#308 Vitamin D, D-dimer, IFNγ and sCD14 predict IRIS in a prospective multi-center study

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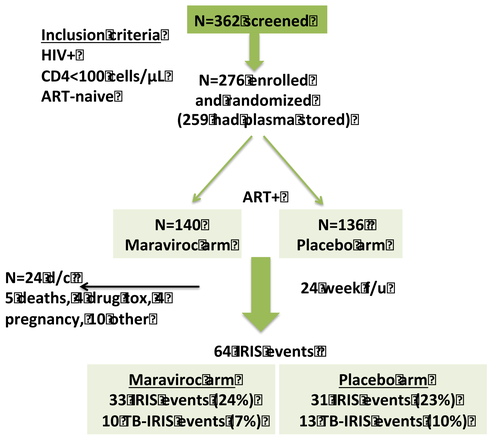
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Introduction and Hypothesis:

- Immune reconstitution inflammatory syndrome (IRIS) in AIDS patients initiating anti-retroviral therapy (ART) is driven by immune dysregulation mechanisms that are poorly understood. In resource-poor settings, IRIS usually occurs within the first few weeks and up to six months of therapy and related resource utilization and mortality can be high. Biomarkers may be useful to risk stratify patients and develop targeted therapies.

- We performed a large prospective substudy within a randomized clinical trial of maraviroc for IRIS prevention, involving South African and Mexican AIDS patients in whom ART was to be initiated, in order to test the hypothesis that pro-inflammatory cytokine expression, myeloid cell activation, coagulation and fibrosis markers were associated with IRIS risk following the reversal of immunosuppression.

Study Design:



Treatment with maraviroc had no effect on the incidence or severity of IRIS

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Methods and Results:

A. Participant data: IRIS events were pre-defined according to the AIDS Clinical Trials Group (ACTG) IRIS criteria and were reviewed prospectively. Clinical data were gathered by health care providers at the point of care.

B. Biomarker measurement: All plasma samples were obtained at study enrollment, prior to ART initiation, and were stored at -80°. Biomarkers were measured in duplicate after a single freeze-thaw cycle in batched assays. The following biomarkers were measured and not significantly associated with IRIS: serum amyloid A, P-selectin, IL-12, IL-17, hyaluronic acid, sCD163, fibrinogen, von Willebrand factor, proteins C & S, IL1-b, and leukotriene B4.

C. Statistical methods: 1) Comparisons of baseline values between participants who did and did not experience IRIS were made using t-tests for continuous variables and chi-square tests for binary variables. 2) Results of laboratory tests were analyzed as continuous variables and non-normal variables were log-transformed prior to comparisons. 3) Biomarkers were individually tested while adjusting for significant covariates selected through forward stepwise selection 4) Logistic regression was used to examine the association between biomarker levels and IRIS by comparing participants who developed IRIS with the remaining participants who did not.

Table 1. Characteristics of the CADIRIS Study Population at Initiation of ART

	All Patients (N=276)	IRIS Diagnosed (N=64)	IRIS not Diagnosed (N=212)	*P-value*
Age in years, median (IQR)	36.0 (31, 41)	35 (30, 41)	37 (31, 43)	0.65
	n (%)	n (%)	n (%)	
Sex				0.001
Female	98 (36)	15 (23)	83 (39)	
Male	178 (64)	49 (77)	129 (61)	
Treatment group				0.74
Maraviroc	140 (51)	33 (52)	107 (50)	
Placebo	136 (49)	31 (48)	105 (50)	
Country				0.08
South Africa	152 (55)	26 (41)	126 (59)	
Mexico	124 (45)	38 (61)	86 (42)	
Baseline characteristics				
Prior AIDS-defining illness	163 (59)	51 (80)	112 (53)	0.0001
Tuberculosis	53 (19)	16 (25)	37 (17)	0.179
CD4+ cell count (mm^3), median (IQR)	34 (18, 59)	30.5 (12, 59.5)	36.0 (19, 58.5)	0.394
CD8+ cell count (mm^3), median (IQR)	476.5 (341.5, 743.0)	431 (313.5, 620.0)	497.5 (348.5, 758.5)	0.192
Albumin (g/dl), median (IQR)	3.8 (3.3, 4.0)	3.68 (3.4, 4.0)	3.8 (3.4, 4.0)	0.515
Hemoglobin (g/dl), median (IQR)	12.1 (10.8, 13.4)	11.8 (10.7, 13.0)	12.3 (11, 13.7)	0.08
Plasma HIV RNA (log copies/ul), median (IQR)	5.4 (5.0-5.7)	3.9 (1.75-7.05)	4.3 (2.3-6.7)	0.442

Table 2. Biomarker Levels (Univariate Analysis)

Biomarker	IRIS	No IRIS	Unadjusted *P-value*	Adjusted *P-value*
IFNγ (pg/mL)	5.65 (2.25, 10.6)	2.72 (1.44, 5.17)	<0.001	0.01*
CRP (mg/L)	4.54 (1.84, 13.7)	2.47 (1.27, 8.99)	0.03	0.28
IP-10 (pg/mL)	3.43 (3.19, 3.59)	3.31 (3.10, 3.49)	0.005	0.16
TNFa (pg/mL)	19.9 (15.4, 28.1)	15.5 (12.1, 21.9)	0.042	0.23
sCD14 (µg/mL)	2400 (1988, 3235)	2014 (1645, 2471)	<0.001	0.01*
IL-6 (pg/mL)	2.48 (1.49, 4.02)	1.71 (1.23, 3.08)	0.048	0.48
IL-8 (pg/mL)	10.5 (6.61, 15.4)	7.62 (4.84, 13.8)	0.04	0.79
IL-10 (pg/mL)	14.0 (9.38, 20.3)	7.60, 15.7)	0.04	0.19
Vitamin D (ng/mL)	8.22 (4.99, 13.8)	9.65 (5.83, 17.9)	0.038	0.04*
D-Dimer (mg/L)	1.32 (0.84, 2.34)	0.85 (0.52, 1.52)	<0.001	0.008*

*Denotes significance after multivariate adjustment for gender, hemoglobin, and prior AIDS-defining illness.

Table 3. Adjusted Odds Ratios for IRIS

Biomarker	Odds ratio	*95% confidence interval*
Vitamin D	0.37	0.14-0.95
D-dimer	3.85	1.43-10.3
IFNγ	2.86	1.28-6.41
sCD14	1.00	1.00-1.001

ORs reported are per unit increase in biomarker level after log transformation. ORs were adjusted for covariates selected through forward stepwise selection

Conclusions:

✓ Elevated markers of the Th1 response and monocyte activation (IFNγ, sCD14), coagulation and low vitamin D are independently associated with IRIS

✓ Further evaluation of these biomarkers as possible clinical prediction tools or targets of intervention for IRIS prevention is merited

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