Corrilynn O Hileman MD, MS
cxh152@case.edu
2500 MetroHealth Drive
Cleveland, OH, USA, 44109
Phone: 216-778-2103
Fax: 216-778-3019

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IMPACT OF INTRAVENOUS HEROIN AND HIV ON GUT INTEGRITY AND IMMUNE ACTIVATION

Corrilynn O. Hileman[1,2], Emily Bowman[3], Janelle Gabriel[3], Aaren Kettlehut[3], Julia Kosco[4], Danielle Labbato[4], Theresa Rodgers[4], Cheryl Smith[1], Nicholas Funderburg[3], and Grace A. McComsey[2,4]
[1]MetroHealth Medical Center, Cleveland, OH, [2]Case Western University School of Medicine, Cleveland, OH, [3]The Ohio State University, Columbus, OH, [4]University Hospitals Cleveland Medical Center, Cleveland, OH

BACKGROUND

- Altered gut integrity and translocation of microbial products appear to be central in HIV-related immune activation. Brenchley JM, et al. *Nature* 2006.
- Excess immune activation increases risk of co-morbid cardio-metabolic conditions and contributes to increased mortality in people with HIV (PWH). This may be augmented in PWH who inject opioids. Trickey A, et al. *PloS One* 2016.
- Opioid use may promote changes in gut permeability potentially augmenting immune activation in people with HIV (PWH) who use opioids. Ancuta P, et al. *PloS one* 2008.
- Injection as a route of administration may also heighten inflammation.

METHODS

This is a prospectively enrolled, matched, cross-sectional study designed to assess:

(1) the effect of heroin on soluble markers of gut integrity, microbial translocation, systemic inflammation, and monocyte activation; cellular markers of immune activation; and

(2) whether HIV infection modifies the associations between heroin and these markers.

We enrolled 4 groups:

HIV+heroin+	HIV+heroin-	HIV-heroin+	HIV-heroin-

INCLUSION: age ≥18 years, self reported heroin use for past month with cumulative use of 1 year in the past (for heroin+); no history of IV drug use (for heroin-).

EXCLUSION: active infection, malignancy, known cardiovascular disease, pregnancy, ALT/AST >2.5x upper limit of normal, hemoglobin <9 g/dL, creatinine clearance <30 ml/min.

MATCHING CRITERIA: age, sex, CD4+ count (HIV+ only)

Soluble markers of gut integrity, microbial translocation, systemic inflammation and monocyte activation were quantified by ELISA using commercially available kits.

Cellular markers of immune activation were quantified by flow cytometry.

ANOVA and multivariable linear regression were used to compare markers between groups and to test for effect modification by HIV status.

RESULTS

TABLE 1
Demographic, HIV and Substance Use Characteristics by Group

	HIV+heroin+ n=19	HIV+heroin- n=19	HIV-heroin+ n=38	HIV-heroin- n=24
Age, years	47	46.5	37.5	44.3
Male	74%	79%	71%	79%
Race/ethnicity				
White-not Hispanic	53%	11%	68%	71%
Black-not Hispanic	11%	79%	13%	21%
Asian-not Hispanic	0%	5%	5%	4%
Hispanic regardless of race	37%	5%	13%	4%
Current smoker	100%	58%	97%	29%
BMI, kg/m²	23.6	26	25.8	26.6
Trunk fat, g	6839	11576	9126	12136
Hepatitis C	56%	0%	55%	0%
HIV duration, years	11.8	13.2	-	-
ART duration, years	4.5	8.7	-	-
On PI	32%	16%	-	-
On ISTI	58%	68%	-	-
CD4+ cell count, cells/mm³	562	767	-	-
Nadir CD4+ cell count, cells/mm³	201	212	-	-
HIV-1 RNA <200	83%	100%	-	-
Heroin route				
IV	74%	-	100%	-
Intranasal	26%	-	0%	-
Substance use				
Cannabis	53%	73%	58%	25%
Cocaine	47%	5%	50%	8%
Methamphetamine	16%	0%	11%	0%

FIGURE 1
Systemic and Vascular Inflammation Markers

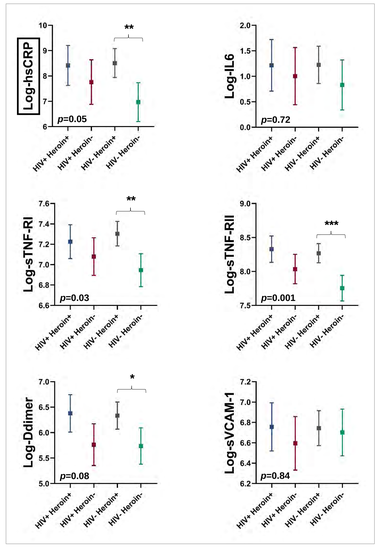
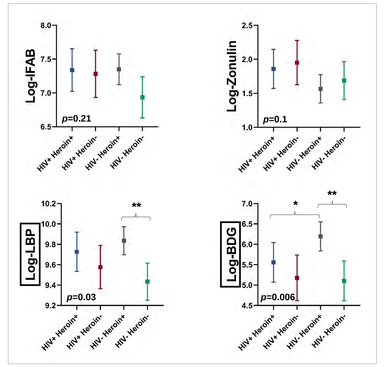


FIGURE 2
Gut Integrity and Microbial Translocation Markers



For all FIGURES, symbols represent adjusted means for each marker by group. Error bars show 95% confidence interval around the means. All means adjusted for age, sex, race, trunk fat, hepatitis c and smoking. $p<0.05$ indicates there are differences in means among the groups. Pairwise comparisons were made including: HIV+heroin+ vs HIV+heroin-; HIV-heroin+ vs HIV-heroin-; and HIV+heroin+ vs HIV-heroin+. For these between group comparisons, * denotes $p<0.05$; ** denotes $p<0.01$; and *** denotes $p<0.001$. Black boxes indicate effect modification by HIV status, ie, $p<0.1$ for heroin use status by HIV status interaction term.

FIGURE 3
Monocyte Activation Markers

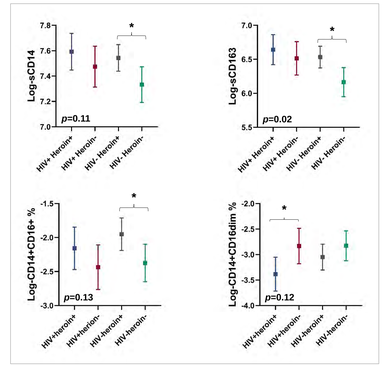
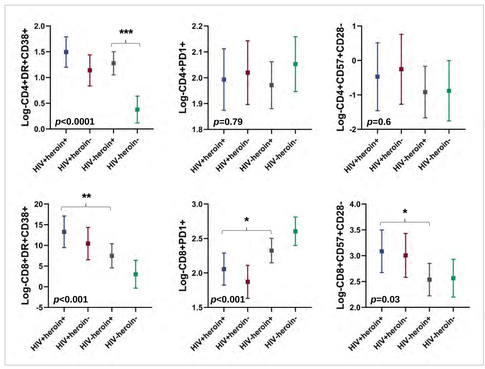


TABLE 2
Association between Heroin Use and % Inflammatory Monocytes (dependent variable)

Variable of interest	Co-variables	Parameter estimate	*p*-value
Heroin use	+ HIV status	**0.20**	0.08
	+ HIV status + **LBP**	**0.06**	**0.60**
	+ HIV status + IFAB	0.19	0.08
	+ HIV status + zonulin	0.21	0.08

FIGURE 4
T Cell Activation, Exhaustion and Senescence Markers



Heroin use is associated with **altered gut integrity, increased systemic inflammation and immune activation**. Some markers were higher in heroin users with HIV which may portend higher risk of poor outcomes; however, having HIV did not appear to substantially worsen the multiple effects heroin had on these immune markers.

CONCLUSIONS

- **Active heroin use** was independently associated with:
  - higher microbial translocation (LBP, BDG),
  - greater systemic inflammation (hsCRP, sTNF-RI and –RII, D-dimer),
  - increased monocyte activation (sCD163 and CD14+CD16+ monocytes),
  - and CD4+ activation (CD4+HLA-DR+CD38+ lymphocytes).
- **HIV infection** was associated with:
  - greater gut permeability (zonulin),
  - increased monocyte activation (sCD163),
  - increased activated CD4+ and CD8+ lymphocytes (HLA-DR+CD38+ lymphocytes)
  - and CD8+ lymphocyte senescence (CD57+CD28- lymphocytes).
- HIV status tended to modify the effect between heroin use and hsCRP, LBP and BDG; however, in stratified models, there were smaller differences in the markers between the groups with HIV compared to the groups without HIV likely because of the heightened concentration of these markers among people with HIV regardless of heroin use.
- Greater microbial translocation (LBP) may be in the causal pathway between heroin use and increased monocyte activation (proportion of CD14+CD16+ monocytes).

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