An Early Decline in HIV Antibody Breadth Predicts More Rapid Disease Progression

Oliver Laeyendecker[1,2], Kai Kammers[2], Athena Chen[2], Mariya V. Sivay[2], Brandon M. Sie[2], Tiezheng Yuan[2], Divya Mohan[2], Sanjay Kottapalli[2], Tomasz Kula[3], Charles Morrison[4], Stephen J. Elledge[3], Ron Brookmeyer[5], Ingo Ruczinski[2], H. Benjamin Larman[2], and Susan H. Eshleman[2]

[1] NIAID, Baltimore, MD, USA; [2] Johns Hopkins University, Baltimore, MD, USA; [3] Harvard University, Boston, MA, USA; [4] FHI 360, Durham, NC, USA; [5] University of California Los Angeles, Los Angeles, CA, USA

Poster 220
Oliver Laeyendecker
Staff Scientist, NIAID
Assistant Prof., JHU, JHSPH
855 North Wolfe St.
Rangos Building, room 538A
Baltimore MD, 21205
410-502-3268

INTRODUCTION

We used a massively-multiplexed antibody profiling system to analyze the fine specificity of the antibody response to HIV infection. This system is based on phage immunoprecipitation sequencing (PhIP-Seq). Antibody abundance and specificity are assessed by immunoprecipitating phage-antibody complexes and sequencing the DNA in the captured phage particles. The "VirScan" phage library includes >3,300 peptides that span the HIV genome. We used the VirScan assay to analyze antibodies from individuals with early to late stage HIV infection, including individuals on antiretroviral therapy (ART) and individuals with advanced HIV disease.

METHODS

SAMPLES USED FOR ANALYSIS

Plasma samples were obtained from the Hormonal Contraception and Genital Shedding Study (HC-GS Study; Uganda and Zimbabwe; 2001-2009, see Poster #943). The sample set included 403 plasma samples from 57 women with known duration of infection (14 days to 8.7 years, all HIV subtype C). Antiretroviral treatment (ART) was recommended for participants with CD4 cell counts <250 cells/mm^3, consistent with local treatment guidelines at the time the study was performed; 32 women started ART during the study.

VIRSCAN ASSAY

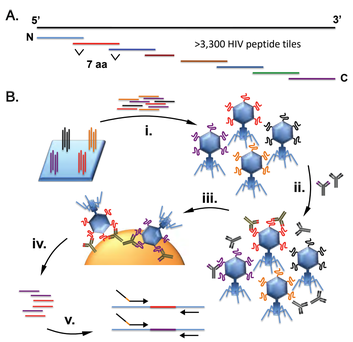


Figure 1. VirScan assay

Synthesize large libraries of overlapping DNA tiles

Express encoded peptides on bacteriophage

Quantify antibody reactivity to each peptide
→ phage immunoprecipitation
→ DNA sequencing

QUANTIFICATION OF ANTIBODY BINDING TO HIV PEPTIDES

Antibody binding to each HIV peptide was quantified by comparing the read count for the sample to the read counts obtained for 40 mock (no plasma) immunoprecipitation reactions. "z-scores" were used to reduce false positivity in cases of low sequencing depth; "relative fold-change" values were used to normalize data for highly-enriched peptides.

DETERMINATION OF ANTIBODY BREADTH

The term, "antibody breadth" (Ab breadth), was used to indicate the number of unique, non-overlapping peptides that had high levels of antibody binding (z-scores >10). Ab breadth was determined using network graphs (Figure 2).

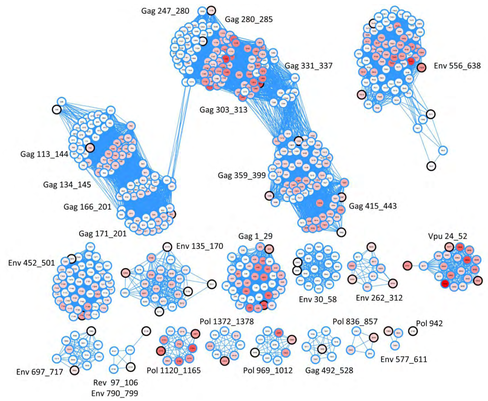


Figure 2. Representative network graph used to determine antibody breadth.

RESULTS

Ab breadth data were compared for participants who did vs. did not start ART during the HC-GS Study (Figure 3). In both groups Ab breadth increased during the first 6 months of infection. In the non-ART group, an Ab breadth set point was established in most individuals ~9-12 months after infection. In the ART group, a decline in Ab breadth was observed ~12 months after infection. In all cases, the fall in antibody breadth occurred at least a year before ART initiation.

RESULTS

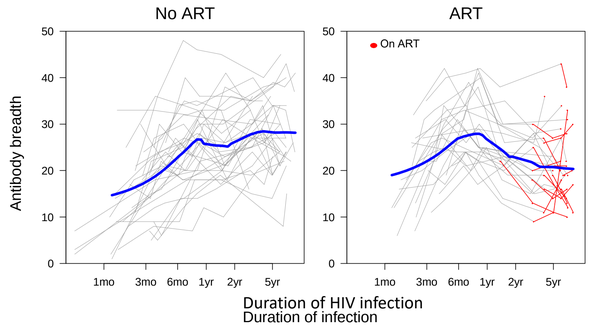


Figure 3. Ab breadth in those who did vs. did not start ART.
The figure shows Ab breadth over time in participants who did vs. did not start ART. Red dots and lines: data from samples collected when participants were on ART. Blue line: locally-weighted regression curve.

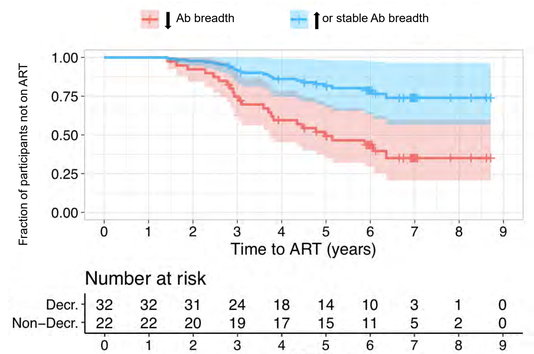


Figure 4. Relationship between change in Ab breadth and time to ART.
We quantified the rate of change of Ab breadth during the period ~9-24 months after HIV infection. Participants were divided into two groups: those with declining breadth and those with stable or increasing breadth. Participants with stable or increasing antibody breadth were less likely to start ART earlier in infection (log-rank test p=0.009, hazards ratio: 0.29, 95% CI: 0.11, 0.78, p=0.014). The average time between study visits was similar in the two groups (p=0.28); this was unlikely to have biased the analysis.

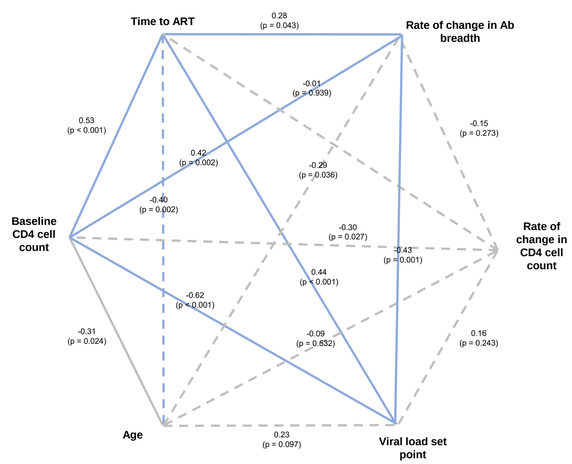


Figure 5. Association of the rate of change in Ab breadth and other factors.
The figure shows the relationship between the rate of change in Ab breadth and other factors. A faster decline in Ab breadth was strongly associated with lower baseline CD4 cell count (R=0.42, 95% CI: 0.17, 0.62; p=0.002) and higher viral load set point (R=-0.43, 95% CI: -0.62, -0.18; p=0.001). A faster decline in Ab breadth was also associated with earlier ART initiation (R=0.28, 95% CI: 0.01, 0.51; p=0.043).

CONCLUSIONS

- We developed a new measure of HIV antibody diversity that reflects the number of unique epitopes targeted.
- Different patterns of Ab breadth were observed in individuals who did vs. did not later start ART.
- A decline in HIV Ab breadth early in infection (~9-24 months) was associated with HIV disease progression (CD4 decline, leading to ART initiation).
- A faster decline in Ab breadth was associated with lower baseline CD4 cell count, higher viral load set point, and a shorter time to ART initiation.

This work was funded by R01-095068 (Eshleman). Additional funding was provided by the HIV Prevention Trials Network (UM1AI068613) and additional funding was provided by the Division of Intramural Research, NIAID.
We would like to thank the participants and staff of the HC-GS Study.
The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Presented at the 2019 CROI Conference Seattle, WA