Anti-Lymphocyte Autoantibodies with Lytic Function Persist after Antiretroviral Therapy in People with HIV

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BACKGROUND

- **Self-reactive IgG antibodies** (Abs), including those targeting the CD4 protein, have been previously identified in people with HIV (PWH), and are thought to mostly originate from a repertoire of cross-reactive anti-viral Ab.[1-5]
- **The kinetics, potential immunological function, and clinical consequences of broad IgM and IgG anti-lymphocyte Abs (ALAb) remain unclear.**

STUDY GOALS

In PWH sera:

1) Analyze IgG/IgM ALAb prevalence.
2) Test complement-dependent cytotoxicity (CDC).
3) Determine if there is a correlation between binding ALAb and CDC.

In PWH PBMC:

4) Analyze in vivo presence of cell-bound ALAb, complement deposition, and direct ex vivo CDC (without sera preincubation).

METHODS

Samples: PWH with pre-ART CD4 count <100 cells/μL sampled at viremic (up to 2 weeks post-ART initiation) and suppressed (80 weeks post-ART initiation) timepoints.

Procedures:

- Flow-based assay to detect ALAb in sera.
- Complement Dependent Cytotoxicity (CDC).
- CDC Ex Vivo.
- Complement Deposition Assay by flow cytometry.

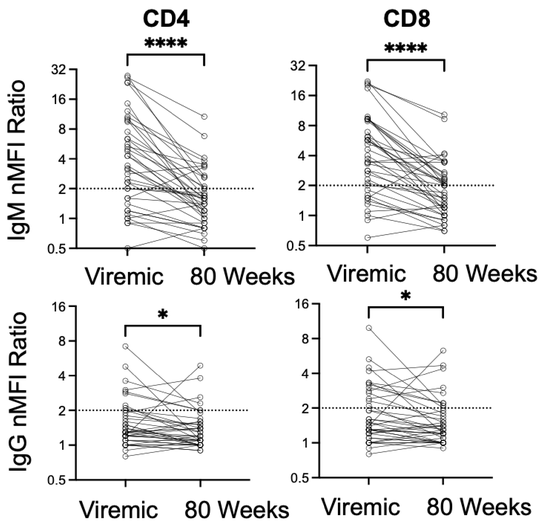
RESULTS

Participant Characteristics:

Baseline Age (yrs)	Sex	Median Viral Load (Viremic/ Suppressed)	Median CD4 Count (Viremic/ Suppressed)
39.2	12 F, 27 M	185,551 cp/mL <40 cp/mL	16 cells/μL 273 cells/μL

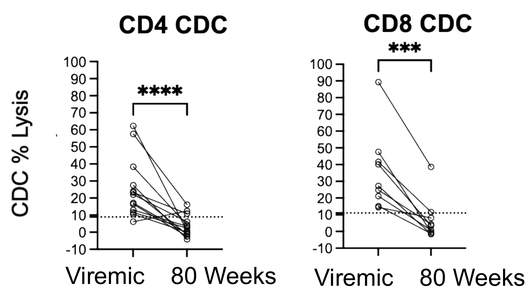
In PWH starting ART with low CD4 counts, IgM anti-CD4 and anti-CD8 anti-lymphocyte antibodies are highly prevalent in sera during viremia, associate with complement dependent cytotoxicity and C3b deposition, and decline after virological suppression.

A) IgG and IgM anti-CD4 and anti-CD8 Ab significantly decrease after 80 weeks of ART, but remain detectable:

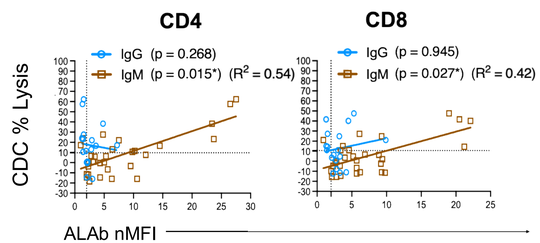


- Anti-CD4 IgG and/or IgM: 74% → 49%
- Anti-CD8 IgG and/or IgM: 79% → 61%

B) CDC of healthy control PBMC induced by PWH sera at viremic and suppressed timepoints:



C) IgM ALAb elicit cytotoxicity by CDC:

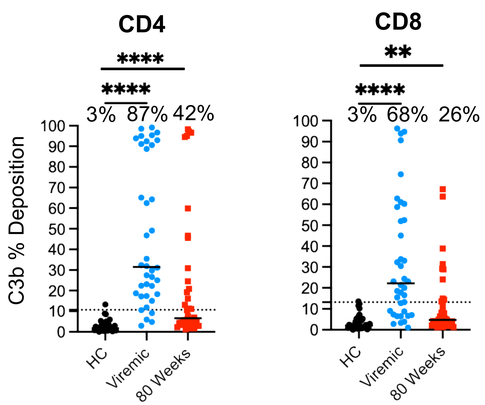


IgM but not IgG binding correlates with CD4 and CD8 complement-dependent cytotoxicity.

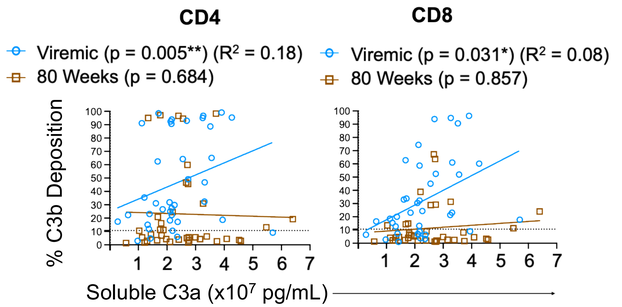
D) Cell-bound ALAb can be measured directly ex vivo on PWH PBMCs while viremic and decrease after 80 weeks of ART:

- Anti-CD4 IgG and/or IgM: 100% → 60%
- Anti-CD8 IgG and/or IgM: 60% → 29%

E) High levels of C3b deposition in PWH CD4 and CD8 T cells, which decreases but does not normalize after ART:



F) Levels of soluble C3a correlate with C3b deposition in PWH T cells during viremia but not after 80 weeks of ART:



G) Ex vivo CDC lysis can be induced directly in PWH T cells both pre- and post-ART.

CONCLUSIONS

- Anti-lymphocyte antibodies, mostly IgM, are highly prevalent in PWH with low CD4 counts at the time of ART initiation.
- These Ab persist, albeit at lower levels, 80 weeks after ART initiation.
- Ex vivo analysis of T cells from PWH demonstrate:
  - Pre-bound anti-lymphocyte antibodies which can mediate complement-dependent cytotoxicity.
  - Evidence of C3b deposition, implying in vivo complement activation.

PLAIN LANGUAGE SUMMARY

Our data suggest a potential role for anti-lymphocyte auto-antibodies and complement-mediated cytotoxicity in persistent T cell perturbations and ongoing immune activation in treated PWH with low pre-ART CD4 counts.

ADDITIONAL KEY INFORMATION

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