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Transcriptomic Signature of Atorvastatin Response Among ART-Treated Adults in Africa

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Background

- Inflammation is a hallmark of chronic HIV disease.
- Persistent immune activation was associated with suboptimal CD4 count recovery despite suppressive antiretroviral therapy (ART).
- Chronic inflammation has been associated with increased risk of cardiovascular disease, end-organ damage and mortality among ART-treated HIV-infected adults.
- Adjunct anti-immune activation agents could optimize immune recovery during ART in African cohorts, where several infections including malaria, tuberculosis and helminths are endemic.
- Atorvastatin (ATV), 80mg daily for 12 weeks, reduced immune activation levels among HIV-infected adults with and without ART (Ganesan *et al.* 2011, Nakanjako *et al. 2015*).
- Mechanism of ATV during ART is however not well understood.

Objectives

To understand the pathways affected by ATV adjunct therapy, we examined the effect of ATV on gene expression among ART-treated suboptimal immune responders.

Experimental approach

- ART-treated adults with CD4 count increase <300 cells/µl after seven years of suppressive therapy, that received ATV 80mg daily for 12 weeks
- Six atorvastatin responders **(ATV-R):** patients that had the highest reduction in immune activation [CD4+HLA+CD38+ expression]) from week 0 to week 12 (NCT01766076) were compared with four non-responders **(ATV-NR):** patients with the least reduction in immune activation from week 0 to week 12
- Paxgene samples were collected (before and after 12 weeks of ATV) among

Results

Table 1: Clinical characteristics of atorvastatin-treated patients

Variables	(N=15)
Demographic data	
Female n (%)	7 (46.7)
Median age (IQR)	41 (40-50)
Past medical history	
Diabetes and Hypertension, n (%)	0 (0.0)
CD4 at HAART initiation, median (IQR)	78 (43-162)
Current HAART regimen, n (%)	
ZDV+3TC+NVP	5 (33.3)
ZDV+3TC+EFZ	5 (33.3)
TDF+FTC+EFZ	1 (6.7)
TDF+FTC+NVP	1 (6.7)
Others	2 (13.3)
HB (g/dl), median (IQR)	14 (12.9-15.2)
WBC (10^3 cells/UL), median (IQR)	3.6 (2.8-5.8)
ESR (mm/hr), median (IQR)	11 (3-15)

- Microarrays done by Sekaly RPôs genomics group.
- DEG analysis of the top 50 genes and top 50 ISG genes associated with interferon were analyzed.
- Network inference using geneMania algorithm, followed by linear regression using clinical parameters and pathway analysis.

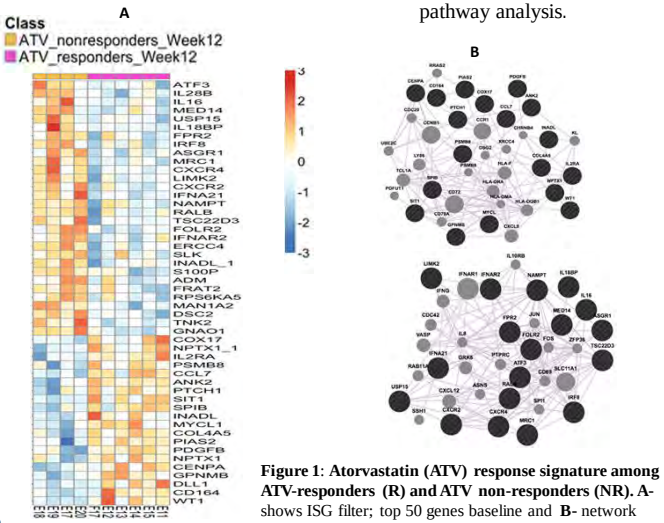

Figure 1: **Atorvastatin (ATV) response signature among ATV-responders (R) and ATV non-responders (NR). A-** shows ISG filter; top 50 genes baseline and **B-** network inference

Results

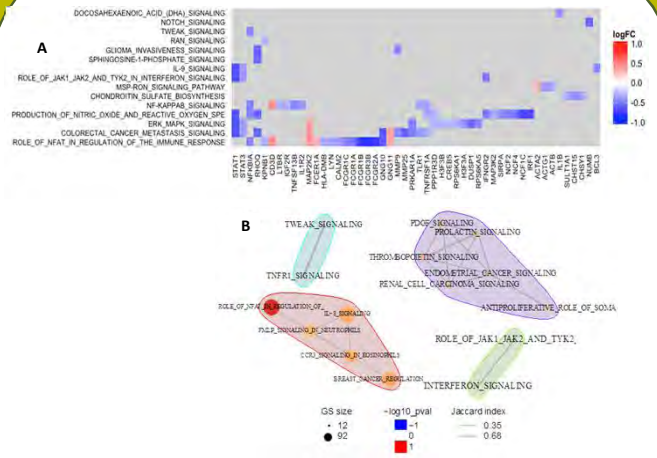

Figure 2: A shows downregulation of the genes among non-responders (ATV-NR); Pink- upregulation, and Blue- downregulation of the genes among ATV-NR. B: top 15 genes enrichment strategy grouping the pathways. ATV down regulating the inflammatory genes IL18, IL16 IFN are up regulated in ATV-NR.

Conclusions

- Effective atorvastatin treatment is associated with downregulation of inflammatory genes among ART-treated adults with poor CD4 reconstitution despite long-term suppressive therapy.
- Transcriptomic signature of atorvastatin response could be used to understand its role as adjunct therapy in prevention of AIDS and non-AIDS related events among ART-treated adults in sub-Saharan Africa.

Acknowledgements

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Slide 1

AE2 I woudl like to see the bullets aligned consistently in this box. Also, occasionally you have a space before the first letter of the first word which interferes with good alignment.
Alison Elliott, 2/17/2016