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HIV Envelope Diversity and Sensitivity to bNAbs Across Stages of Acute and Early HIV

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Introduction

- Broadly neutralizing antibodies (bNAbs) against HIV-1 may recognize virally infected cells expressing viral envelope (Env) protein and target them for elimination; however, the high genetic diversity of Env impacts viral susceptibility to bNAbs and may limit their applicability across a wide patient population
- Starting antiretroviral therapy (ART) during acute or early HIV infection (AEHI) may limit reservoir genetic diversity and size, thereby increasing the likelihood of susceptibility to bNAbs
- Understanding the extent of viral diversity and susceptibility to bNAbs in people with HIV initiating ART during AEHI and their evolution during long-term ART may inform use of bNAbs in HIV treatment and cure
- The ACTG A5354/EARLIER study (NCT02859558) is a multinational prospective study that initiated ART during AEHI[1]

Objective

- To characterize Env diversity and sensitivity to bNAbs targeting Env epitopes (V3 glycan and CD4 binding site) in ACTG A5354 study participants at ART initiation and after ART suppression

Methods

Study Design

PBMC, peripheral blood mononuclear cell.

- Plasma and PBMCs were collected prior to ART initiation (pre-ART plasma and pre-ART PBMC) and after 60 wk of ART (post-ART PBMC) from 89 A5354 participants who initiated ART during Fiebig I–V phases of HIV-1 infection
- HIV Env was genotyped from plasma virus and PBMC provirus by next-generation sequencing (MiSeq™ System, Illumina®, Inc., San Diego, CA)
- HIV subtyping was based on the consensus HIV Env gene obtained from plasma RNA
- Env diversity was estimated by average pairwise distance analysis using a sliding windows approach across the HIV Env gene
- Viral sensitivity to the bNAbs elipovimab (EVM; an engineered PGT121 variant; V3 glycan antibody) and 3BNC117 (CD4 binding site antibody) was assessed by the presence of previously defined HIV-1 Env genotypic signatures[2]; to qualify virus for a given HIV Env signature, sequence variability was not permitted at the positions interrogated (variability threshold set to <1% to ensure signature is present in all viral quasi-species)

bNAb Genotypic Sensitivity Signatures*

EVM (elipovimab)	
Env amino acid positions	**PPV (%)**
No signature	62
N332	75
N332/D325	80
N332/D325/H330	83
N332/D325/H330/T63	91
N332/D325/H330/T63/T320	93
N332/D325/H330/T63/T320/L179	97

3BNC117	
Env amino acid positions	**PPV (%)**
No signature	75
I201	78
I201/F353	84
I201/F353/I108	86
I201/F353/I108/A281	91
I201/F353/I108/A281/E102	92
I201/F353/I108/A281/E102/Y318	93

*HXB2 numbering used for HIV Env amino acid positions. N332, N332 glycan N-X-S/T; PPV, positive predictive value (probability that a virus with a given signature is sensitive to bNAb).

- Statistical analyses were conducted using Prism 8 (GraphPad Software, San Diego, CA)

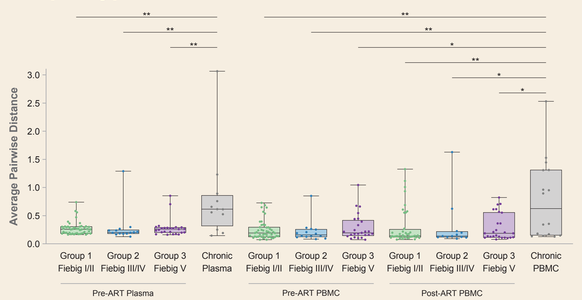
Results

HIV Env Sequencing Data

	Participant Samples With Available Data, n			
Sample	**Group 1 Fiebig I/II n=49**	**Group 2 Fiebig III/IV n=14**	**Group 3 Fiebig V n=26**	**Total N=89**
Pre-ART plasma	48	14	25	87
Pre-ART PBMC	49	14	26	89
Post-ART PBMC	40	13	26	79

- Participants were mostly infected with subtype B viruses (n=76), followed by subtype C (n=8) and other types (n=5)

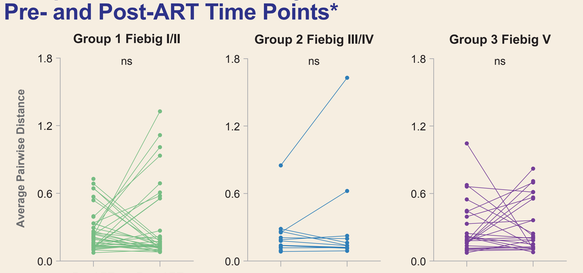
Comparison of HIV Env Sequence Diversity in All Sample Types and Time Points†



*p<0.05, **p<0.01: group comparisons obtained by 2-sided Mann Whitney test; †Data shown as *box and whisker plots* including all data points; plasma and PBMC virus from individuals in clinical trials who initiated ART during chronic infection were included for comparisons (chronic plasma and chronic PBMC; data provided by Gilead).

- HIV Env diversity was significantly lower in virus from individuals who initiated ART during AEHI vs chronic infection
- Env diversity of virus from pre-ART plasma, pre-ART PBMC, and post-ART PBMC was not significantly different between Groups 1, 2, and 3
- Env diversity of PBMC provirus from pre-ART samples was not significantly different vs post-ART samples in Groups 1, 2, and 3

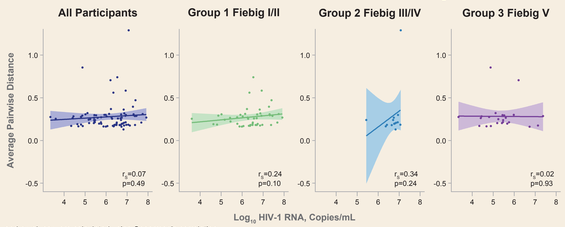
Comparison of Env Diversity in PBMC Provirus at Pre- and Post-ART Time Points*



*Each *line* represents an individual participant; paired analysis by Wilcoxon matched-pairs signed rank test at 2-sided 0.05 significance level. ns, not significant.

- No consistent change in Env diversity was observed in PBMC provirus following suppressive ART

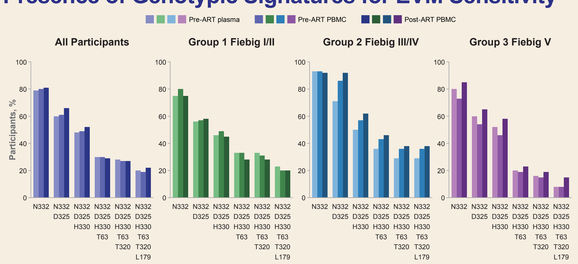
Correlation of Viral Load With Env Diversity*



*r_s and p-values were calculated using Spearman's correlation.

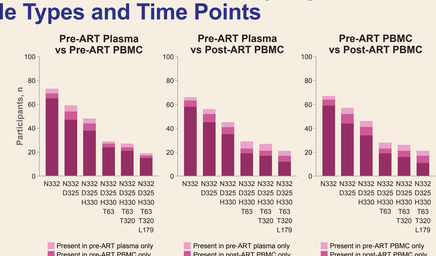
- Env diversity in pre-ART plasma virus was not associated with plasma HIV-1 RNA levels at ART initiation

Presence of Genotypic Signatures for EVM Sensitivity



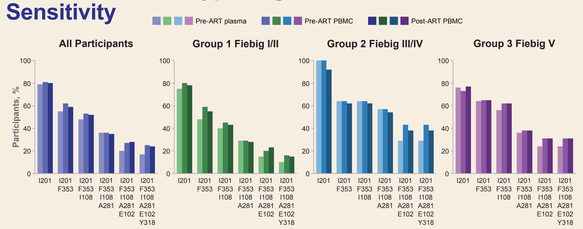
- The proportions of EVM signatures were similar in pre-ART plasma, pre-ART PBMC, and post-ART PBMC virus across all participants, and within or between Groups 1, 2, and 3 (p>0.05; comparisons by chi-square test)
- Susceptibility to EVM (N332glycan/D325/H330 signature) was comparatively higher in post-ART PBMC from participants who initiated ART during AEHI vs chronic infection: 18 of 40 Group 1 participants (45%), 8 of 13 Group 2 participants (62%), and 15 of 26 Group 3 participants (58%) were susceptible compared with 6 of 15 chronic participants (38%; p>0.05, Fisher's exact test)

Concordance of EVM Sensitivity Signatures Across Sample Types and Time Points



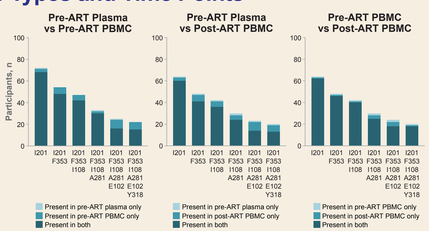
- There was a high level of concordance for EVM signatures between pre-ART plasma, pre-ART PBMC, and post-ART PBMC

Presence of Genotypic Signatures for 3BNC117 Sensitivity



- The proportions of 3BNC117 signatures were similar in pre-ART plasma, pre-ART PBMC, and post-ART PBMC virus across all participants, and within or between groups (p>0.05, comparisons by chi-square test)

Concordance of 3BNC117 Sensitivity Signatures Across Sample Types and Time Points



- There was a high level of concordance for 3BNC117 signatures between pre-ART plasma, pre-ART PBMC, and post-ART PBMC virus

Presence of Sensitivity Signatures to EVM and 3BNC117*

	Participants, n (%)		
Sensitivity Category	**Pre-ART Plasma n=87**	**Pre-ART PBMC n=89**	**Post-ART PBMC n=79**
EVM†	42 (48)	44 (49)	41 (52)
3BNC117†	48 (55)	55 (62)	47 (59)
EVM + 3BNC117	27 (31)	29 (33)	25 (32)

*Sensitivity predictions for EVM using N332glycan/D325/H330 signature (83% PPV) and for 3BNC117 using I201/F353 (84% PPV); †Includes viruses susceptible to both bNAbs.

Conclusions

- In the ACTG A5354 study, participants who initiated ART during AEHI had lower HIV Env sequence diversity compared with people with HIV who initiated ART during chronic infection
- Viral Env diversity and prevalence of genotypic bNAb sensitivity signatures were comparable across participants in Fiebig I–V
- There were no significant differences in Env diversity or bNAb sensitivity signatures before and after ART
- Data in this population indicate that the viral reservoir formed during AEHI is representative of the circulating virus at ART initiation and suggest that there is limited evolution of the provirus during >1 y of suppressive ART

References: 1. Crowell TA, et al. Clin Infect Dis 2021;73:e643-51; 2. Moldt B, et al. J Acquir Immune Defic Syndr 2021;88:61-9. **Acknowledgments:** We are grateful to all study participants, the ACTG A5354 clinical study investigators and their study teams, and to SEQ-IT GmbH & Co.KG (Kaiserslautern, Germany) for sequence analysis. This work was funded by Gilead Sciences, Inc. Editing and production assistance were provided by BioScience Communications, New York, NY, funded by Gilead.

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