Poster #853

Sex-related Inflammatory Marker Changes Pre and Post Antiretroviral Treatment (ART) Initiation

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Background

- Immune activation and inflammation are associated with HIV progression and death[1,2]
- ART reduces morbidity and mortality of HIV but only partially reduces immune activation[2]
- Women, on average, have lower plasma HIV RNA (VL) early in HIV infection compared to men, but progress to AIDS at the same rate, if not faster, than men[3,4].
- Sex-specific differences in immune activation and inflammation pre- and post- ART initiations could explain these observed clinical differences, but these have not been well studied.[5]

Methods

We measured inflammatory and immune activation markers (IFNγ, TNFα, IL6, IL18, IP10, CRP, lipopolysaccharide (LPS), sCD14, EndoCAb IgM, activated CD4+/DR+/38+ and activated CD8+/DR+/38+) pre-ART, at week 24 and at week 48 post-ART

Study population: Random sub-cohort enrolled in ACTG A5175 (PEARLS), a study comparing 3 different ART regimens in 9 different countries, who achieved virologic suppression (< 400 copies/mL) by week 24 or 48 of ART.

Study Sites:



Analysis:

- Within-sex comparison of median marker levels between baseline and week 48
- Multivariable random effects modeling adjusting for age, country, BMI, baseline CD4, log_{10}VL, hemoglobin (Hb) and randomized ART arm

Results

Table 1. Baseline characteristics, by sex

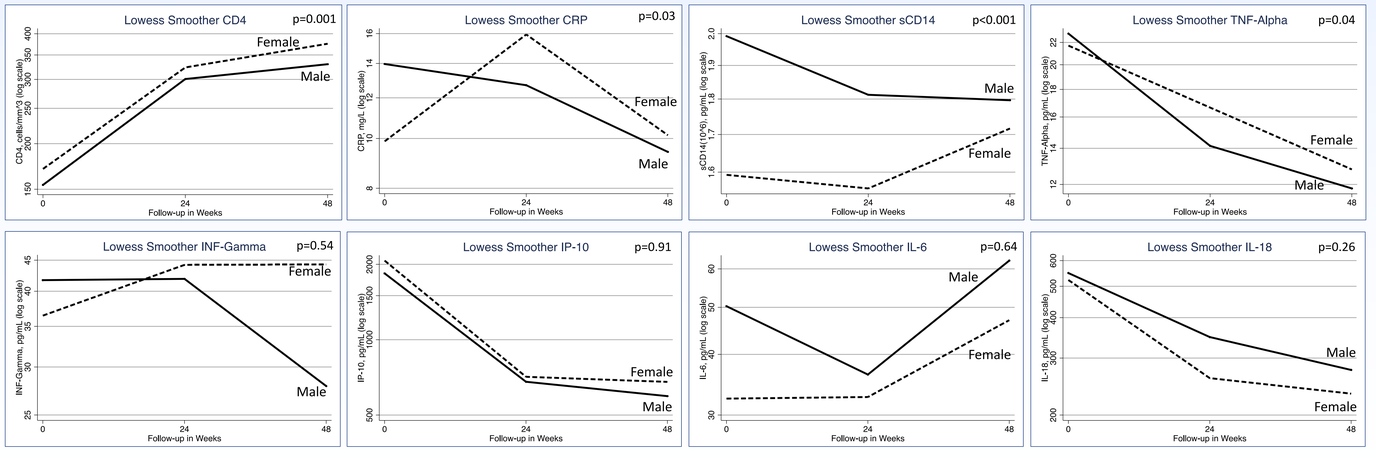
Characteristics	Male (n=125)	Female (n=121)	p value
Age, median (IQR) (years)	36 (31-41)	33 (29-40)	0.03
BMI, median (IQR)	21 (20-24)	22 (19-25)	0.37
Country			
Brazil	25 (20%)	4 (3%)	<0.001
Haiti	15 (12%)	15 (12%)	
India	14 (11%)	12 (9%)	
Malawi	5 (4%)	21 (17%)	
Peru	17 (13%)	11 (9%)	
South Africa	9 (7%)	19 (15%)	
Thailand	11 (8%)	17 (14%)	
US	17 (13%)	7 (5%)	
Zimbabwe	12 (9%)	15 (12%)	
Race			
White	25 (20%)	2 (1%)	<0.001
Black	54 (43%)	77 (64%)	
Asian	25 (20%)	29 (24%)	
Other	21 (16%)	12 (10%)	
ART regimen			
3TC/ZDV+EFV	45 (36%)	42 (34%)	0.57
ATV/FTC/DDI-EC	38 (30%)	44 (36%)	
FTC/TDF+EFV	42 (33%)	35 (28%)	
Median baseline CD4, cells/mm^3 (IQR)	165 (82-219)	195 (119-23)	0.02
Baseline CD4			
>=200	42 (33%)	56 (46%)	0.09
100-199	42 (33%)	37 (30%)	
<100	41 (32%)	28 (23%)	
Median baseline log VL, c/mL (IQR)	5.1 (4.7-5.5)	4.9 (4.4-5.4)	0.01
Median baseline Hb	13 (12-14)	11 (10-12)	<0.001

Table 2. Summary of markers at weeks 0, 24, and 48, by sex

Median Marker	Week 0			Week 24			Week 48		
	Male (n=125)	Female (n=121)	p-value	Male (n=119)	Female (n=115)	p-value	Male (n=118)	Female (n=113)	p-value
CD4, cells/mm^3 (IQR)	165 (82 – 219)	195 (119 – 234)	**0.01**	292 (191 – 391)	318 (238 – 408)	0.51	316 (228 – 424)	374 (270 – 505)	**0.04**
Log 10 VL, c/mL (IQR)	5.1 (4.7 – 5.5)	4.9 (4.4 – 5.4)	**0.01**	NA	NA	-	NA	NA	-
INF-γ, pg/mL (IQR)	16 (6 – 55)	19 (6 – 47)	0.46	19 (6 – 40)	22 (2 – 56)	0.32	13 (3 – 36)	20 (7 – 64)	**0.04**
TNF-α, pg/mL (IQR)	20 (13 – 26)	17 (12 – 26)	0.15	10 (8 – 16)	12 (9 – 19)	0.12	9 (7 – 13)	11 (7 – 16)	0.06
IL-6, pg/mL (IQR)	25 (9 – 53)	23 (8 – 38)	0.38	23 (9 – 43)	23 (7 – 57)	0.88	16 (7 – 35)	23 (6 – 54)	0.35
IL–18, pg/mL (IQR)	383 (163 – 848)	307 (138 – 737)	0.34	219 (110 – 417)	159 (60 – 347)	0.14	198 (85 – 340)	152 (40– 347)	0.46
IP-10, pg/mL (IQR)	1289 (584 – 2325)	1203 (590 – 2856)	0.73	405 (245 – 762)	471 (200 – 815)	0.48	325 (196 – 622)	419 (196 – 748)	0.07
CRP, mg/L (IQR)	4.86 (1.7 – 12)	2.1 (0.96 – 8.9)	**0.002**	2.8 (1.3 – 8.7)	4 (1.3 – 8.8)	0.30	3.3 (1.1 – 8.3)	3.3 (1.2 – 8.3)	0.88
Detectable LPS n (%)*	66 (53%)	38 (36%)	**0.01**	61 (55%)	46 (46%)	0.21	65 (61%)	52 (51%)	0.16
EndoCAb, MMU/mL (IQR)	45 (28 – 62)	52 (31 – 83)	**0.04**	NA	NA	-	NA	NA	-
sCD14 (10^6), pg/mL (IQR)	2.3 (0.71 – 2.8)	1.8 (0.48 – 2.6)	**0.009**	2.0 (0.9 – 2.6)	1.5 (0.4 – 2.4)	**0.03**	2.0 (1.1 – 2.5)	1.9 (0.6 – 2.6)	0.93
CD4+/ DR+/38+ (IQR)#	25 (15 – 38)	21 (15 – 29)	0.09	NA	NA	-	NA	NA	-
CD8+/DR+/38+ (IQR)#	47 (36 – 56)	44 (35 – 55)	0.40	NA	NA	-	NA	NA	-

NA= results unavailable at the time of abstract/poster preparation
** Percent detectable LPS was used as many had no detectable LPS; # Viable samples available for 47 men and 55 women*

Figure 1. Unadjusted random effects model of sex differences in inflammatory markers over 48 wks represented as Lowess curves



Results (cont'd)

In **multivariate analysis** of changes over 48 weeks, women compared to men had:

- Greater slope change: CD4 (42.15/mm^3, CI 18.11-66.2, p=0.001), TNFα (3.51 ng/mL (CI 0.20-6.82, p=0.04)
- Less slope change: Log VL (0.27 c/mL, CI 0.05-0.49, p=0.02), CRP (6.28mg/L, CI 0.65-11.91, p=0.03), log sCD14 (3.8 ng/mL, CI 1.7-5.9, p<0.001)

Conclusions & Implications

1. Before ART, women had a more favorable immune profile than men, including:
   - Higher CD4 count
   - Lower viral load
   - Lower CRP
   - Lower detectable LPS
   - Lower sCD14
2. In the multivariate analysis, women had a greater slope change in CD4 and TNF-α than men, but less of a change in
   - Log viral load
   - CRP
   - sCD14
3. By week 48, men and women had similar levels of CRP, detectable LPS and sCD14
   - At week 48, men still had a significantly lower CD4 than women, but also had significantly lower IFN-γ levels with a trend towards lower TNF-α and IP-10 levels.
4. Increased inflammation/immune activation may result in functional T cell anergy and premature CD4 apoptosis, both of which can lead to HIV progression. These factors should improve with decreased viral loads post-ART.
5. Post-ART increases in markers such as CRP, LPS, and sCD14 in women may reflect an ongoing sex-related inflammatory response and explain why women progress to AIDS with lower viral loads.

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