Poster 401

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Low-Level HIV RNA Declines Over Time in CSF but not in Plasma

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Objective

We assayed CSF and plasma samples from 99 multiply sampled, ART-treated individuals using an assay capable of quantitating HIV RNA to 2 copies/mL to determine the correlates of low-level HIV RNA with disease, treatment, and neurocognitive characteristics.

Background

Analyses of HIV RNA levels in cerebrospinal fluid (CSF) have provided valuable insights into the pathogenesis of HIV-associated neurocognitive disorder (HAND). Their value has diminished with the advent of combination antiretroviral therapy (ART) since therapy suppresses HIV RNA below the lower limit of quantitation of commercial assays in a substantial majority of patients, in some cases even when it fails to do so in plasma. A more sensitive assay would be better suited to assessing residual HIV replication during antiretroviral treatment.

In a prior cross-sectional analysis, we found that 41% of 329 CSF specimens that had HIV RNA levels below 50 copies/mL still had HIV RNA of at least 2 copies/mL using a more sensitive assay [Muñoz-Moreno, et al. 16th CROI. Abstract 484b]. HIV RNA levels in CSF > 2 copies/mL were associated with worse estimated ART distribution into the CNS and HIV RNA levels in plasma that were also > 2 copies/mL. Subjects who had low-level HIV RNA in CSF but not in plasma had worse neurocognitive functioning, supporting a possible role for persistent low-level HIV replication in HAND pathogenesis during ART.

The primary objective of this analysis was to confirm these findings using longitudinal data.

Results

Table. Summary of the results of univariable and multivariable analyses predicting HIV RNA levels in CSF between 2 and 50 copies/mL or Global Deficit Score over time. Odds ratios (OR) greater than one indicate that higher levels are associated with HIV RNA in CSF between 2 and 50 c/mL. Positive β values indicate that higher values are associated with worse global neurocognitive functioning.

	Univariable		Multivariable	
	OR	p value	OR	p value
HIV RNA in CSF 2-50 copies/mL				
Duration of Current Regimen	1.1	0.06	1.1	0.07
HIV RNA in Plasma 2-50 copies/mL	2.7	0.03	2.5	0.04
CPE Score	-	> 0.20	-	-
Nadir CD4+ T-cell Count	-	> 0.20	-	-
Current CD4+ T-cell Count	-	> 0.20	-	-
HCV Serostatus	-	> 0.20	-	-
Global Deficit Score	β	p value	β	p value
HIV RNA in Plasma 2-50 copies/mL	0.12	0.009	0.14	0.003
Neuropsychiatric Comorbidities	0.17	0.09	0.18	0.06
HIV RNA in CSF 2-50 copies/mL	0.12	0.06	-	-
Number of Antiretrovirals	0.10	0.06	-	-
Ethnicity (White)	0.17	0.08	-	-

Results

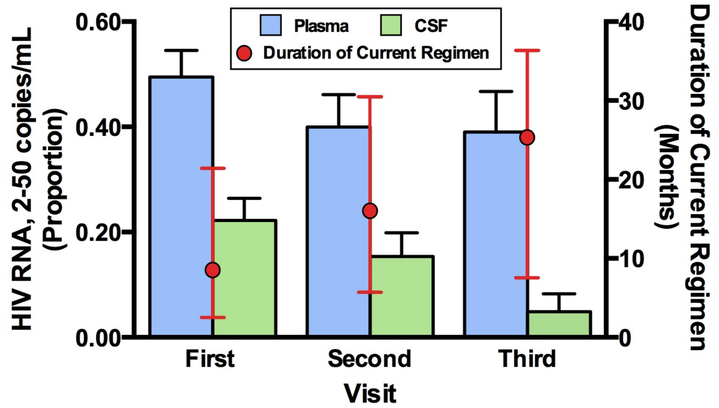

Figure. Relationship between visit, HIV RNA levels between 2 and 50 copies/mL, and duration of the current ART regimen. Longer durations of therapy were associated with reductions in the proportion of detectable HIV RNA levels in CSF but not in plasma. Column bars are standard errors of the mean. ART durations are medians and interquartile ranges.

- Demographics and disease characteristics: Most subjects were middle-aged (mean 47 years) men (89%) who had AIDS (72%) and were HCV seronegative (68%). Forty-five percent were white and 38% were black. All HIV RNA levels were ≤ 50 copies/mL in CSF and plasma. Median nadir CD4+ T-cell count was 102/mm^3 and the median CD4+ T-cell count at baseline was 436/mm^3. Global neurocognitive functioning was impaired in 37%.
- ART characteristics: The median duration of the current ART regimen was 9 months at the first visit. The mean ART CPE value was 8.4. The most common regimens were ATV/r-TDF-FTC (n = 8) and EFV-TDF-FTC (n = 7).
- Duration of observation and frequency of HIV RNA between 2 and 50 copies/mL: Subjects had a mean of 2.1 visits with a median duration between visits of 188 days. The proportion of specimens with HIV RNA between 2 and 50 copies/mL declined from the first to the third visit in CSF (20% to 16% to 5%, p = 0.046) but not in plasma (48% to 41% to 39%, p = 0.21). See the Figure.
- Correlates of HIV RNA in CSF between 2 and 50 c/mL over time: Multivariable modeling identified that HIV RNA in CSF between 2 and 50 copies/mL was associated with shorter duration of ART and HIV RNA in plasma between 2 and 50 copies/mL. The Table also summarizes the covariates included in the best multivariable model. See the Table.
- Correlates of global neurocognitive functioning: Multivariable modeling identified that worse GDS values were associated with HIV RNA in plasma between 2 and 50 copies/mL and worse neurocognitive comorbidities. An interaction indicated that subjects who had HIV RNA in both CSF and plasma between 2 and 50 copies/mL may have had the worst performance (p=.06).

Conclusions

- In this longitudinal analysis of effectively treated individuals, HIV RNA levels in CSF were between 2 and 50 c/mL in 20% of all subjects at baseline after approximately 9 months of therapy
- Over time, the proportion of specimens with HIV RNA between 2 and 50 copies/mL declined in CSF but not in blood
- Over time, the presence of HIV RNA between 2 and 50 copies/mL in plasma and perhaps in CSF was associated with worse neurocognitive functioning
- These findings do not exactly match prior analyses but do support that suppressing HIV RNA below 2 copies/mL may have nervous system benefits

Methods

Design: 99 subjects participated in one of two NIH-funded clinical trials, "The Cognitive Intervention Trial 2" or "Antiretroviral-Induced Immune Recovery and the Central Nervous System". Inclusion criteria included ART use, HIV RNA ≤ 50 copies/mL in CSF and plasma, absence of severe neurocognitive comorbidities, and up to 3 assessments that included veni- and lumbar-puncture with specimens stored at -80° C.

Lab: HIV RNA between 2 and and 50 copies/mL was measured using a validated quantitative assay, HIV-1 SuperLow assay (bioMONTR Labs), that incorporates a proprietary algorithm and molecular beacons for detection. Other lab data were measured by routine clinical methods.

Medical and Neurocognitive: ART distribution into the central nervous system (CNS) was estimated by the 2010 CNS penetration-effectiveness (CPE) method (Letendre et al, 17th CROI, Abstract 172). ART adherence was estimated by the ACTG 4-day method. Neurocognitive functioning was assessed using standardized comprehensive testing and summarized by the global deficit score (GDS) method.

Analysis: Mixed effects logistic regression, with subjects treated as random effects, was used to estimate the probability that HIV RNA declined over time. Mixed effects linear regression, also with subjects as random effects, was performed to estimate the mean T-score for the neurocognitive measures. For all modeling, initial univariable variable screening was at the 20% significance level. Backward elimination was performed using Akaike Information Criterion (AIC) until the minimum AIC was attained.

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