Prevalence and activity of anti-interferon auto-antibodies in people living with HIV

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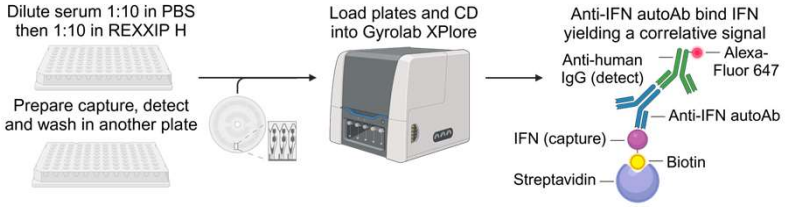
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Background

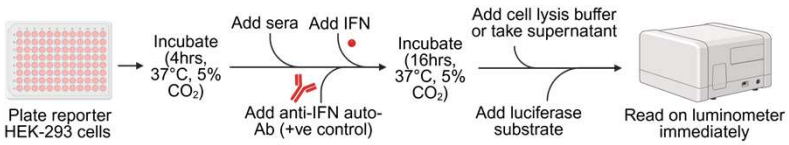
- The interferon (IFN) cytokine family, encompassing sub-types 1-3 (T1-3) is fundamental in controlling HIV replication[1]
- Autoantibodies (auto-Abs) targeting IFN promote severe acute viral infection outcomes, e.g. COVID-19[2], but data are limited in chronic disease
- A single cohort study of people living with HIV (PLWH) reported anti-T1 IFN auto-Abs[3], but not function *in vitro* or anti-T2/-3 auto-Abs
- We undertook the first multi-centre observational study of pan-anti-IFN auto-Abs in PLWH to delineate prevalence, function and clinical impact

Methods

(A) Gyrolab automated immunoassay workflow



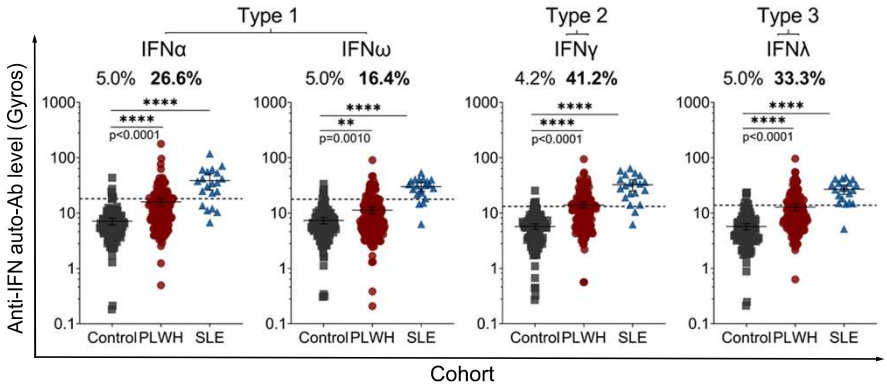
(B) Luciferase reporter neutralisation assay workflow



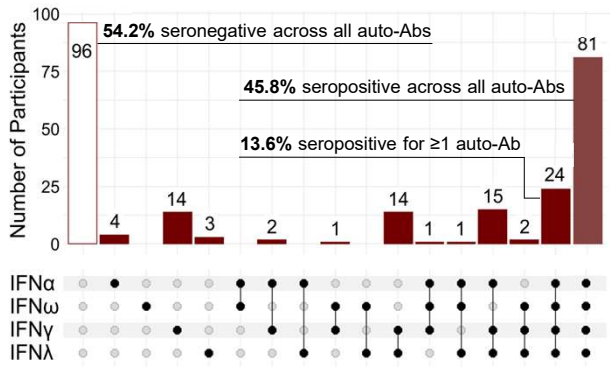
Serum from HIV negative control group (n=119) and PLWH (n=177) provided by Mortimer Market and Ian Charleson Day Centres in London. Results normalised to control group. Statistical significance determined by Mann-Whitney-U and Fischer-Irwin tests in GraphPad Prism (v10). Error bars denote median values with 95% CI.

1. PLWH display higher anti-IFN auto-Ab levels across T1-3

(A) Auto-Ab detection by Gyros immunoassay



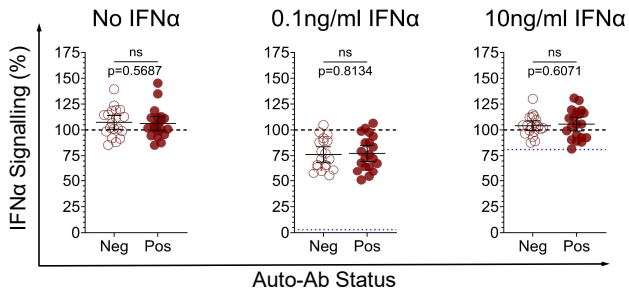
(B) Upset plot for concordance of auto-Ab positivity against all IFN sub-types



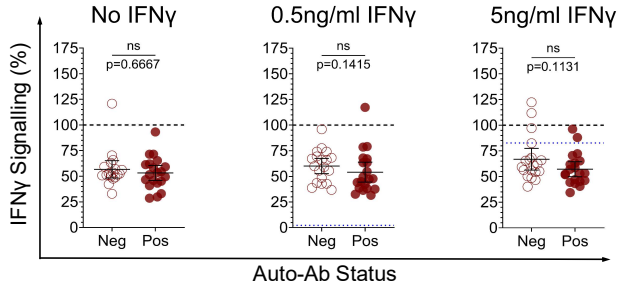
(A) Auto-Ab positivity (%) provided for controls and PLWH. People with systemic lupus erythematosus (SLE) with known auto-Ab as positive control. Cut-off at 2*S.D. above control mean (black dash).
(B) Interlinked lines represent co-carriage of auto-Ab.

2. T1 and T2 anti-IFN auto-Abs do not display significant neutralisation

(A) IFNα (T1 IFN) neutralisation



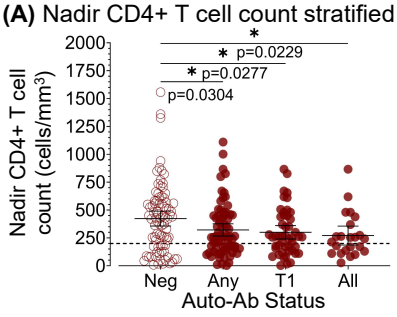
(B) IFNγ (T2 IFN) neutralisation



Data are fold-change expressed as a percentage of negative control cells (black dash); anti-IFN mAb control (blue dotted).

3. Anti-IFN auto-Abs associate with impaired immune status

(A) Nadir CD4+ T cell count stratified by auto-Ab status



Neg = negative for auto-Ab
Any = positive for any ≥1
T1 = positive for IFNα or IFNω
All = positive for IFNα, IFNω, IFNγ, and IFNλ

(B) PLWH clinical associations stratified by auto-Ab status

*M=median, VL=viral load	All PLWH (n=177)	Auto-Ab- (n=96)	Auto-Ab+ (n=81)
Age (yrs; M,IQR)	51 (43-57)	52 (42-59)	49 (43-57)
Male Sex (n,%)	150 (86.2%)	83 (87.4%)	67 (84.8%)
Ethnicity (%) White: Black: Other	69:16:14	68:15:17	70:16:14
Nadir CD4 (cells/mm³; M,IQR)	340 (157-532)	430 (179-574)	262 (154-452)
Recent CD4 (cells/mm³; M,IQR)	627 (454-849)	586 (457-811)	698 (446-934)
Recent VL (log_{10}; cpy/ml; M,IQR)	3.7 (2.3-5.0)	3.5 (2.2-5.2)	4.9 (2.9-5.0)
Detectable VL (n,%)	30 (17.2%)	17 (18.3%)	13 (18.1%)
Receiving ART (n,%)	107 (79.9%)	48 (77.4%)	59 (81.9%)
ART Duration (yrs; M,IQR)	12.8 (6.8-18.2)	15.0 (7.5-19.5)	12.1 (6.3-17.7)

Conclusions

- Anti-IFN auto-Abs are significantly in PLWH, when compared against age-matched HIV negative controls
- High concordance for auto-Ab positivity against all IFN sub-types suggests broader loss of tolerance in PLWH
- Detectable auto-Abs are non-neutralising, potentially owing to B cell exhaustion - other roles, e.g. complement activation, need to be evaluated
- Correlation with impaired immunity; longitudinal immunophenotyping and mechanistic studies are required to delineate implications fully

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References:
1. Stacey *et al.*, J Virol, 2009
2. Bastard *et al.*, Science, 2020
3. Fernbach *et al.*, J Exp Med, 2024

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