HCV Cure in HIV Coinfection Dampens Inflammation and Improves Cognition through Multiple Mechanisms

Bing Sun[1], Linda Abadjian[2], Alexander Monto[3,4], Heather Freasier[3] and Lynn Pulliam[1,3,4]

[1]Department of Laboratory Medicine, [2] Department of Mental Health, [3]Department of Medicine, San Francisco Veterans Affairs Medical Center and [4]University of California, San Francisco, CA, USA

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Lynn.pulliam@ucsf.edu

Abstract

Background
Chronic inflammation in HIV/HCV coinfection increases cognitive impairment. With newer direct-acting antiviral (DAA) therapies for HCV, our objective was to determine if chronic inflammation would be decreased and cognition improved with HCV sustained viral response (SVR) in coinfection.

Methods
We studied 41 participants before and after treatment for HCV alone or with viral controlled HIV coinfection. We measured monocyte activation and gene expression, plasma inflammation and cognitive impairment. Monocyte-derived exosome miRNAs were studied with RNA sequencing and qRT-PCR after therapy.

Results
All HCV coinfected subjects achieved SVR but one. Blood CD16+ monocytes were decreased in coinfection after HCV treatment. Overall cognition improved 25% in coinfection. Plasma sCD163 and neopterin were decreased in HCV mono and coinfected persons. HCV SVR decreased monocyte interferon genes MX1, IFI27 and CD169 in coinfection and MX1, CXCL10, LGALS3BP and TNFAIP6 in HCV monoinfection. Monocyte exosomes from coinfected persons after treatment were significantly increased in miR-19a, miR-221 and marginally miR-223, all associated with decreasing inflammation.

Conclusions
HCV cure in coinfection brings monocyte activation markers to levels of HIV alone. Cognitive impairment is significantly improved with cure but not better than HIV infection alone strongly suggesting that cognitive impairment was driven by both HIV and HCV.

Methods

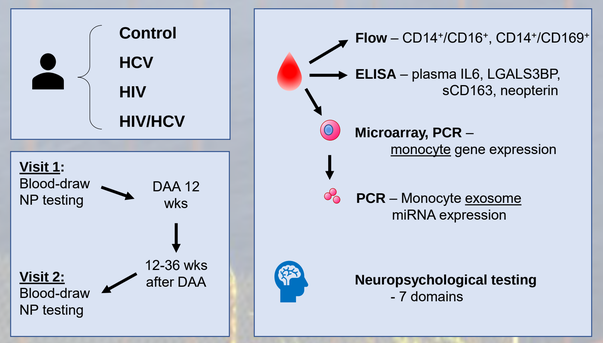

Table 1. Characteristics of participants

	Control	HCV	HIV	HIV/HCV	P value
N	9	8	12	12	0.764 [a]
Age	55.3 (3.6)	62.8 (4.2)	59.8 (5.8)	57.0 (8.4)	0.073
Education	14.6 (1.8)	14.3 (2.2)	14.6 (2.2)	13.8 (1.7)	0.722
Ethnicity					0.360 [b]
African-American	3	1	3	4	
Asian	2	0	0	0	
Caucasian	4	6	8	7	
Hispanic	0	1	1	1	
Estimated IQ (T score)	51.9 (8.5)	54.5 (8.4)	56.2 (7.6)	56.5 (9.4)	0.611
BDI Depression score	10.9 (13.0)	14.3 (10.6)	7.6 (7.2)	9.6 (9.7)	0.540
Global Deficit Score	0.29 (0.18)	0.48 (0.59)	0.55 (0.43)	0.62 (0.46)	0.356
HIV Viral Load	NA	NA	< 40	< 40	
CD4 Count	NA	NA	831.0 (400.8)	631.4 (221.4)	0.180
HCV Viral Load (log10)	NA	5.98 (0.63)	NA	5.90 (0.67)	0.800
Years HCV infection	NA	12.0 (9.3)	NA	11.2 (7.0)	0.835
Alanine Transaminase	34.0 (19.8)	108.9 (42.2)	30.0 (6.1)	90.3 (85.1)	0.002 *

NA: not available. P values were determined with *ANOVA* tests except [a] for *Fisher's* exact test and [b] for X^2 test. Star (*) indicates HCV and HIV/HCV had significantly higher levels of ALT compare to Controls. IQ, Beck depression inventory II score, global deficit score, HCV viral load, CD4 count and alanine transaminase levels are before DAA treatment. Data are shown as mean (s.d.).

Results

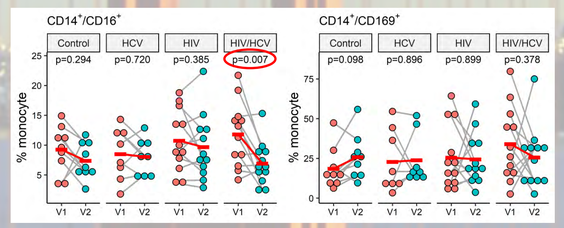

Figure 1. CD14$^+$/CD16$^+$ and CD14$^+$/CD169$^+$ monocyte activation**.** The monocyte CD14$^+$/CD16$^+$ population decreased in visit 2 (7.33% of monocytes) compared to visit1 (12.1% of monocytes) in HIV/HCV subjects (p=0.007, paired t test). This denotes a 39.5% decrease in an inflammatory monocyte subset but no change in an interferon marker, CD169. Black bars indicate the means of each group at visit 1 (V1) and visit 1 (V2).

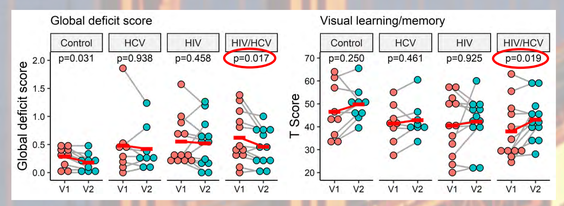

Figure 2. Cognition improves in coinfection after HCV treatment. HIV/HCV subjects showed a decrease in GDS (increase in cognitive function) (p=0.017, paired Mann-Whitney test) from visit 2 (mean GDS=0.48) compared to visit 1 (mean GDS=0.64). This denotes a 25% decrease in GDS. Visual learning/memory increased after treatment in HIV/HCV coinfection. Wilcoxon signed-rank test with BH multiple comparison correction. Black bars indicate the means of each group at visit 1 (V1) and visit 2 (V2).

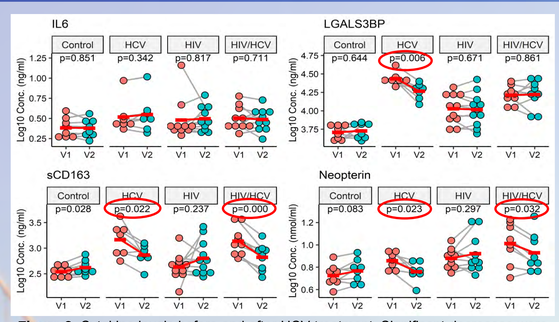

Figure 3. Cytokine levels before and after HCV treatment. Significant decreases were found in sCD163 and neopterin in both treated HCV and coinfected subjects; LGALS3BP was lower in treated HCV monoinfected patients (paired Student's t test). Black bars are group means at visit 1 (V1) and visit 2 (V2).

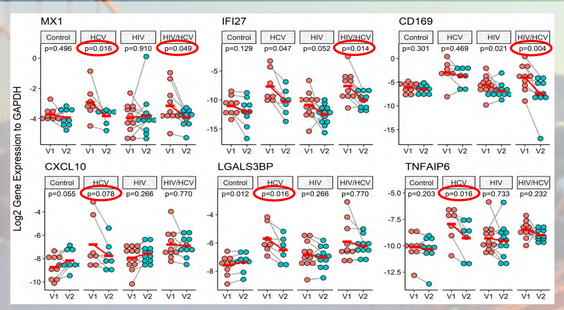

Figure 4. Selected monocyte gene expression before and after treatment. SVR in HCV monoinfection had significant decreases in MX1, CXCL10, LGALS3BP and TNFAIP6. HCV cure in coinfection had decreases in MX1, IFI27 and CD169. Wilcoxon signed-rank test with BH multiple comparison correction. Visit 1 (V1) and visit 2 (V2).

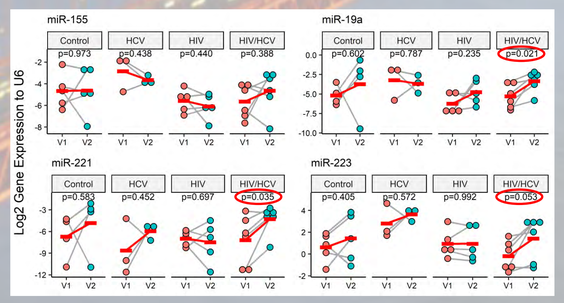

Figure 5. miR expression of monocyte exosomes before and after treatment. miR-19a, miR-221 and miR-223 (marginally) showed increases in the coinfected group after HCV treatment. Paired Student's t test. Visit 1 (V1) and visit 2 (V2).

Table 2. NP test results significantly changed after HCV therapy in coinfection

Neuropsychological test	HCV			HIV/HCV			
	Visit 1	Visit 2	p value	Visit 1	Visit 2	p value	
Information processing speed	42.1 (7.6)	42.8 (6.8)	0.813	42.0 (6.2)	42.8 (6.0)	1.000	
Symbol digit written	40.6 (9.9)	39.8 (10.2)	0.813	40.2 (7.0)	44.0 (6.2)	0.041	*
Visual learning / memory	41.1 (9.2)	42.4 (8.5)	0.688	38.0 (12.4)	43.1 (9.4)	0.019	*
BVMT trials 1-3	39.7 (11.0)	42.9 (8.1)	0.172	36.8 (13.2)	42.6 (10.0)	0.039	*
BVMT delay	42.6 (10.1)	42.0 (9.4)	1.000	39.2 (12.5)	43.7 (10.2)	0.047	*

All test results were in T scores and presented as mean (standard deviation). P values were calculated with paired exact Wilcoxon signed rank test between visit 1 and visit 2. Domain scores are the average of all the tests in each domain. * p<0.05.

Summary of significant findings after DAA therapy for HCV

Assay	HCV	HIV/HCV
Monocyte activation		
CD14+/CD16+	–	↓
sCD163	↓	↓
MX1	↓	↓
Neopterin	↓	↓
IFI27	–	↓
CD169	–	↓
LGALS3BP	↓	–
TNFAIP6	↓	–
CXCL10	↓	–
IL6	–	–
Monocyte exosome cargo		
miR−19a	–	↑
miR−221	–	↑
miR−223	–	marginally ↑
Cognitive Impairment		
Global deficit score	–	↓
Visual learning/ memory	–	↑

Conclusion

- **All HCV infected individuals achieved SVR12 after DAA except one.**
- **Monocyte activation decreased to levels of HIV alone after DAA.**
- **Most improved domain is visual learning/memory**
- **Cognitive impairment was significantly improved with cure but not better than HIV infection alone strongly suggesting that cognitive impairment was driven by both HIV and HCV.**