Acute Infection B cell Determinants Predict the Development of Neutralization Breadth

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BACKGROUND

Determining which immunological mechanisms contribute to the development of broadly neutralizing antibodies (bNAbs) during HIV-1 infection is a major goal to inform vaccine design. It is not fully understood if factors during the acute stages of infection impact the generation of neutralization breadth years later.

METHODS:

Utilizing 178 longitudinal samples from 72 HIV-1 infected, ART-naïve individuals within the RV217 cohort, we identified 16 individuals who were able to neutralize >70% of a panel of 34 viruses (broad neutralizers) and 12 individuals not able to neutralize >35% after 3 years of infection (non-broad neutralizers). Founder *env* genes were sequenced, and gp140 founder Env proteins were produced to characterize respective early autologous B cell responses. Founder Env+ and total B cell populations were phenotyped at pre-infection, peak viral load (day 11-18), month 1 (day 30-43), and chronic infection timepoints (day 391-2115).

RESULTS:

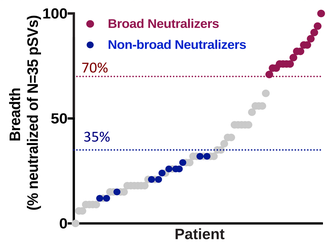
Reduced peripheral B cells starting at month 1 post-viremia were predictive of the development of bNAbs (HR=0.37, 95% CI: 0.18-0.76, p=0.007). Individuals with less than 160 B cells/mm3 at month 1 were 42 times more likely to develop neutralization breadth. Reduced peripheral B cells were driven by a reduction in peripheral naïve B cells occurring as early as 14 days post-viremia. Naïve B cell frequencies at day 14 inversely correlated with frequencies of founder Env-specific (p<0.02), plasmablast (p<0.0001), and integrin β7+ (p<0.001) B cell populations, suggesting early B cell engagement, differentiation, and migration to lymph nodes. Additionally, increased B cell engagement of respective founder gp140 Envelopes at 1 month predicted the development of bNAbs (OR=1.13, 95% CI: 1.02-1.28, p=0.035). Individuals with high engagement of their respective autologous founder Env at 1 month had a higher probability of developing neutralization breadth compared to individuals with low engagement of their autologous founder Env (p=0.02).

Key findings:

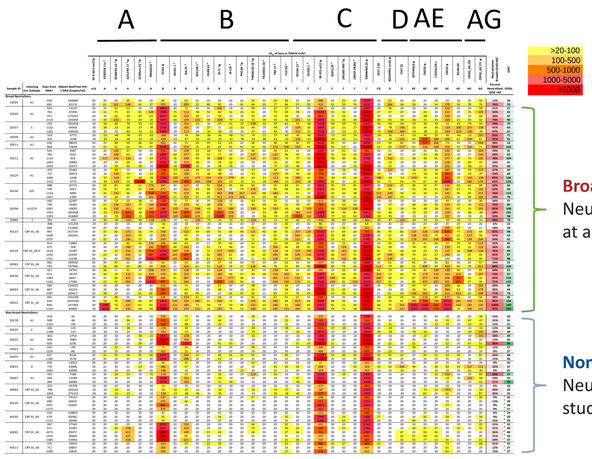
The **initial interaction of naïve B cells to founder HIV Env is important** for the development of neutralization breadth

- Higher frequencies of founder Env-specific B cells 1 month following infection predict neutralization breadth
- Engagement of founder with naïve B cells leads to greater B cell migration, activation, and differentiation
- Reduction in total peripheral B cells is a strong indicator of a robust B cell response
- Diversifying immunogens is advantageous for vaccine strategies (50% of broad neutralizers had multiple founders)

Fig. 1. Identification of Broad and Non-broad Neutralizers



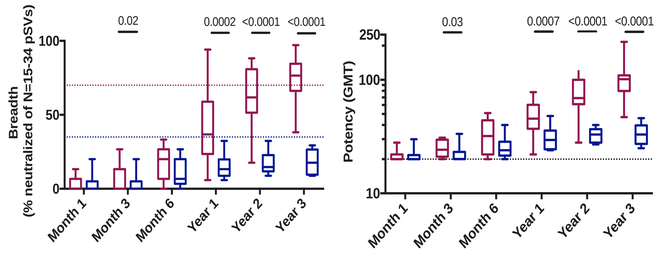
- Neutralization breadth assessed using a 35 virus panel representing diverse Envs
- Assessed 179 longitudinal samples from 72 individuals
- Time range was 30-2115 days after RNA+ and prior to ART initiation



Broad Neutralizers: Neutralize >70% of viruses at any time (N=16)

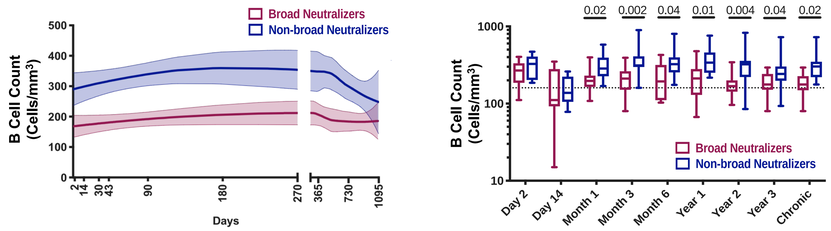
Non-broad Neutralizers: Neutralize <35%, must be in study through year 3 (N=12)

Fig. 2. Early onset of cross-neutralization in Broad Neutralizers



- Broad neutralizers were significantly increased in cross-neutralization compared to non-broad neutralizers by month 3
- Events prior to month 3 impact the development of cross-neutralizing antibodies

Fig. 3: Individuals with reduced peripheral B cell counts are more likely to develop neutralization breadth



Logistic Regression: Month 1 B Cell Counts

B Cell Quantiles	OR	L95	U95	p-value	B Cell Count Cut-off	Likelihood of Breadth
Lower 75%	0.400	0.049	2.356	0.334	298	3x
Lower 65%	0.175	0.022	0.957	0.061	269	6x
Lower 50%	0.121	0.018	0.625	0.017	226	8x
Lower 35%	0.024	0.001	0.190	0.002	160	42x
Lower 25%	0.071	0.003	0.539	0.026	152	14x

- Individuals with **<160 B cells/mm3 are 42 times** more likely in developing neutralization breadth

Fig. 4. Reduction of naïve population drives reduced peripheral B cell count in broad neutralizers

Marker	Associated with
CXCR5	B Cell Chemokine Receptor
B7 Integrin	Gut Homing
CD21	Naive, Exhausted
IgM	Naive
CD19	B Cells
Founder gp140	**HIV-Specific**
IgD	Naive
CD38	Activation
CD43	B1 & Spontaneous AB Secretors
CD95	Activation
CD10	Developing
CD11c	Chronic stimulation/Memory/Activation
CD27	Memory
CD20	Plasmablasts (-)
Aqua/CD3/CD16/CD14/CD56/CD4/CD8	Dead/Non-B cells
IgG	Mature

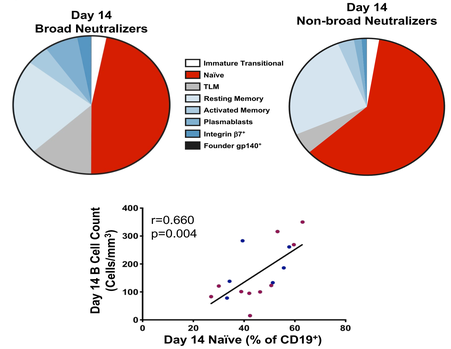


Fig. 5: Total B cell Subset Changes are more dynamic in Broad Neutralizers

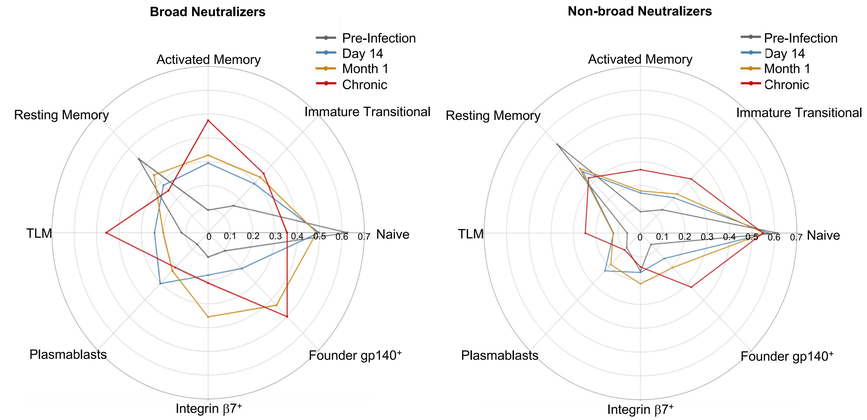
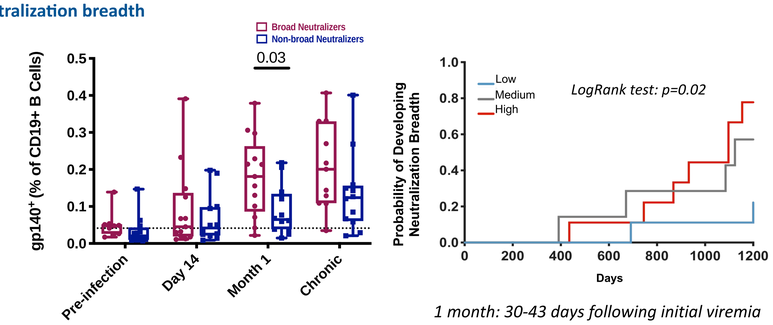


Fig. 6: Individuals with higher B cell engagement of their founder Env 1-month post-infection predict development of neutralization breadth



1 month: 30-43 days following initial viremia

CONCLUSIONS:

These data demonstrate development of neutralization breadth is influenced by early immunological mechanisms within the first month of acute infection. The reduction of peripheral naïve B cells in broad neutralizers and early, heightened engagement of the founder Env favored the development of broadly neutralizing antibodies, providing evidence that acute infection events lead to downstream functional outcomes.

The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army, the Department of Defense, or HJF. The investigators have adhered to the policies for protection of human subjects as prescribed in AR 70–25.