# Distinct Interferomes Associate with Chronic HIV Pathogenesis in the Gut

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## BACKGROUND

- Type I interferons (IFN-Is) are innate cytokines that include 12 different IFNα subtypes and IFNβ and induce hundreds of Interferon-stimulated genes (ISGs) that comprise the 'interferome'.
- IFN-Is protect against early HIV infection, but have also been linked to pathogenesis during the chronic stages.
- We showed that IFNβ, but not IFNα gene expression was higher in the colonic tissue of untreated, chronically infected people with HIV (PWH) versus controls, but IFNβ was rarely detected in peripheral blood mononuclear cells.[1]
- Transcriptomic profiling of uninfected gut CD4 T cells exposed to dominant IFNα subtypes (α1, α2, α5, α8, α14)[1,2] or IFNβ *in vitro* revealed a set of ISGs induced by all IFN-Is tested (core-ISGs) and ISGs specifically induced by IFNβ (β-ISGs).
- To better understand how IFNβ influences chronic gut HIV pathogenesis, these two gene sets were evaluated in the colon of chronic PWH and potential links between these interferomes and features of HIV pathogenesis determined.

## METHODS

- Colon biopsies, previously obtained with informed consent from 19 untreated, chronically infected PWH and 13 uninfected controls[3] (Table 1) were transcriptomically profiled using RNAseq with data generated using the HiSeq 2500 platform (Illumina). Gene counts were normalized using the trimmed mean of M values (TMM) normalization.
- Differential gene analysis was conducted using *edgeR* and correlations tested using linear regression models adjusted for age and gender and corrected for multiple comparisons.
- Significance was established at False Discovery Rate (FDR) <5% for all analyses.

## Study Participant Characteristics.

| | Controls (N=13) | PWH (N=19) | P value* |
|---|---|---|---|
| **Sex** (M/F) | 8/5 | 13/6 | P=0.72 |
| **Age** (years) | 33 (23-54) | 33 (22-58) | P=0.96 |
| **CD4 T cell count** (cells/μl) | 720 (468-1071) | 429 (221-836) | P=0.002 |
| **Plasma Viral Load** (HIV-1/ml) | N/A | 26,000 (2880-196,000) | |
| **Plasma IL-6** (pg/ml) | 0.69 (0.19-2.2) | 1.2 (0.43-5.1) | P=0.007 |
| **Plasma hsCRP** (μg/ml) | 0.65 (0.23-12.4) | 1.3 (0.2-11.3) | P=0.16 |
| **Plasma sCD27** (U/ml) | 32 (23-43) | 50 (29-106) | P=0.0002 |
| **Plasma iFABP** (pg/ml) | 2363 (548-5352) | 2718 (530-6005) | P=0.44 |
| **Plasma sCD14** (ng/ml) | 1757 (1184-2146) | 1969 (1450-3318)$^{\Sigma}$ | P=0.02 |
| **Plasma LPS** (pg/ml) | 9.5 (6.0-14.5) | 16.5 (8.3-27.0)$^{\Sigma}$ | P<0.0001 |
| **Plasma LTA** (OD) | 0.14 (0.07-0.38) | 0.28 (0.17-0.64)$^{\Sigma}$ | P<0.0001 |
| **Colon IFNα gene expression**^ | 3.6 (2.0-9.0) | 1.4 (0.7-2.6)$^{\Sigma}$ | P<0.0001 |
| **Colon IFNβ gene expression**^ | 0.3 (0.2-1.0) | 0.9 (0.3-1.5)$^{\Sigma}$ | P<0.0001 |
| **Colon CD4 T cells (%)**‡ | 32.0 (20.4-49.9) | 12.4 (5.2-23.4) | P<0.0001 |
| **Colon HIV RNA levels**† | N/A | $9.8x10^6$ ($5.1x10^3$-$2.3x10^8$) | |

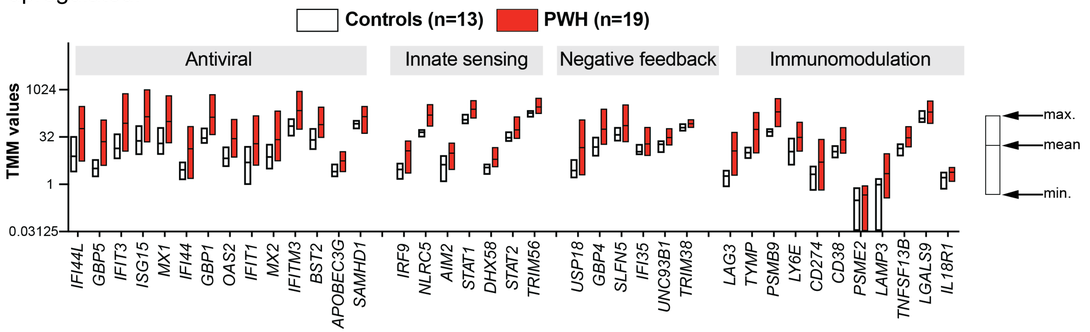
Systemic and colonic parameters were measured as part of previous studies[1,3]. *Statistical analysis: Mann-Whitney test. ^copies per $10^4$/GAPDH; ‡ % of viable, CD45$^+$ cells; †copies per CD4 T cell; $^{\Sigma}$N=17.

**Transcriptomic analysis of distinct interferon-stimulated gene sets (interferomes) provide potential mechanisms on how the unique expression of gut IFNβ during chronic HIV infection may drive inflammation and pathogenesis.**

## RESULTS

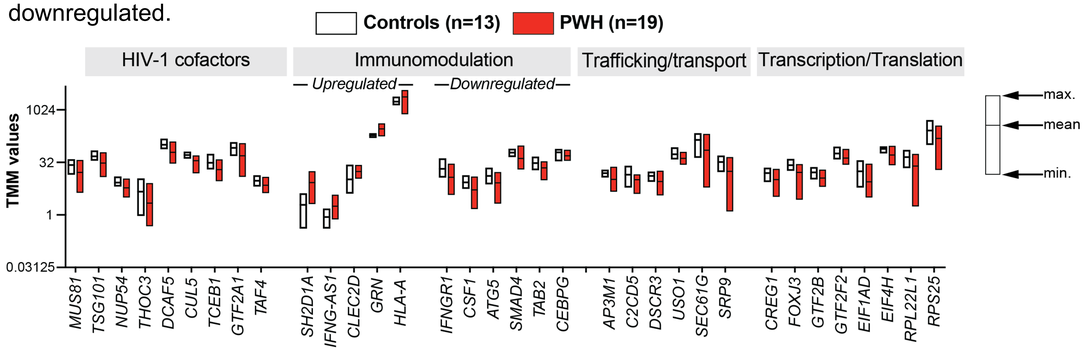
### Chronic HIV-1 infection is associated with a strong type I IFN response in colonic tissue.

- Of 246 **core ISGs**, 126 (51%) were significantly altered in PWH versus controls with 89% being upregulated.



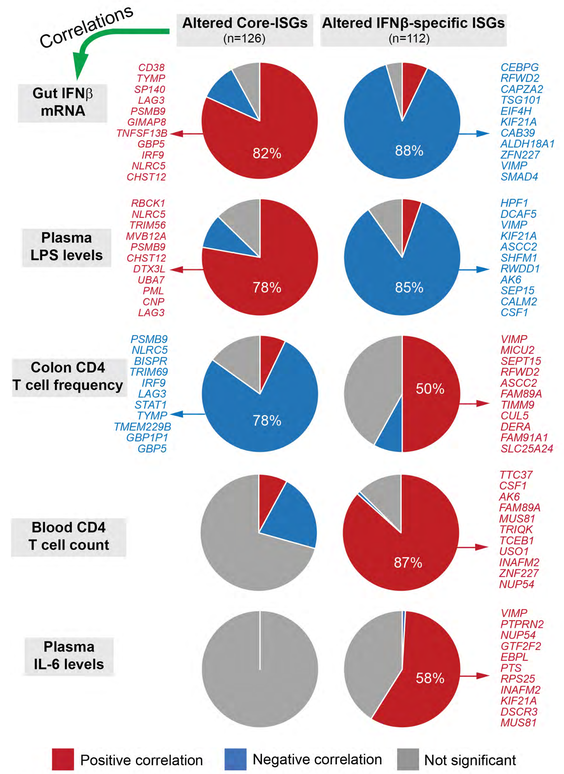

### Suppression of IFNβ-specific ISGs in colonic tissue during chronic HIV infection.

- Of 406 **β-ISGs**, 112 (28%) were significantly altered in PWH versus controls with >90% being downregulated.




### Distinct interferomes are linked to pathogenic outcomes.

- Expression of core-ISGs and β-ISGs significantly correlated with colonic IFNβ, but not IFNα gene transcript levels:
  - higher expression of IFNβ correlated with higher expression of core-ISGs, but lower expression of β-ISGs.
- Discordant correlations between core-ISGs or β-ISGs were also observed for plasma LPS levels, gut and blood CD4 T cell frequencies and plasma IL-6.




Top genes in the relevant categories with ≥50% representation are highlighted. Correlations with other clinical or immune parameters (Table 1) were not observed.

## CONCLUSIONS

- Colonic IFNβ expression in chronic, untreated PWH correlated with increased expression of ISGs that were linked to inflammation, immune activation and exhaustion, but also associated with decreased expression of genes with anti-inflammatory properties.
- **This study reveals a complex picture of how IFNβ may promote HIV pathogenesis in the gut.**

## ACKNOWLEDGEMENTS

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**REFERENCES.**

1. Dillon *et al*. PMID 29762170; 2. Harper *et al*. PMID 26529416; 3. Dillon *et al*. PMID 24399150