Pro-inflammatory markers in persons living with HIV, HCV, and/or drug use

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Background

The US is experiencing a major drug epidemic that is attributed in large part to synthetic opioids such as fentanyl. We previously reported that fentanyl enhanced the replication of several viruses including HIV. Here, we considered how fentanyl use impacted inflammatory markers in persons living with HIV.

Methods

Whole blood was collected from adults living with HIV, HCV, and/or opioid use, as well as non-opioid using controls. Plasma samples were screened for commonly abused drugs, pro-inflammatory cytokines/chemokines (IL-6 ,IL-8, SDF-1a, MIP-1a, MIP-1b, RANTES, TNFa), and the apoptosis marker M30 by Liquid Chromatography Mass Spectrometry, Luminex multiplex cytokine array, and the M30 Apoptosense ELISA, respectively. Median values were compared by HIV or HCV status, and the Kruskal-Wallis test was conducted to assess differences between positive and negative groups. Multiple regression models were used to explore the associations between the $\log_{10}$-transformed cytokine/chemokine/M30 values and other covariates.

Results

37 of 98 (37.8%) individuals had a diagnosis of opioid use disorder (OUD), and 48 (53.9%) had ever injected drugs. Of those ever-having opioids, 95.9% (47/49) had used fentanyl. HIV-positive status indicated higher RANTES levels (363.1 vs. 174.9; p = 0.014) and lower M30 levels (84.4 vs. 114.7; p = 0.009) compared to HIV-negative status. Being HCV positive was linked to higher IL-8 (9.6 vs. 6.3; p = 0.023), MIP-1b (25.7 vs. 18.4; p = 0.029), TNFa (17.3 vs. 10.7; p = 0.033), and M30 (105.7 vs. 90.0; p = 0.029) and lower RANTES (210.5 vs. 363.9; p = 0.044), compared to HCV-negative status. After adjusting for other covariates, IL-8 was associated with both HIV status and HCV status, SDF-1a with ever having injected drugs, and MIP-1b with HCV status. There were no significant associations between the number of drugs of abuse detected and cytokine/chemokine/M30 levels after controlling for covariates.

Discussion

Drugs of abuse may alter the immune system and viral pathogenesis in several ways. Enhanced pro-inflammatory cytokine and chemokine production represent potential mechanisms by which opioids impact viral infection. Future research that antagonize these processes may provide new therapeutic interventions that reduce morbidity/mortality among persons with HIV and HIV/HCV co-infected with OUD.

Table 1. Characteristics of study participants.

Variable	HIV Status		HCV Status		
	Positive (n = 69)	Negative (n = 28)	Positive (n = 40)	Negative (n = 50)	All (n = 98)
Age, mean (SD)	43 (12.7)	43.4 (12.1)	41.5 (9.9)	46.9 (14.2)	44.1 (12.4)
Sex (n, %)					
Male	57 (82.6%)	17 (60.7%)	28 (70.0%)	39 (78.0%)	74 (75.5%)
Female	12 (17.4%)	11 (39.3%)	12 (30.0%)	11 (22.0%)	24 (24.5%)
Race (n, %)					
White	43 (62.3%)	20 (71.4%)	33 (82.5%)	24 (48.0%)	63 (64.3%)
African American	26 (37.7%)	8 (28.6%)	7 (17.5%)	26 (52.0%)	35 (35.7%)
Currently receiving HIV treatment (n, %)					
Yes	49 (73.1%)	-	16 (72.7%)	27 (61.4%)	49 (66.2%)
No	18 (26.9%)	-	6 (27.3%)	17 (38.6%)	25 (33.8%)
Currently receiving hepatitis C treatment (n, %)					
Yes	2 (3.3%)	0 (0%)	2 (5.1%))	-	2 (2.4%)
No	58 (96.7%)	23 (100%)	37 (94.9%)	-	82 (97.6%)
Hepatitis C genotype (n, %)					
Genotype 1 (1a/1b)	6 (28.6%)	5 (29.4%)	9 (25.7%)	-	11 (29.0%)
Genotype 2	2 (9.5%)	1 (5.9%)	3 (8.6%)	-	3 (7.9%)
Genotype 3	4 (19.1%)	2 (11.8%)	6 (17.1%)	-	6 (15.8%)
Genotype 4	1 (4.8%)	1 (5.9%)	2 (5.7%)	-	2 (5.3%)
unknown	8 (38.1%)	8 (47.1%)	15 (42.9%)	-	16 (42.1%)
OUD diagnosis (n, %)					
Yes	23 (33.3%)	14 (50.0%)	29 (72.5%)	4 (8.0%)	37 (37.8%)
No	46 (66.7%)	14 (50.0%)	11 (27.5%)	46 (92.0%)	61 (62.2%)
Drug use ever (n, %)					
Injection drugs	29 (47.5%)	19 (70.4%)	36 (94.7%)	9 (20.5%)	48 (53.9%)
Opioids	30 (49.2%)	19 (70.4%)	36 (97.3%)	10 (22.2%)	49 (55.1%)
Fentanyl	30 (48.4%)	18 (66.7%)	36 (94.7%)	9 (20.0%)	48 (53.3%)
Drug use in last 24 hours (n, %)					
Injection drugs	14 (21.9%)	13 (48.2%)	23 (60.5%)	2 (4.3%)	27 (29.4%)
Opioids	16 (25.4%)	13 (48.2%)	24 (64.9%)	3 (6.4%)	29 (31.9%)
Fentanyl	15 (23.4%)	12 (44.4%)	24 (63.2%)	2 (2.13%)	27 (29.4%)
The most recent value (median, Q1-Q3)					
CD4 cell count	368 (160.4-643)	-	379.5 (247.7-652.0)	307 (126.0-466.8)	368 (160.4-643.0)
ALT value	21.5 (13-40)	30 (18-43)	34.5 (19-75)	18 (13-38)	22 (15.0-41.5)
AST value	25 (19-41)	32 (24-46)	36 (19-86)	25 (19-32)	26.5 (19.0-42.5)
Albumin value	4.1 (3.6-4.5)	3.9 (3.4-4.0)	3.9 (3.4-4.2)	4 (3.5-4.5)	3.9 (3.5-4.4)
Platelet count	209 (161-251	260 (228-293)	239 (164-286)	220 (161-274)	232 (162-274)

Table 2. Cytokine/Chemokines/M30 values by HIV and HCV status.

	HIV Status		Kruskal-Wallis Test	HCV Status		Kruskal-Wallis Test	
	Positive (n = 69)	Negative (n = 28)		Positive (n = 40)	Negative (n = 50)		All (n = 98)
	Median (Q1-Q3)	Median (Q1-Q3)	p-value	Median (Q1-Q3)	Median (Q1-Q3)	p-value	Median (Q1-Q3)
IL-6 pg/mL	3.895 (1.460-8.840)	5.550 (2.285-18.140)	0.079	5.055 (1.485-12.408)	3.140 (1.368-7.688)	0.160	4.255 (1.505-9.305)
IL-8 pg/mL	7.195 (4.255-15.855)	8.440 (4.675-12.775)	0.595	9.608 (5.485-20.903)	6.343 (3.758-13.693)	**0.023***	7.695 (4.280-14.660)
SDF1 alpha	790.5 (684.500-954.195)	701.730 (630.535-868.775)	0.160	799.345 (634.348-970.875)	750.943 (650.578-847.428)	0.323	773.805 (644.065-921.285)
Mip-1 alpha	7.610 (4.002-12.630)	7.250 (3.653-20.000)	0.890	8.788 (3.827-17.153)	6.680 (3.937-13.488)	0.458	7.425 (3.937-14.570)
Mip-1beta	20.730 (15.200-28.565)	25.895 (15.760-32.365)	0.419	25.708 (18.123-32.495)	18.383 (14.915-27.183)	**0.029***	20.840 (15.525-29.655)
RANTES	363.050 (171.220-584.160)	174.890 (76.375-361.895)	**0.014***	210.540 (80.868-499.935)	363.940 (173.055-554.855)	**0.044***	299.740 (150.600-559.470)
TNFalpha	15.185 (9.505-24.450)	12.900 (10.185-30.915)	0.724	17.290 (10.688-31.660)	10.718 (8.505-20.673)	**0.033***	13.325 (9.505-25.435)
M30 U/L	84.427 (72.618-108.422)	114.746 (93.734-136.012)	**0.009***	105.668 (79.654-209.438)	90.049 (70.775-114.817)	**0.029***	96.105 (74.932-118.935)

Table 3. Regression models for transformed chemokines outcomes.

	IL-8 pg/mL			SDF1 alpha			Mip-1beta		
Covariates	Coefficient Estimate	t-test p-value	95% Confidence Interval	Coefficient Estimate	t-test p-value	95% Confidence Interval	Coefficient Estimate	t-test p-value	95% Confidence Interval
Age	0.000	0.994	(-0.010, 0.010)	0.001	0.639	(-0.002, 0.004)	-0.001	0.815	(-0.006, 0.005)
Sex	0.029	0.807	(-0.206, 0.264)	0.014	0.710	(-0.062, 0.091)	0.082	0.239	(-0.056, 0.220)
Race	-0.139	0.234	(-0.371, 0.092)	-0.016	0.672	(-0.091, 0.059)	-0.133	0.056	(-0.268, 0.003)
HIV status	0.363	**0.038***	(0.021, 0.706)	0.055	0.330	(-0.057, 0.166)	0.161	0.113	(-0.039, 0.362)
HCV status	0.518	**0.036***	(0.035, 1.002)	-0.060	0.452	(-0.217, 0.098)	0.387	**0.008***	(0.103, 0.671)
HIV and HCV interaction	-0.651	0.008*	(-1.124, -0.178)	-0.036	0.644	(-0.190, 0.118)	-0.301	**0.034***	(-0.579, -0.023)
Drug Use Ever - Injection drugs	0.123	0.526	(-0.262, 0.508)	0.142	**0.027***	(0.017, 0.267)	-0.115	0.312	(-0.341, 0.111)
Drug Use Ever - Opioids + Fentanyl	0.003	0.988	(-0.389, 0.395)	0.018	0.783	(-0.110, 0.145)	0.011	0.927	(-0.219, 0.240)
Drug Use in last 24 hours - Injection drugs	-0.058	0.737	(-0.403, 0.287)	-0.051	0.370	(-0.163, 0.061)	-0.007	0.943	(-0.209, 0.195)
Drug Use in last 24 hours - Opioids	0.057	0.749	(-0.300, 0.415)	-0.097	0.101	(-0.213, 0.019)	0.091	0.390	(-0.119, 0.301)
Drug Use in last 24 hours - Fentanyl	-0.005	0.981	(-0.419, 0.409)	0.136	0.048	(0.001, 0.271)	-0.139	0.256	(-0.382, 0.104)

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