Persistently High IL-18 and sCD14 are Independently Associated with Clinical Failure

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Abstract #313

Background

Despite the success of combination antiretrovirals (ARV), a subset of HIV-infected patients who initiate ARV develop early clinical progression to AIDS; therefore some ARV initiators are not fully benefitted by ARV. AIDS progression is driven by immune activation that is only partially attenuated by ARV. We studied the effect of persistent inflammation on clinical failure during ARV among multi-country ACTG 5175 trial participants.

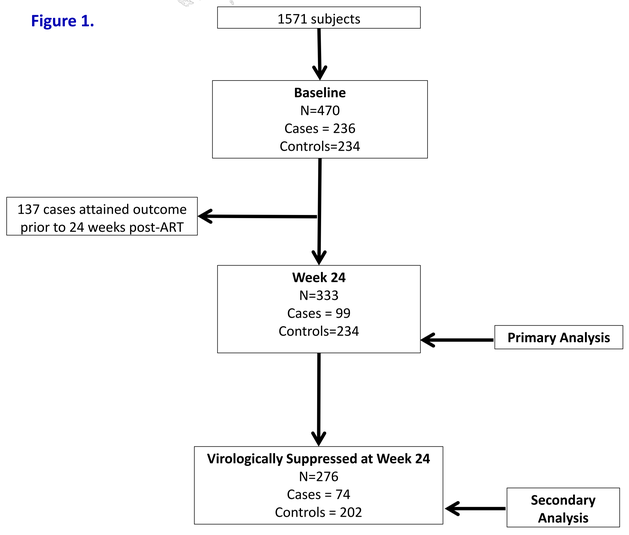
Methods

A nested case-control study was designed within the A5175 multi-national randomized trial of three ARV regimens in ARV-naïve individuals who were followed for 96 weeks. Cases of clinical failure (defined as WHO Stage 3 or 4 disease after 24 weeks of ARV) and controls were randomly selected from the full cohort. Biomarkers of immune activation (IL-6, IP-10, IL-18, sCD14, TNFα, and IFNγ) were measured in plasma samples obtained at baseline and 24 weeks. Persistent immune activation was defined as having an elevated immune activation biomarker at baseline and after 24 weeks of ARV. Associations between biomarkers and clinical failure were examined using weighted multivariate Cox-proportional hazard models.

In a secondary analysis, only cases and controls among persons who were virologically suppressed by 24 weeks were examined for persistently elevated biomarkers that predicted clinical failure.



Figure 1.



Results

Table 1. Baseline characteristics of study population for the Primary Analysis

Baseline Characteristics	Overall (n=333)	Cases (n=99)	Controls (n=234)	P-value
Female, n (%)	160 (48%)	45 (45%)	115 (49%)	0.55
Age, Median (IQR)	34 (29 – 40)	34 (28 – 38)	35 (29 – 41)	0.20
Country				p < 0.001
Brazil	36 (11%)	7 (7%)	29 (12%)	
Haiti	30 (9%)	5 (5%)	25 (11%)	
India	53 (16%)	33 (33%)	20 (9%)	
Malawi	44 (13%)	20 (20%)	24 (10%)	
Peru	32 (10%)	4 (4%)	28 (12%)	
South Africa	38 (11%)	13 (13%)	25 (11%)	
Thailand	31 (9%)	3 (3%)	28 (12%)	
US	37 (11%)	8 (8%)	29 (12%)	
Zimbabwe	32 (10%)	6 (6%)	26 (11%)	
CD4+ T cells/µL, Median (IQR)	180 (94 – 229)	182 (108 – 216)	180 (90 – 233)	0.42
Log_{10} HIV RNA , Median (IQR)	5.05 (4.54 – 5.45)	5.05 (4.53 – 5.43)	5.02 (4.55 – 5.47)	0.91
TB, n(%)	67 (20%)	30 (30%)	37 (16%)	0.004
HBsAg, n(%)	15 (5%)	2 (2%)	13 (6%)	0.25
HIV RNA < 400 cp/mL (Week 24), n (%)	276 (87%)	74 (77%)	202 (91%)	0.002

Table 2. Prevalence of persistent Immune Activation at Week 24

Marker	N	Prevalence	95% Exact Binomial CI
IL-6 (pg/mL)	249	13%	10% - 19%
IP-10 (pg/mL)	249	2%	0.7% - 5%
IL-18 (pg/mL)	242	7%	4% - 11%
sCD14 (pg/mL)	246	13%	9% - 18%
TNFα (pg/mL)	249	4%	2% - 7%
IFNγ (pg/mL)	249	14%	10% - 19%

Among subjects from the random sub-cohort, persistent inflammation was defined at week 24 by values in the highest quartile at baseline and at week 24.

Table 3. Univariable and multivariable analysis for clinical failure at 96 weeks

Marker > Q3 (24 wks)	Overall	Control	Case	Univariable Analysis		Multivariable Analysis Model 1		Multivariable Analysis Model 2	
				IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value
IL-6 (pg/mL)	34 (14%)	28 (15%)	6 (11%)	0.65 (0.28 – 1.52)	0.33	0.65 (0.26 – 1.63)	0.36	0.66 (0.26 – 1.65)	0.38
IP-10 (pg/mL)	5 (2%)	3 (2%)	2 (4%)	2.39 (0.58 – 9.79)	0.23	2.15 (0.42 – 11.1)	0.36	2.34 (0.45 – 12.26)	0.31
IL-18 (pg/mL)	16 (7%)	8 (4%)	8 (14%)	2.86 (1.35 – 6.04)	0.006	3.84 (1.62 – 9.14)	0.002	3.59 (1.48 – 8.74)	0.005
sCD14 (pg/mL)	33 (13%)	20 (10%)	13 (24%)	2.42 (1.30 – 4.51)	0.006	2.34 (1.08 – 5.06)	0.03	2.21 (1.01 – 4.80)	0.046
TNFα (pg/mL)	9 (4%)	6 (3%)	3 (5%)	1.23 (0.38 – 3.93)	0.73	1.30 (0.37 – 4.62)	0.69	1.16 (0.32 – 4.13)	0.82
IFNγ (pg/mL)	36 (14%)	35 (18%)	1 (2%)	0.10 (0.01 – 0.74)	0.02	0.08 (0.01 – 0.61)	0.02	0.08 (0.01 – 0.66)	0.02

Two multivariable models were fitted.
Model 1: was adjusted for, age, sex, country, random treatment assignment, baseline BMI CD4, log viral load and TB.
Model 2: was adjusted for, age, sex, country, random treatment assignment, baseline BMI CD4, log viral load, viral suppression at week 24 (VL < 400) and TB.

Table 4. Persistent Inflammation at Week 24 among virologically suppressed

Marker	N	Prevalence	95% Exact Binomial CI
IL-6 (pg/mL)	218	14%	9% - 19%
IP-10 (pg/mL)	218	2%	0.5% - 5%
IL-18 (pg/mL)	212	6%	3% - 10%
sCD14 (pg/mL)	216	12%	8% - 17%
TNFα (pg/mL)	218	3%	1% - 6%
IFNγ (pg/mL)	218	16%	11% - 22%

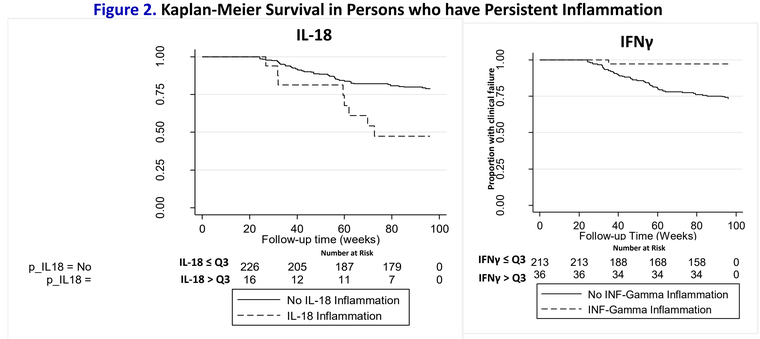
Persistent inflammation was defined by values greater in the highest quartile at baseline and at week 24.

Table 5. Univariable and multivariable analysis for clinical failure at 96 weeks among virologically suppressed

Marker > Q3 (24 wks)	Overall	Control	Case	Univariable Analysis		Multivariable Analysis	
				IRR (95% CI)	p-value	IRR (95% CI)	p-value
IL-6 (pg/mL)	30 (14%)	25 (14%)	5 (11%)	0.72 (0.28 – 1.81)	0.48	0.63 (0.23 – 1.74)	0.37
IP-10 (pg/mL)	4 (2%)	2 (1%)	2 (6%)	2.93 (0.71 – 12.1)	0.14	2.82 (0.52 – 15.2)	0.23
IL-18 (pg/mL)	12 (6%)	7 (4%)	5 (12%)	2.68 (1.05 – 6.82)	0.04	3.10 (1.08 – 9.02)	0.04
sCD14 (pg/mL)	26 (12%)	17 (10%)	9 (22%)	2.51 (1.20 – 5.26)	0.02	2.0 (0.77 – 5.25)	0.16
TNFα (pg/mL)	6 (3%)	5 (3%)	1 (3%)	0.62 (0.09 – 4.51)	0.64	0.64 (0.08 – 5.42)	0.68
IFNγ (pg/mL)	35 (16%)	34 (20%)	1 (2%)	0.12 (0.02 – 0.87)	0.04	0.07 (0.01 – 0.64)	0.02

The multivariate model was adjusted for, age, sex, country, random treatment assignment, baseline BMI CD4, log viral load, viral suppression at week 24 (VL < 400) and TB.

Figure 2. Kaplan-Meier Survival in Persons who have Persistent Inflammation



Summary of Key Results

We found evidence that HIV-infected ARV initiators with persistently high levels of IL-18 and sCD14 before and after ARV initiation were more likely to develop clinical failure than persons who had lower levels of IL-18 and sCD14 at either or both time points. IL-18 and sCD14 are both measures of monocyte activation, which potentially implicates monocytes as contributing to clinical progression. Persistently high levels of IL-18, a result of inflammasome activation, was strongly associated with clinical failure after 24 weeks when only persons who were virologically suppressed at 24 weeks were studied. Persistently elevated IFNγ levels were strongly associated with protection from clinical failure, and this was also true in persons who were virologically suppressed at 24 weeks; persistently elevated IFNγ levels may reflect active CD8+ T cell responses to many of the opportunistic infections to which HIV-infected persons are susceptible.

Acknowledgements

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