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

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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, 2001-2005, see Poster #543). 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/mm³, 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

Sythesize large libraries of overlapping DNA tiles
Express encoded peptides on bacteriophage
Quantify antibody reactivity to each peptide
> phage immunoprecipitation
> DNA sequencing

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.

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

Antibody breadth 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. Two 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.

QUANTIFICATION OF ANTIBODY BINDING TO HIV PEPTIDES

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

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 = 0.16; 95% CI: 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.

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.

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