumbar puncture (LP).
- Cerebrospinal fluid (CSF) antiviral (ARV) concentrations, cell-associated HIV DNA and inflammatory biomarkers were measured at LP. ARV levels were quantified by LC/MS/MS.
- Population pharmacokinetic (PK) modeling was used to estimate CSF drug exposure.
- A neuropsychological test battery (outcome=global deficit score, GDS) was administered just prior to or at LP.
- CSF inhibitory quotients (IQ) were calculated for each ARV in a regimen as a ratio of predicted CSF trough to literature values for in vitro HIV inhibitory concentration (i.e., IC_{50}, IC_{90}, [**Figure 1**]). The geometric mean of CSF IQs of all drugs in each participant's ARV regimen was calculated (ART-IQ-GeoM, [**Figure 2**]).
- Statistical analyses evaluated associations among the ART-IQ-GeoM and CSF HIV DNA, biomarkers, and GDS.

RESULTS

- CSF ARV levels were measured in 44 chronic-treated participants on TDF/FTC-based ART: 43 (98%) male sex at birth; 36 (97% of 37) male gender; 33 (75%) white non-Hispanic, 6 (14%) black non-Hispanic; median age, 49 yrs; median CD4 count, 642 cells/µL; 43 (98%) with plasma HIV RNA <40 copies/mL **(Table 1).**
- Third drugs in ARV regimens were: EFV (n=17), ATV/r (8), RAL (8), EVG/c (5), DRV/r (4) and DTG (2).
- The median (Q1, Q3) ART-IQ-GeoM was higher in those with undetectable vs detectable CSF HIV DNA 0.9 (0.5, 1.6) vs 0.5 (0.3, 0.9), p=0.027 (**Table 2 & Figure 3**). A rank-based analysis gave similar findings.
- Higher ART-IQ-GeoM was associated with lower GDS (i.e., better global cognitive function, Spearman: -0.30, p=0.05, **Table 3**).
- There was no association between CSF inflammatory biomarkers and ART-IQ-GeoM (**Table 4**).

Fig 1. CSF IQ SCORES OF EACH ARV

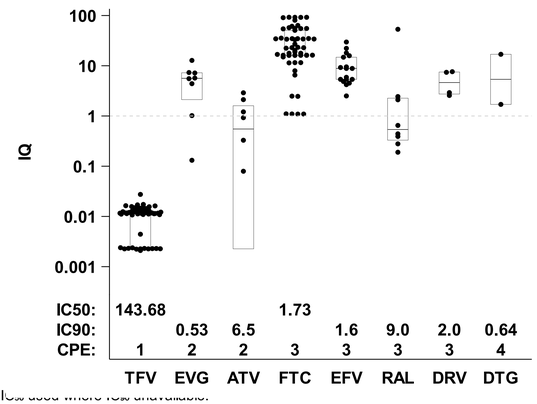
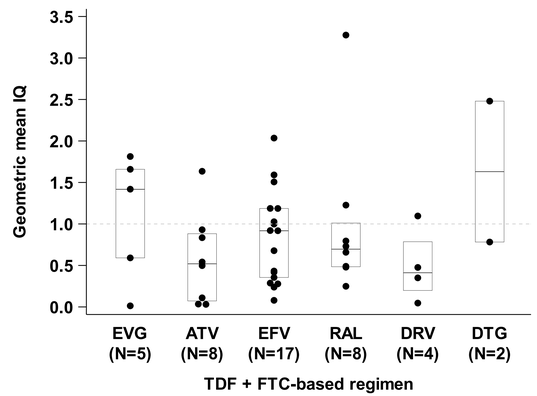


Fig 2. ART-IQ-GeoM CSF IQ RANKS



Abbreviations: TFV, tenofovir disoproxil fumarate; FTC, emtricitabine; EFV, efavirenz; DTG, dolutegravir; RAL, raltegravir; EVG, elvitegravir; ATV, atazanavir; DRV, darunavir/ritonavir; IQ, inhibitory quotients; CSF, cerebrospinal fluid; IC, inhibitory concentration; CPE, CNS penetration effectiveness score; ARV, antiviral agent

CONCLUSIONS and FUTURE DIRECTIONS

- **The ART IQ metric is a new approach to assess ART regimen activity (vs. only individual drugs).**
- **Higher ART-IQ-GeoM was associated with a lack of detection of CSF HIV DNA and better global cognitive function.**
- **These findings suggest ART regimen activity affects HIV persistence in CSF. This tool provides a basis for further investigations of relationships between regimen activity and biomarkers of HIV persistence in the CSF and other viral reservoirs.**

Table 1: Patient demographics

		Total (N=44)
Sex	Male	43 (98%)
	Female	1 (2%)
Gender	N	37
	Male	36 (97%)
	Female	1 (3%)
Race/ethnicity	White Non-Hispanic	33 (75%)
	Black Non-Hispanic	6 (14%)
	Hispanic (Regardless of Race)	4 (9%)
	American Indian, Alaskan Native	1 (2%)
Age (years) at LP	N	44
	Median	49
	Q1, Q3	42, 57
	Min, Max	26, 72
Years on ART at LP	N	44
	Median	8.1
	Q1, Q3	6.3, 9.4
	Min, Max	5.4, 16.4
Other ARVs in regimen	EFV	17 (39%)
	RAL	8 (18%)
	RTV ATV	8 (18%)
	EVG COBI	5 (11%)
	RTV DRV	4 (9%)
	DTG	2 (5%)
Pre-ART CD4+ T-cell count (cells/mm³)	N	44
	Median	267
	Q1, Q3	139, 316
	Min, Max	17, 533
CD4+ T-cell count (cells/mm³) most recent prior to LP	N	44
	Median	642
	Q1, Q3	498, 822
	Min, Max	240, 1,099
Pre-ART CD4:CD8 ratio	N	44
	Median	0.2
	Q1, Q3	0.1, 0.4
	Min, Max	0.0, 1.3
CD4:CD8 ratio most recent prior to LP	N	44
	Median	1.0
	Q1, Q3	0.7, 1.3
	Min, Max	0.4, 2.0
Pre-ART plasma HIV-1 RNA (log_{10}cps/mL)	N	44
	Median	4.7
	Q1, Q3	4.5, 5.0
	Min, Max	3.7, 6.1
Plasma HIV-1 RNA (cps/mL) most recent prior to LP	<40	43 (98%)
	≥40	1 (2%)

Abbreviations: EFV, efavirenz; DTG, dolutegravir; RAL, raltegravir; EVG, elvitegravir; ATV, atazanavir; DRV, darunavir/ritonavir; LP, lumbar puncture; ART, antiviral therapy

RESULTS

Table 2: CSF HIV DNA vs. measures of ARV drug activity in [IQ-based approach for 3rd drug]

		CSF HIV DNA Total (N=44)	TND (N=22)	Detected (N=22)	P-Value*
IQ_{50} for TFV C_{trough}	Median	0.01	0.01	0.01	0.17
	Q1, Q3	0.00, 0.01	0.00, 0.01	0.00, 0.01	
	Min, Max	0.00, 0.02	0.00, 0.02	0.00, 0.02	
IQ_{50} for FTC C_{trough}	Median	21.1	28.0	17.0	0.20
	Q1, Q3	15.5, 54.7	16.2, 54.3	6.5, 55.0	
	Min, Max	1.1, 92.2	1.1, 92.2	1.1, 80.5	
IQ_{50} for 3rd drug C_{trough}	Median	4.4	3.7	4.8	0.87
	Q1, Q3	1.0, 8.8	1.2, 9.5	0.9, 7.6	
	Min, Max	0.0, 53.3	0.1, 22.2	0.0, 53.3	
Arithmetic mean IQ	Median	10.8	11.5	7.5	0.16
	Q1, Q3	6.2, 18.6	8.2, 18.9	5.7, 18.4	
	Min, Max	2.2, 36.2	2.2, 32.5	2.2, 36.2	
Geometric mean IQ	Median	0.7	0.9	0.5	0.027
	Q1, Q3	0.4, 1.2	0.5, 1.6	0.3, 0.9	
	Min, Max	0.0, 3.3	0.0, 2.5	0.0, 3.3	

*Exact Wilcoxon Test

Table 4: Spearman rank-based correlation between CSF inflammatory biomarkers and ARV drug activity in CSF

	Arithmetic mean IQ				Geometric mean IQ			
	Spearman	P-value	Partial Spearman	P-value	Spearman	P-value	Partial Spearman	P-value
CSF IL-6 (pg/mL)	0.16	0.31	0.10	0.54	0.10	0.50	0.13	0.41
CSF IP-10 (pg/mL)	0.11	0.46	0.10	0.53	-0.19	0.23	-0.20	0.20
CSF MCP-1 (pg/mL)	-0.02	0.87	-0.23	0.14	-0.26	0.08	-0.27	0.08
CSF neopterin (nMol/L)	0.08	0.59	0.15	0.35	0.04	0.82	0.01	0.95
CSF sCD14 (ng/mL)	0.13	0.39	0.06	0.70	0.13	0.41	0.13	0.40
CSF sCD163 (ng/mL)	0.22	0.15	0.15	0.35	-0.01	0.94	-0.02	0.90

Spearman rank-based correlation between CSF inflammatory biomarkers and ARV drug activity in CSF. No associations were found.

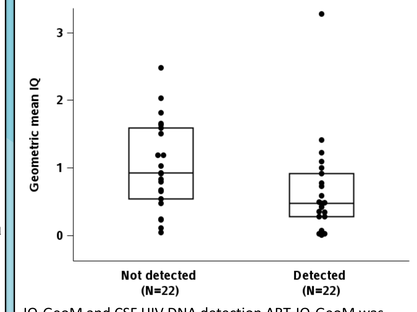
Abbreviations: TFV, tenofovir disoproxil fumarate; FTC, emtricitabine; IQ, inhibitory quotients; CSF, cerebrospinal fluid; IC, inhibitory concentration; ARV, antiviral agent; TND, not detected

Table 3: Spearman rank-based correlation between global deficit scores (GDS) and measures of ARV drug activity in CSF

	IQ50 for TFV			IQ50 for FTC			IQ90 for 3rd drug			Arithmetic mean IQ			Geometric mean IQ		
	N	Spearman	P-value	N	Spearman	P-value	N	Spearman	P-value	N	Spearman	P-value	N	Spearman	P-value
Mean GDS	41	-0.41	0.007	41	-0.10	0.55	41	-0.09	0.56	41	-0.10	0.52	41	**-0.30**	**0.05**
Fine motor GDS	41	-0.10	0.54	41	0.09	0.57	41	-0.08	0.60	41	0.06	0.72	41	-0.14	0.38
Verbal learning GDS	41	-0.22	0.16	41	-0.11	0.49	41	0.12	0.46	41	-0.10	0.52	41	-0.02	0.90
Verbal memory GDS	41	-0.24	0.12	41	-0.33	0.037	41	0.26	0.09	41	-0.26	0.11	41	-0.07	0.68
Executive functioning GDS	41	-0.24	0.13	41	-0.05	0.76	41	-0.07	0.68	41	-0.04	0.80	41	-0.19	0.24
Speed of processing GDS	41	-0.43	0.005	41	-0.06	0.73	41	-0.20	0.21	41	-0.15	0.35	41	-0.44	0.004
Attention GDS	41	-0.22	0.16	41	-0.08	0.60	41	-0.01	0.97	41	-0.02	0.92	41	-0.17	0.28
Language GDS	39	-0.10	0.53	39	0.27	0.09	39	-0.33	0.041	39	0.22	0.17	39	-0.24	0.15

Abbreviations: GDS, global deficit scores; IQ, inhibitory quotients

Fig 3.



IQ-GeoM and CSF HIV DNA detection ART-IQ-GeoM was higher in those with undetectable vs detectable CSF HIV DNA 0.9 (0.5, 1.6) vs 0.5 (0.3, 0.9), p=0.027.