Female-predominant anti-CD4 IgG autoantibody in HIV on ART and its correlations with plasma levels of progesterone, microbial translocation, and blunted immune reconstitution under suppressive ART

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BACKGROUND

Autoimmunity contributes to HIV immunopathogenesis even in the absence of overt autoimmune disease. We previously showed that anti-CD4 autoantibodies from people with HIV (PWH) on suppressive antiretroviral therapy (ART) can mediate cytotoxicity against CD4+ T cells, implicating a role in impaired immune reconstitution. Despite viral suppression, many PWH with poor CD4 recovery exhibit chronic immune activation, microbial translocation, and dysregulated humoral immunity.

In 2017, we reported the first evidence that autoimmunity can drive HIV immunopathogenesis without overt autoimmune disease (1).

METHODS

The prospective study enrolled 42 study participants at the Medical University of South Carolina (MUSC), and Ralph H. Johnson VA Health Care System (RHJ VAHCS), Charleston, SC, USA, including 28 PWH on stable suppressive ART (17 HIV+ males, 9 HIV+ females) and 16 HIV-seronegative controls (5 non-HIV males, 11 non-HIV females) in the HIV cohort. The second HIV cohort, a retrospective study including 16 non-HIV males, 22 HIV+ males on suppressive ART, and 4 HIV+ females on suppressive ART, was from Sahlgrenska University Hospital, Gothenburg, Sweden, and San Francisco General Hospital, University of California, San Francisco (UCSF), USA.

Blood Samples were collected for ELISA testing for anti-CD4, anti-CD8, ds-DNA and ANA IgGs for immunological testing. Endocrine testing included progesterone, 17β-estradiol and testosterone levels. For evaluation of microbial translocation markers included sCD14, LPS and LBP. Correlations were analyzed using Spearman's rank. $p \leq 0.05$ is considered significant. Analyses performed in GraphPad Prism 9 and SPSS v16.

ACKNOWLEDGMENTS

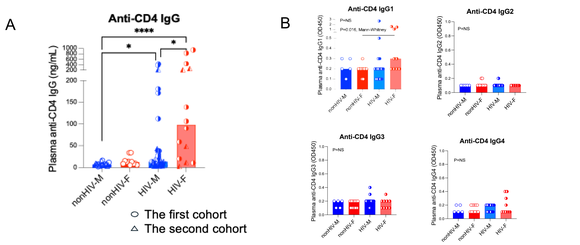
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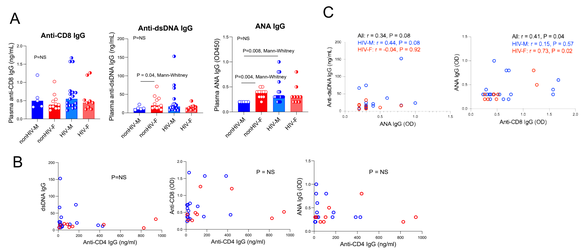
RESULTS

Increased anti-CD4 autoantibody production in PWH on suppressive ART in females but not males.



(A) Median plasma levels of total anti-CD4 IgG in non-HIV males (non-HIV-M, blue circles), non-HIV females (non-HIV-F, red circles), HIV+ males on suppressive ART (HIV-M, blue squares), and HIV+ females on suppressive ART (HIV-F, red squares). Samples were obtained from the two cohorts. (B) Median plasma levels of anti-CD4 IgG subclasses (IgG1, IgG2, IgG3, IgG4) across the same four groups. Statistical significance was determined by the non-parametric Kruskal-Wallis tests and non-parametric Mann-Whitney tests; *p < 0.05. All subclasses showed no significant differences (P=NS) using Kruskal-Wallis tests, except for a significant increase in anti-CD4 IgG1 in HIV-F vs. non-HIV-F using a non-parametric Mann-Whitney test. Samples of the first cohort were analyzed.

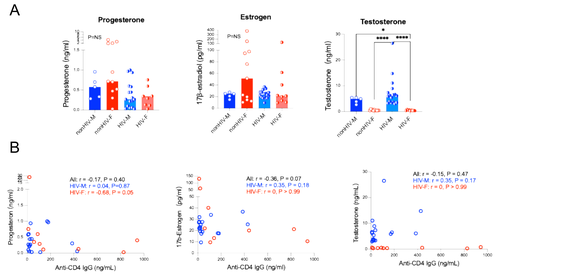
Sex-specific elevation of anti-CD4 IgG in PWH on suppressive ART is not associated with anti-dsDNA IgG, ANA IgG, or anti-CD8 IgG.



(A) Plasma levels of anti-CD8 IgG, anti-dsDNA IgG, and ANA IgG in non-HIV males (non-HIV-M, blue circles), non-HIV females (non-HIV-F, red circles), HIV+ males on suppressive ART (HIV-M, blue squares), and HIV+ females on suppressive ART (HIV-F, red squares). Anti-CD8 IgG showed no significant differences across groups (P=NS). Data are shown as individual points with median and interquartile range. Non-parametric Kruskal-Wallis and Mann-Whitney tests. (B) Correlation scatter plots of anti-CD4 IgG (ng/mL) with anti-CD8 IgG, anti-dsDNA IgG, and ANA IgG. No significant correlations were observed (P=NS for all, Spearman Correlation tests). (C) Correlation of ANA IgG with anti-CD4 IgG in HIV+ individuals and anti-dsDNA IgG with ANA IgG. Data points represent individual participants; blue = males, red = females. Samples of the first cohort were analyzed.

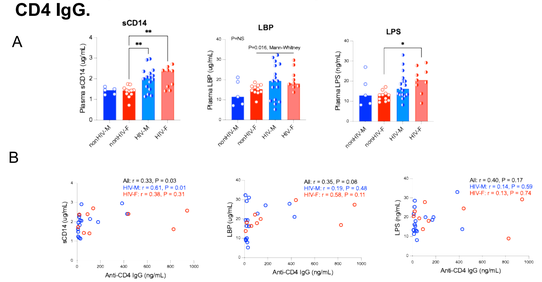
RESULTS

Plasma progesterone levels are inversely correlated with anti-CD4 IgG in HIV+ females.



(A) Plasma concentrations of progesterone, 17β-estradiol, and testosterone were measured using ELISA in the four study groups. (B) Correlations between anti-CD4 IgG and each sex hormone level. Non-parametric Kruskal-Wallis and Spearman correlation tests. Samples of the first cohort were analyzed.

Plasma sCD14, LBP, & LPS are elevated in PWH on suppressive ART, mainly in female patients; only sCD14 correlates with anti-CD4 IgG.

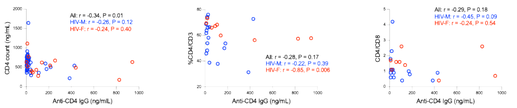


(A) Plasma levels of soluble CD14 (sCD14), lipopolysaccharide-binding protein (LBP), and lipopolysaccharide (LPS) in non-HIV males (non-HIV-M, blue circles), non-HIV females (non-HIV-F, red circles), HIV+ males on suppressive ART (HIV-M, blue squares), and HIV+ females on suppressive ART (HIV-F, red squares). sCD14 was significantly higher in both HIV-M and HIV-F vs. non-HIV groups. LBP showed no overall group difference by ANOVA but was higher in HIV-F vs. HIV-M (P=0.016, Mann-Whitney). LPS was higher in HIV-F vs. non-HIV-F. Data are individual points with a median. (B) Correlations of anti-CD4 IgG with sCD14, LBP, and LPS in PWH. Only sCD14 showed a significant positive correlation. Blue = males, red = females. Non-parametric Kruskal-Wallis and Spearman correlation tests. Samples of the first cohort were analyzed.

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RESULTS

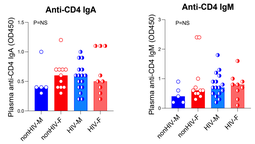
Correlations between plasma anti-CD4 IgG levels in PWH on suppressive ART and CD4+ T cell counts, percentages of CD4+ T cells in total CD3+ T cells, or CD4/CD8 ratios.



Correlation between plasma anti-CD4 IgG and absolute CD4+ T cell count (A), percentages of CD4+ T cells in CD3+ T cells (B), and CD4/CD8 ratio (C) in PWH on suppressive ART. Blue circles = males, red circles = females. Data represents individual participants. Spearman correlation tests. Samples of the first cohort were analyzed.

No differences in plasma anti-CD4 IgA or IgM levels in the four study groups.

Plasma anti-CD4 IgA and IgM levels in the four groups. Non-parametric Kruskal-Wallis tests. Samples of the first cohort were analyzed.



Key Findings

- Female-predominant elevation of plasma anti-CD4 IgG autoantibodies in PWH on suppressive ART.
- Across two independent cohorts, HIV-positive females, but not males, displayed significantly higher anti-CD4 IgG, predominantly IgG1, compared with HIV-negative controls, without parallel increases in anti-CD4 IgA or IgM.
- This sex-specific pattern was unique to anti-CD4 IgG and was not observed for anti-CD8 IgG, or other antibodies.
- Elevated anti-CD4 IgG levels were associated with lower plasma progesterone levels and reduced absolute CD4+ T-cell counts.
- Markers of microbial translocation, soluble CD14 (sCD14), lipopolysaccharide-binding protein (LBP), and lipopolysaccharide (LPS), were also selectively increased in HIV-positive females, with sCD14 and LBP showing significant or borderline associations with anti-CD4 IgG.

CONCLUSION

Together, these findings identify anti-CD4 IgG as a sex-dimorphic autoimmune signature in treated HIV infection, linked to progesterone levels, persistent microbial translocation, and incomplete immune recovery. This work highlights an under-recognized intersection of sex, mucosal barrier dysfunction, and autoimmunity in HIV pathogenesis and suggests potential therapeutic targets to improve immune reconstitution in women.