



# Immune activation and risk of HIV-1 transmission among HIV-1 serodiscordant couples

Contact Information:  
Erin Kahle  
Emory University  
1518 Clifton Rd NE  
Atlanta, GA 30307  
404-712-8738  
erin.kahle@emory.edu

Erin M. Kahle<sup>1</sup>, Michael Bolton<sup>2</sup>, James Hughes<sup>1</sup>, Deborah Donnell<sup>2</sup>, Connie Celum<sup>1</sup>, Jairam Lingappa<sup>1</sup>, Allan Ronald<sup>3</sup>, Guy de Bruyn<sup>4</sup>, Julie McElrath<sup>2</sup>, Jared M. Baeten<sup>1</sup> for the Partners in Prevention HSV/HIV Transmission Study

<sup>1</sup> University of Washington, Seattle, WA, USA; <sup>2</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA; <sup>3</sup> Makerere University, Kampala, Uganda; <sup>4</sup> University of Witwatersrand, Johannesburg, South Africa

## BACKGROUND

- Immune activation is a distinctive, well-known characteristic of chronic HIV infection associated with faster disease progression<sup>1-3</sup>
- A heightened pro-inflammatory state has been hypothesized to enhance HIV-1 transmission - both susceptibility of HIV-1-exposed persons and infectiousness of HIV-1-infected persons, although few studies have directly addressed the role of immune activation in HIV-1 transmission
- Insight into the role of innate and adaptive immune function and HIV-1 susceptibility and infectiousness is an important factor in the development of effective prophylactic and therapeutic HIV-1 vaccines.
- We assessed whether differences in immune activation, as measured by a panel of cytokines, were associated with increased risk of HIV-1 transmission among heterosexual HIV-1 serodiscordant couples

**Table 1. Characteristics of case-control cohort**

Couple Characteristics	Number (%) or median (IQR)	
	Couples with HIV-1 acquisition, N=120	Couples without HIV-1 acquisition, N=321
<b>Couple Characteristics</b>		
Female gender, HIV-1 infected partner	60 (50.0%)	114 (35.5%)
East African (vs. southern African)	79 (65.8%)	219 (68.2%)
Married/living with HIV-1 infected partner	112 (93.3%)	299 (93.2%)
Number of children within partnership	1 (0-2)	1 (0-2)
Unprotected sex at visit selected for cytokine testing	50 (41.7%)	61 (19.0%)
<b>Characteristics of HIV-1 susceptible partner</b>		
Age, in years	29 (24-37)	33 (28-41)
Any syndromic diagnosis of genital tract infection*	18 (15.0%)	15 (4.7%)
<b>Characteristics of HIV-1 infected partner</b>		
Age, in years	30 (26-35)	33 (27-39)
Any syndromic diagnosis of genital tract infection*	14 (11.8%)	35 (10.9%)
HIV-1 plasma viral load, log <sub>10</sub> copies/mL	4.9 (4.3-5.3)	4.0 (3.3-4.8)

\*Includes urethritis, cervicitis, vaginitis, genital ulcer disease, pelvic inflammatory disease, herpes simplex virus and lymphogranuloma venereum  
IQR=interquartile range

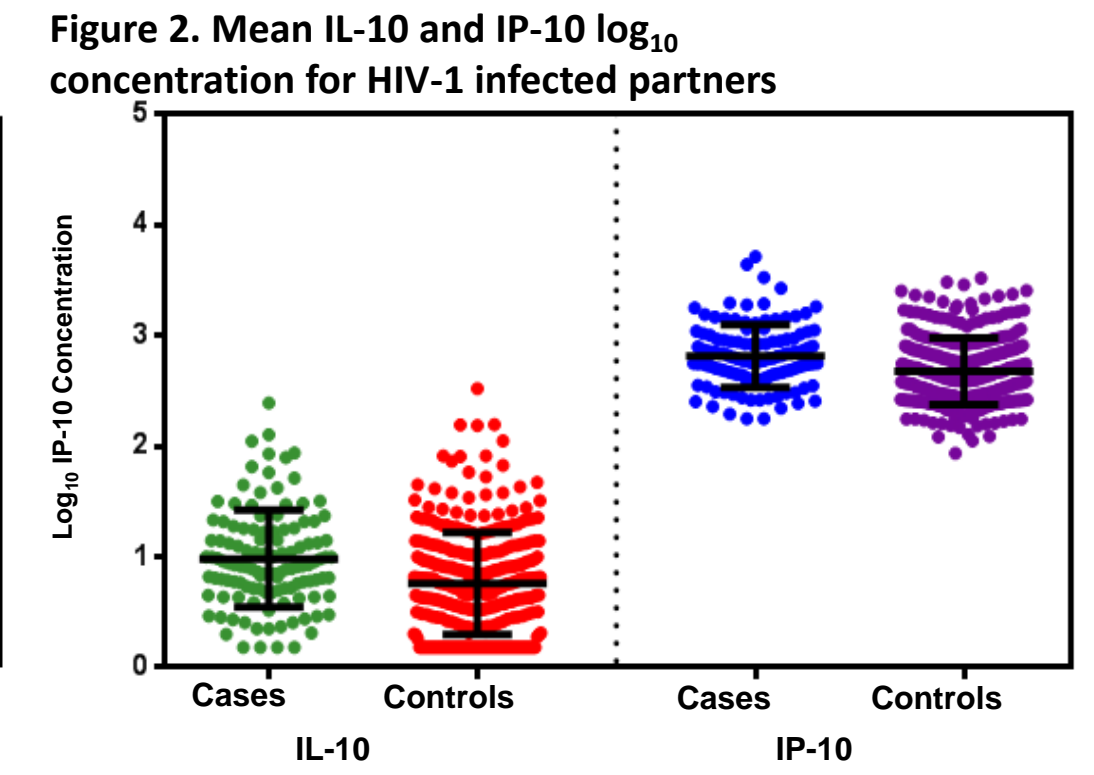
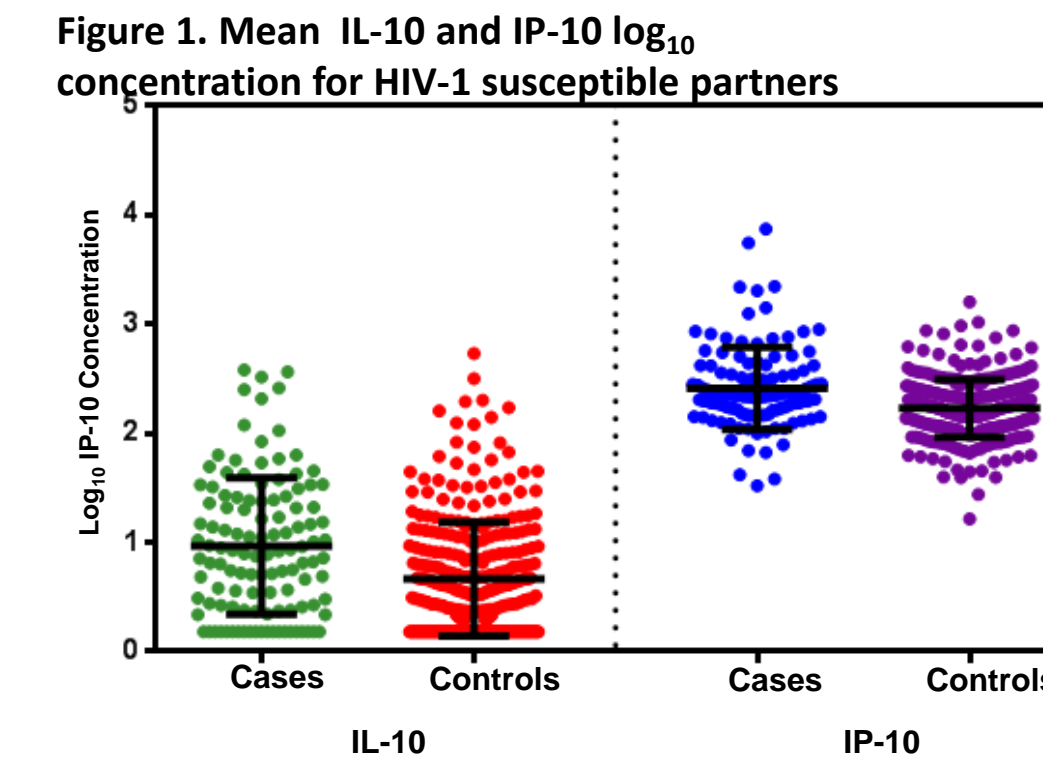
**Table 2. Mean (range) log<sub>10</sub> concentration of cytokine analytes in blood plasma**

Analyte	HIV-1 susceptible partners				HIV-1 infected partners			
	Seroconverters, N=120	Non-seroconverters, N=321	Unadjusted p-value	Adjusted p-value**	Transmitters, N=120	Non-transmitters, N=321	Unadjusted p-value	Adjusted p-value**
EGF	2.23 (0.18-3.21)	2.35 (0.18-3.33)	0.02	0.3	2.14 (0.18-3.15)	2.23 (0.18-3.13)	0.1	0.3
Eotaxin	1.98 (0.18-2.87)	1.93 (0.18-2.88)	0.1	0.9	1.93 (0.18-3.18)	1.98 (0.65-2.66)	0.2	0.99
Fractalkine	1.27 (0.18-3.78)	1.14 (0.18-3.81)	0.2	0.99	1.07 (0.18-3.41)	1.02 (0.18-3.54)	0.6	0.99
G-CSF	1.57 (0.18-3.06)	1.46 (0.51-3.35)	0.004	0.1	1.64 (0.52-2.52)	1.56 (0.18-2.84)	0.01	0.1
GM-CSF	0.92 (0.18-3.58)	0.86 (0.18-3.37)	0.5	0.99	0.82 (0.18-3.49)	0.8 (0.18-3.43)	0.8	0.99
IFN $\gamma$	1 (0.18- 3.1)	0.86 (0.18-2.86)	0.07	0.8	1.13 (0.18- 3.4)	1.16 (0.18-3.27)	0.7	0.99
IL-10	0.91 (0.18-2.97)	0.66 (0.18-2.73)	<0.001	0.001	0.98 (0.18-2.39)	0.76 (0.18-2.52)	<0.001	0.003
IL-12 (p40)	0.69 (0.18-2.76)	0.54 (0.18-2.99)	0.03	0.4	0.92 (0.18-3.29)	0.75 (0.18-3.13)	0.03	0.3
IL-12 (p70)	0.68 (0.18-3.16)	0.49 (0.18-3.16)	0.01	0.2	0.49 (0.18-2.92)	0.56 (0.18-3.72)	0.3	0.99
IL-13	0.49 (0.18-2.86)	0.39 (0.18-2.63)	0.09	0.8	0.32 (0.18-2.36)	0.3 (0.18-3.02)	0.7	0.99
IL-17	0.71 (0.18- 2.6)	0.6 (0.18-2.56)	0.1	0.9	0.47 (0.18-2.54)	0.52 (0.18-2.61)	0.4	0.99
IL-1 $\alpha$	0.5 (0.18-3.31)	0.49 (0.18-3.21)	0.9	0.99	0.29 (0.18- 2.9)	0.3 (0.18-2.45)	0.9	0.99
IL-1 $\beta$	0.47 (0.18-2.99)	0.41 (0.18-2.73)	0.3	0.99	0.34 (0.18-2.97)	0.28 (0.18-2.68)	0.2	0.99
IL-1 $\alpha$	0.61 (0.18-2.45)	0.58 (0.18- 2.6)	0.6	0.99	0.58 (0.18-3.66)	0.56 (0.18-3.27)	0.8	0.99
IL-2	0.5 (0.18-2.79)	0.42 (0.18-2.43)	0.1	0.9	0.35 (0.18- 2.8)	0.34 (0.18-2.78)	0.8	0.99
IL-4	0.26 (0.18- 2.7)	0.2 (0.18-2.57)	0.07	0.8	0.31 (0.18-3.17)	0.23 (0.18-2.73)	0.1	0.8
IL-5	0.32 (0.18-1.81)	0.27 (0.18-1.84)	0.1	0.9	0.33 (0.18- 1.7)	0.27 (0.18-2.02)	0.06	0.9
IL-6	0.81 (0.18-3.01)	0.73 (0.18-2.97)	0.3	0.99	0.5 (0.18-2.52)	0.48 (0.18-3.44)	0.6	0.99
IL-7	0.59 (0.18-2.84)	0.5 (0.18-2.46)	0.1	0.9	0.42 (0.18-2.31)	0.38 (0.18-2.31)	0.3	0.8
IL-8	1.64 (0.18- 4)	1.7 (0.33- 4)	0.4	0.99	1.61 (0.18- 4)	1.62 (0.41- 4)	0.9	0.99
IP-10	2.37 (1.52-3.87)	2.23 (1.21- 3.2)	<0.001	<0.001	2.81 (2.25-3.71)	2.68 (1.94-3.52)	<0.001	0.001
MCP-1	2.35 (0.18-3.36)	2.34 (1.47-3.63)	0.9	0.99	2.43 (1.4-3.67)	2.45 (1.25-3.74)	0.6	0.99
MIP-1 $\alpha$	1.83 (0.18- 4)	1.9 (0.18- 4)	0.4	0.99	1.72 (0.18-3.71)	1.82 (0.18- 4)	0.3	0.99
MIP-1 $\beta$	1.97 (0.18-3.11)	1.96 (0.66- 3.1)	0.8	0.99	1.88 (0.74-3.12)	1.85 (0.18-3.16)	0.4	0.99
RANTES	3.18 (0.18-3.83)	3.21 (0.18-3.84)	0.4	0.99	3.16 (0.83- 3.7)	3.13 (1.59- 4)	0.3	0.99
scd40l	2.88 (0.18-3.75)	2.85 (0.18-3.74)	0.6	0.9	2.55 (0.18-3.06)	2.62 (0.18-3.22)	0.1	0.99
TGF- $\alpha$	1.03 (0.18- 2.8)	0.96 (0.18- 3.7)	0.1	0.7	0.83 (0.18-1.82)	0.79 (0.18-2.28)	0.2	0.05
TNF- $\alpha$	1.04 (0.18-2.62)	0.96 (0.18-2.55)	0.06	0.99	1.12 (0.18-2.49)	1 (0.18-2.59)	0.002	0.4
VEGF	2.13 (0.18-3.33)	2.16 (0.18-3.38)	0.7	0.99	2.06 (0.18-3.32)	2.2 (0.18-3.47)	0.1	0.8

\*P-value estimated from two-sided Student's T-test comparing mean difference in mean concentrations between seroconverters and non-seroconverters  
\*\*P-value adjusted for multiple comparisons using permutation t-test for means

Hotelling T<sup>2</sup> p<0.001 comparing global mean cytokine concentrations between cases and controls for both HIV-1 susceptible and HIV-1 infected partners

After controlling for multiple comparisons, higher mean log<sub>10</sub> concentrations of IL-10 and IP-10 were significantly associated with HIV-1 acquisition and transmission



**Table 3. Logistic regression models associating cytokine concentrations with HIV-1 risk**

	Adjusted, individual cytokine models				Adjusted, HIV-1 susceptible partner only	Adjusted, HIV-1 infected partner only	Adjusted, both partners*
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
<b>HIV-1 susceptible partner</b>							
IL-10, per 1 log <sub>10</sub> increase	2.15 (1.43-3.23)				1.61 (1.03-2.54)		1.55 (0.97-2.48)
IP-10, per 1 log <sub>10</sub> increase		6.62 (2.78-15.78)			4.51 (1.77-11.48)		4.76 (1.85-12.23)
<b>HIV-1 infected partner</b>							
IL-10, per 1 log <sub>10</sub> increase			2.04 (1.21-3.44)			1.96 (1.16-3.32)	1.87 (1.08-3.23)
IP-10, per 1 log <sub>10</sub> increase				1.85 (0.79-4.33)		1.59 (0.67-3.75)	1.74 (0.71-4.25)

All models adjusted for gender of HIV-1 infected partner, plasma HIV-1 RNA concentration for the HIV-1 infected partner (log<sub>10</sub> copies/mL), report of unprotected sex within the partnership (yes/no), and any STI diagnosis in either the HIV-1 susceptible or infected partner

\*In this model with IL-10 and IP-10 in both HIV-1 susceptible and infected partners, the adjusted ORs for the covariates were: female gender of HIV-1 infected partner (adjOR 1.74, 95% CI 1.04-2.93, p=0.04), plasma HIV-1 RNA (adjOR 1.93 per 1 log<sub>10</sub> increase, 95% CI 1.42-2.63, p<0.001), unprotected sex (adjOR 3.18, 95% CI 1.85-5.44, p<0.001), STI in the HIV-1 susceptible partner (adjOR 2.17, 95% CI 0.88-5.33, p=0.09), and STI in the HIV-1 infected partner (adjOR 0.97, 95% CI 0.45-2.09, p=0.9)

- Inhibitory activities of IL-10 may limit the immune response necessary to prevent HIV-1 transmission, as well as allowing for greater viral load production to increase infectiousness
- IP-10 not well understood in HIV-1 transmission but may contribute to increased T-cell production in HIV-1 susceptible partner
- Role of immune activation in HIV-1 transmission is critical in understanding HIV-1 pathogenesis
- Results of these data may be applicable to future research of immune response in HIV-1 transmission and vaccine development

Higher concentrations of blood plasma IL-10 and IP-10 in both HIV-1 transmitting partners and HIV-1 acquiring partners compared to non-transmitting couples suggest a potential parallel function of immune activation risk for HIV-1 susceptibility and infectiousness

## REFERENCES

- Lawn SD, Butera ST, Folks TM. Contribution of immune activation to the pathogenesis and transmission of human immunodeficiency virus type 1 infection. *Clin Microbiol Rev* 2001;14:753-777, table of contents.
- Hazenberg MD, Otto SA, van Benthem BH, Roos MT, Coutinho RA, Lange JM, et al. Persistent immune activation in HIV-1 infection is associated with progression to AIDS. *AIDS* 2003;17:1881-1888.
- Bentwich Z, Kalinkovich A, Weisman Z, Grossman Z. Immune activation in the context of HIV infection. *Clin Exp Immunol* 1998;111:1-2.
- Celum C, Wald A, Lingappa JR, Magaret AS, Wang RS, Mugo N, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med* 2010;362:427-439.
- Lingappa JR, Petrovski S, Kahle E, Fellay J, Shianna K, McElrath MJ, et al. Genomewide association study for determinants of HIV-1 acquisition and viral set point in HIV-1 serodiscordant couples with quantified virus exposure. *PLoS One* 2011;6:e28632

Funding: US National Institutes of Health (grant R01 AI09696) and the Bill & Melinda Gates Foundation (grants 26469 and 41185)