Macrophage Activation and Hepatitis C Disease Progression in HIV-infected Women Participating in the Women's Interagency HIV Study (WIHS)

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Background

- ✧ Microbial translocation is increased in HIV infection and our group and others have found that markers of microbial translocation are associated with more rapid hepatitis C disease progression in HIV.
- ✧ Hepatic macrophage activation by endotoxin is postulated to be a mechanism by which microbial translocation contributes to hepatic fibrosis in hepatitis C infection
- ✧ We sought to confirm the relationship of microbial translocation to liver disease progression and further characterize the role of macrophage activation by studying soluble markers in HIV/HCV coinfected women with varied trajectories of liver disease progression

Methods

- ✧ WIHS is a multisite observational study of women with HIV-infected and demographically similar HIV-uninfected women who are seen semiannually for interview, physical exam and specimen collection. Included in this substudy are women from Chicago, San Francisco, Los Angeles, Washington DC and New York City.
- ✧ Soluble CD163 and CD14, lipopolysaccharide (LPS) tumor necrosis factor receptor II, chemokine ligand -2 (CCL2) and interleukin-6 (IL-6) were measured by ELISA at three timepoints (T) 2.5 years apart on stored serum from HIV/HCV coinfected women. Laboratory investigators were blinded to liver disease status.
- ✧ The study includes women with active HCV (HCV RNA+) who were HBsAg negative and had no hazardous drinking (≥ 7 drinks/week) during the study period.
- ✧ (T1) was a visit at which each woman had no or minimal fibrosis by liver biopsy or APRI and FIB-4 (<0.5 and <1.45 respectively). For LDP, T3 was a visit where there was a liver biopsy with cirrhosis or bridging fibrosis, imminent liver death or APRI and FIB-4 consistent with cirrhosis (>1.5 and >3.25 respectively). For NP T3 was a visit where biopsy or both APRI and FIB-4 remained consistent with no or minimal fibrosis.

Results

- ✧ Soluble markers were measured in 31 liver disease progressors and 84 non-progressors. The median time between T1 and T3 was 4.9 years.
- ✧ The groups were well matched for race, age, HIVRNA, CD4 and nadir CD4, HAART use (Table 1) as well as crack, cocaine (p>0.5) and injection drug use (p=0.229) (data not shown).
- ✧ LPS, sCD14, IL-6, CCL-2 levels did not differ in slope or quantity over time between women who had rapid liver disease progression and non-progressors (Table 2).
- ✧ TNFRII levels were higher overall in progressors in unadjusted analysis and analysis adjusted for HIVRNA with a trend at T2 (Figure). sCD163 showed the most difference between LDP and NP with higher levels in progressors at T2 and T3 in adjusted and unadjusted models and a significantly higher slope.

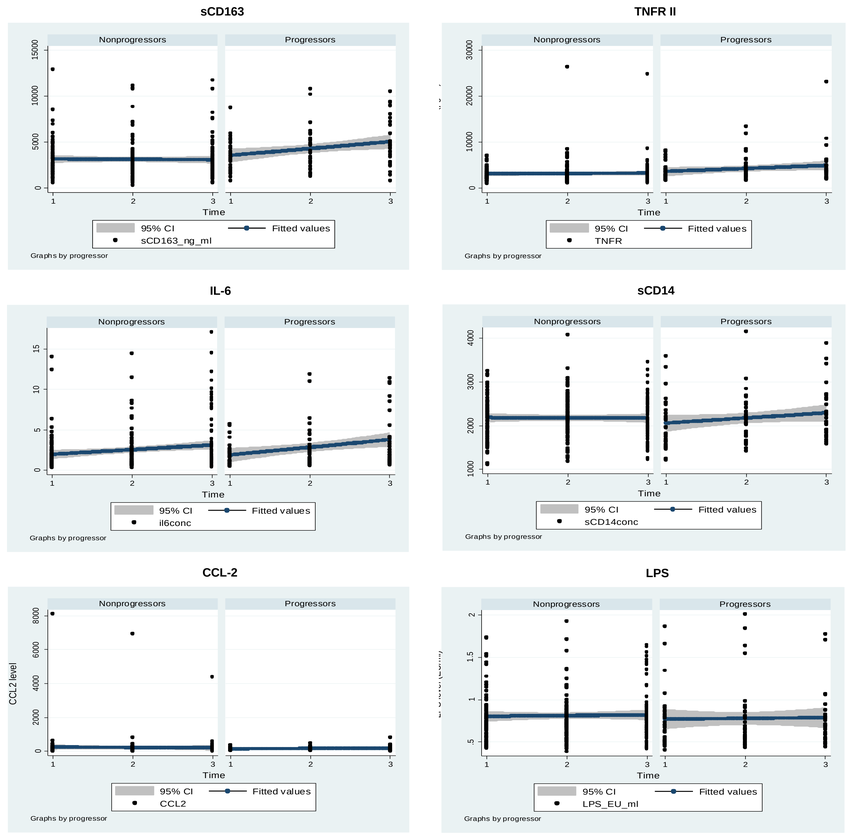
Baseline Characteristics of Liver Disease Progressors vs Non-Progressors

Baseline Characteristic	Progressor N=31	Non-Progressor N=84	p-value
Race/Ethnicity			1.00
White	6 (19.4)	17 (20.2)	
Black, non-Hispanic	20 (64.5)	53 (63.1)	
Hispanic	5 (16.1)	12 (14.3)	
Other race	0 (0.0)	2 (2.4)	
Age, median (IQR)	42 (39-45)	40 (36-44)	0.182
Baseline CD4, median (IQR)	462 (289-661)	487 (323-663)	0.491
CD4 nadir, median (IQR)	214 (113.5-359.5)	226 (153-318)	0.919
Viral load, median (IQR)	1100 (130-7900)	763.5 (80-16250)	0.772
On HAART			0.548
Yes	11 (35.5)	35 (41.7)	
No	20 (64.5)	49 (58.3)	
Alcohol use prior to study			0.179
None	18 (60.0)	51 (61.5)	
<3 drinks/week	9 (30.0)	29 (34.9)	
3-13 drinks/week	1 (3.3)	3 (3.6)	
≥14 drinks/week	2 (6.7)	0 (0.0)	

Differences in Soluble Markers between Liver Disease Progressors and Non-Progressors for all Visits

All visits lab data	Total N=342	Porgressors N=92	Non-Progressors N=250	Wilcoxon Rank sum p-value	Model adjusted for HIV RNA p-value
Mean LPS eu_ml (sd) (n=341)	0.80 (0.31)	0.78 (0.35)	0.81 (0.30)	0.05	0.41
Mean soluble CD14 (sd) (n=342)	2176.7 (523.3)	2172.4 (578.6)	2178.3 (502.7)	0.38	0.67
Mean IL-6 (sd) (n=342)	2.62 (2.77)	2.83 (2.72)	2.54 (2.79)	0.17	0.49
Mean TNFR II (pg/ml) (sd) (n=341)	3474.2 (2631.2)	4251.8 (3016.2)	3191.1 (2421.5)	**<0.0001**	**0.002**
Mean CCL2 (sd) (n=338)	202.0 (624.4)	160.6 (118.6)	217.3 (726.7)	0.14	0.46
Mean soluble CD163 (ng/ml) (n=341)	3423.3 (2132.1)	4268.9 (2289.6)	3115.5 (1988.9)	**<0.0001**	**<0.0001**

Longitudinal Soluble Markers in Liver Disease Progressors vs Non-Progressors



Conclusions

✧ We found that classic markers of microbial translocation