Exuberant Pathogen-Specific Th1 CD4+ T-Cell Responses in MAC-IRIS in HIV Infection

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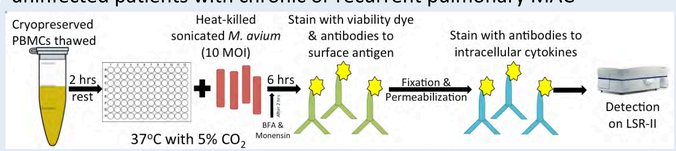
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Background

- Immune reconstitution inflammatory syndrome (IRIS): abberant inflammatory immune response that can occur after initiation of antiretroviral therapy (ART) in HIV-infected patients.[1]
- *Mycobacterium avium* complex (MAC): non-tuberculous mycobacterium that can cause pulmonary infections in immunocompetent hosts and can cause disseminated disease in HIV-infected patients (usually at ≤50 CD4⁺ T cells/μL).[2]
- IRIS pathogenesis has not been fully elucidated but dysregulated activation of CD4⁺ T cells[3] and monocytes[4] and excessive cytokine production[5-6] are involved.
- IRIS events can have high morbidity and mortality.[1]

Methods

- Clinical trials at the NIH:
  - NCT00286767: a completed prospective study of HIV-infected, ART-naïve patients with CD4⁺ T cells <100 cells/μL. Patients were followed for up to 96 weeks after ART-initiation.
  - NCT00018044: a natural history study of mycobacterial disease in HIV-uninfected patients.
- Samples: PBMCs isolated from whole blood obtained pre-ART (week 0), during IRIS, and post-IRIS resolution (week 48) in HIV-infected patients; PBMCs isolated from HIV-uninfected patients with chronic or recurrent pulmonary MAC



- Data was analyzed using FlowJo version 9.7.6. Statistical analyses were performed using GraphPad Prism version 6 using Wilcoxon Sign Ranked test (between time points) and Mann Whitney test (HIV-infected vs. –uninfected patients).

Table 1: Patient characteristics

All values are medians unless otherwise stated

		HIV infected patients	HIV uninfected patients
Number of patients		14	14
Age (IQR)		37 (31-43)	59 (53-69)
Male Gender (%)		10 (71%)	1 (7%)
Race	White Non-Hispanic	1 (7%)	11 (79%)
	White Hispanic	4 (29%)	0
	Black	9 (64%)	1 (7%)
	Asian	0	2 (14%)
BMI Baseline (IQR)		21.3 (19.1-23.7)	22.2 (19.2-24.6)
CD4 Count Baseline (IQR)		8 (5-34)	N/A

Results

Fig 1: IFNγ⁺ & TNF⁺ MAC sp CD4⁺ T cells were increased at IRIS and remained elevated at follow up

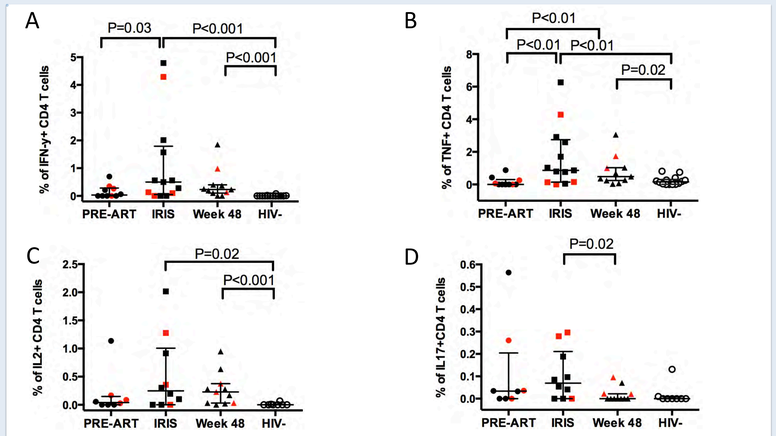


Fig 2: CD4⁺ T cells from HIV-infected patients produced more cytokines following MAC stimulation

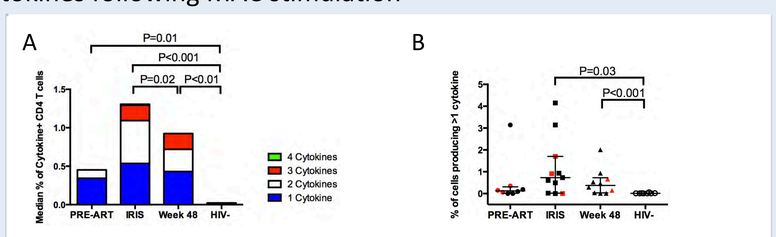
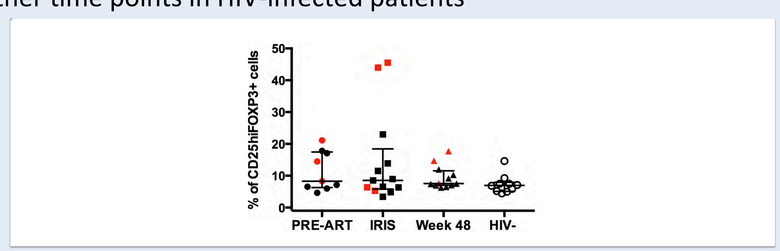


Fig 3: Frequency of T regulatory cells did not differ between IRIS and other time points in HIV-infected patients



Results (cont.)

Fig 4: CD4⁺ T cells from HIV-infected patients had increased inhibitory receptors at IRIS time point and these remained elevated at follow up

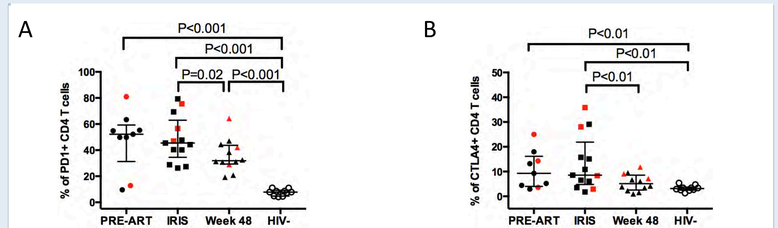
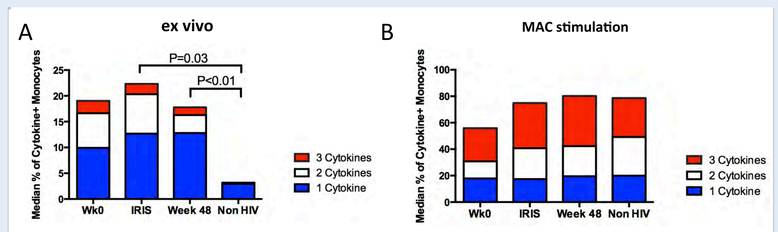


Fig 5: Monocytes *ex vivo* produced more cytokines in IRIS patients, but had similar profiles after stimulation with MAC



Conclusions

- MAC-IRIS is characterized by exuberant and polyfunctional antigen-specific CD4⁺ T-cell responses that persist during ART despite the presence of regulatory T cells and increased expression of inhibitory receptors on T cells.
- Monocytes from MAC-IRIS patients appear more activated with production of pro-inflammatory cytokines directly *ex vivo*, even in the absence of additional stimuli.
- These data suggest that activated monocytes in conjunction with polyfunctional CD4⁺ T cells play a central role in MAC-IRIS pathogenesis.

Acknowledgements

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